The Ontario Prehospital Advanced Life Support (OPALS) Study: Rationale and Methodology for Cardiac Arrest Patients

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The Ontario Prehospital Advanced Life Support Study represents the largest prehospital study yet conducted, worldwide. This study will involve more than 25,000 cardiac arrest, trauma, and critically ill patients over an 8-year period. The study will evaluate the incremental benefit of rapid defibrillation and prehospital Advanced Cardiac Life Support measures for cardiac arrest survival and the benefit of Advanced Life Support for patients with traumatic injuries and other critically ill prehospital patients. This article describes the OPALS study with regard to the rationale and methodology for cardiac arrest patients.

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INTRODUCTION

The Ontario Prehospital Advanced Life Support (OPALS) Study represents the largest prehospital study yet conducted, worldwide. This study will involve more than 25,000 cardiac arrest, trauma, and critically ill patients over an 8-year period (1994–2002). Ontario is Canada's most populous province with 11 million people occupying a large land mass 50% larger than the state of Texas. Prehospital Advanced Cardiac Life Support (ACLS) and rapid defibrillation have traditionally not been provided for most Ontario citizens. The OPALS study will evaluate the incremental benefit of rapid defibrillation and prehospital ACLS for cardiac arrest survival and the benefit of advanced life support (ALS) for patients with traumatic injuries and other critically ill prehospital patients. This article describes in detail the OPALS Study with regard to the rationale and methodology for cardiac arrest patients.

BACKGROUND

Prehospital resuscitation

The treatment of cardiac arrest with defibrillation, advanced airway techniques, and intravenous drug therapy has become standardized through the American Heart Association (AHA) ACLS guidelines.[1] The concept of providing ACLS care to cardiac arrest victims outside the hospital was introduced by Pantridge and Geddes with mobile intensive care vehicles in Belfast in the late 1960s.[2] Since then, many countries have introduced varying degrees of prehospital cardiac care to their ambulance services by use of automated defibrillators operated by ambulance attendants or full ACLS measures provided by physicians, nurses, or paramedics.

In Ontario, most communities have been served by ambulance officers trained to provide only basic life support (BLS) measures. Communities in 11 base hospital regions also have had the benefit of defibrillators operated by the ambulance officers; only two communities had land paramedic programs that provided full ACLS measures.

Survival after cardiac arrest

Survival rates for out-of-hospital cardiac arrest in Ontario communities are among the lowest reported at 2.5% overall.[3] The reported survival rates for out-of-hospital cardiac arrest vary widely throughout the world from less than 1%[4] to 20%.[5] These differences in survival rates can be attributed to how the data are reported, population density, and organization of the local EMS system. Use of more favorable denominators such as witnessed ventricular fibrillation subgroups rather than all cardiac arrest victims can "inflate" survival rates and cause confusion.[6] The adoption of uniform international standards (the Utstein style) for reporting cardiac arrest data should help avoid this confusion.[7,8] Population density can adversely affect outcomes, if too high, by delaying EMS access as in some large cities[9,10] or, if too low, by lengthening response interval as in many small communities. The variation in reported cardiac arrest survival rates can also be attributed to local differences in the "chain of survival" links as described by the AHA[11]: early access, early CPR, early defibrillation, and early ACLS.[1]

Effectiveness of prehospital cardiac arrest interventions

There is increasing pressure to identify the relative importance or effectiveness of each of the links in the chain of survival. In an era of limited health care dollars, it is becoming increasingly important for communities to prioritize their use of resources for a local emergency response system. Although the AHA teaches that "weakness in any link lessens the chance of survival," there is no clear evidence to guide local health care planners in choosing the most cost-effective prehospital care programs.[11] Some US communities such as Seattle and King County, Washington, have good cardiac arrest survival rates associated with strong chains of survival. Other US cities such as Chicago and New York with strong fourth links (ie, paramedic programs) have poor survival rates because of defects in other links such as slow times to defibrillation or low rates of bystander CPR.[9,10]

Even in communities with good survival rates the relative importance of the third and fourth links remains unclear. Most US communities introduced the fourth link, through paramedics, before achieving a strong third link. Successful communities introduced both links simultaneously—early defibrillation (provided by paramedics) and early ACLS (provided by paramedics). Some communities have subsequently improved their third link by introducing rapid first-responder defibrillation programs by use of firefighters carrying automated defibrillators. Very few US systems have introduced a strong rapid defibrillation link without the ACLS link already established. Consequently, the impact of rapid defibrillation, without early ACLS, on cardiac arrest survival is not clear.

Canadian cost-effectiveness study

Investigators at the Universities of Ottawa and Toronto have recently completed a cost-effectiveness study of providing different levels of prehospital care for cardiac arrest in Canada.[12,13] The study was comprised of four steps: (1) metaanalysis, (2) calculation of Canadian costs, (3) estimation of the quality of life of survivors, and (4) decision analysis. The study identified 36 primary articles describing 41 EMS systems.[3-6,9,14-43] There were no randomized controlled studies, and data were missing for nine of the systems data even after the original authors had been contacted. The metaanalysis found that survival was associated with decreased EMS response interval and use of a two-tiered EMS system (ambulance or first-responder plus paramedic).[12] The study did not identify an improvement in survival with increased bystander CPR proportions or between any of the one-tiered EMS systems (ambulance, ambulance with defibrillator, or paramedic). The most cost-effective system appeared to be the addition of first-responder firefighters to an ambulance system ($37,000 per quality-adjusted life year [QALY]).[13] The least cost-effective system was improved response time within an existing ambulance system ($187,000 per QALY).

The study was limited by missing data, the potential for confounders when comparing EMS systems in different communities and countries, and the high correlation between response interval and sophistication of the EMS systems. The investigators concluded, therefore, that more methodologically rigorous research is warranted to establish the relative effectiveness of prehospital interventions in cardiac arrest.

Rapid defibrillation in cardiac arrest

How effective are cardiac arrest programs in which early defibrillation is provided by ambulance officers or first-responders rather than paramedics? Five US communities found better survival (ranging from 5% to 19%) for cardiac arrest with the introduction of ambulance defibrillation programs without paramedics.[25,27,32,35,44] In contrast, an Ontario study in five communities recently found that an ambulance defibrillation program did not significantly improve survival rates (from 2.1% before to 2.9% after introduction of the program).[3] The major problem in these communities was that they provided what Cummins et al term "late defibrillation"[11] with mean response intervals of 7.8 minutes to scene and 13.1 minutes to defibrillation. Early defibrillation may be defined as EMS systems that can have a defibrillation-capable responder arrive at scene within 8 minutes of dispatch in at least 90% of cases.[35,45-48] No data are available on the improvement in survival seen with the addition of first-responder firefighter defibrillation to a non-paramedic ambulance system.

How effective are first-responder defibrillation programs when added to an existing paramedic system? Both Seattle and King County demonstrated improved survival rates when first-responding ambulance officers were equipped with defibrillators and were able to reach the scene in a mean time of 3.2 and 4.8 minutes, respectively.[20,34] Memphis did not show improved survival with firefighter defibrillation, partly because the paramedics responded as quickly (mean time to scene 5.8 minutes) as the firefighters in the majority of cases.[49,50] In Hamilton, where the paramedics responded more slowly (mean time to scene 7.8 minutes), the response interval to defibrillation was reduced by 3.5 minutes after the introduction of firefighter defibrillation.[51] The 60% improvement in survival seen in this study was not statistically significant, possibly because of the small numbers of patients. An indirect benefit of firefighter defibrillation may be that paramedics are able to proceed more quickly to other interventions such as intubation and intravenous drug therapy.[48,52] In conclusion, the unanswered question regarding early defibrillation is "What incremental benefit in cardiac arrest survival may be expected when first-responder firefighter defibrillation is added to a non-paramedic ambulance system?"

Early ACLS in cardiac arrest

No communities have studied the incremental effect on survival of adding ACLS (ie, endotracheal intubation and intravenous drug therapy) to an early defibrillation program. All existing studies describe the effect of early defibrillation provided by paramedics or in addition to paramedics. Consequently, the incremental value of endotracheal intubation and intravenous drug therapy, either separately or together, beyond the benefit provided by early defibrillation is not known.[11] Many have questioned the relative cost-effectiveness of providing an early defibrillation program versus that of training, equipping, and paying ACLS personnel in intubation techniques and administration of intravenous drugs. One US EMS expert recently wrote that "…emergency medical services (EMS) providers must prove what is beneficial."[53-55]

After defibrillation, many cardiac arrest victims either fail to regain spontaneous circulation and respiration or remain obtunded. The presumed benefits of endotracheal intubation in prehospital cardiac arrest include improved ventilation and oxygenation, as well as protection from aspiration.[56-60] However, no studies have isolated the impact of intubation alone on prehospital cardiac arrest survival. The benefits of intravenous drug therapy in prehospital cardiac arrest are even less clear. Again, no human studies have isolated the effect of drug therapy on survival. In fact, data supporting the benefit of most cardiac arrest drugs in ACLS protocols are weak in that virtually no randomized controlled trials have been conducted.[61,62]

The AHA ACLS Committee has concluded that survival is the same for single-tier paramedic and single-tier early defibrillation systems because defibrillation is performed late in the former systems.[11] In the report of this committee, Cummins et al write "…it is difficult to separate the value of defibrillation from the value of intubation and intravenous medications." Although the committee believes that intubation and intravenous drug therapy improve survival in two-tiered systems with early defibrillation, they clearly give priority to establishing early defibrillation: "Resources may prevent establishment of a tiered response system that includes first-responder defibrillation as well as paramedics. In these circumstances, first-responder defibrillation, rather than paramedics alone, is probably the most efficient method to improve survival from cardiac arrest. For locations without an effective method of rapid delivery of prehospital

defibrillation, the rational approach is to start with first-responder automated defibrillation."

In conclusion, the unanswered question regarding early ACLS is "What incremental benefit in cardiac arrest survival may be expected when early ACLS provided by paramedics is added to an early defibrillation program?"

STUDY RATIONALE

Ontario emergency health care providers have been striving to improve the poor survival for out-of-hospital victims of cardiac arrest in the province. Many providers believe that much better survival rates can be achieved through implementation of prehospital ACLS measures. The Ontario Ministry of Health, however, has been reluctant to commit the millions of dollars required for widespread implementation of prehospital ACLS programs throughout the province. The Ministry of Health has argued that the effectiveness of prehospital ACLS programs or individual interventions has not been clearly demonstrated in the literature and that further research is required. In this era of limited health care resources, the Ministry of Health is seeking to provide the most cost-effective care to patients.

Rapid defibrillation may be highly effective and may be relatively inexpensive if provided by a first-responder program. Full ACLS is known to be more expensive and is believed to be most effective in the setting of rapid defibrillation. Therefore first-responder defibrillation may be more appropriate and cost-effective for some communities than full ACLS programs. The OPALS study will assess the relative benefit of rapid defibrillation and full ACLS for cardiac arrest survival in a variety of communities.

PREPARATION FOR THE OPALS STUDY

Three consensus retreats on prehospital ALS, sponsored by the Ministry of Health, were held in Toronto during 1993 and 1994. Participants included representatives of the Ministry of Health, Provincial Base Hospital Advisory Group, Ontario Ambulance Operators Association, prehospital provider unions, as well as research consultants. These retreats developed a consensus proposal on the training and operational standards for implementing prehospital ALS in Ontario. At the same time, the retreat participants developed a research plan for evaluating the effect of prehospital ALS measures. That research plan constitutes the basis for the OPALS Study. Parallel committees were proposed to oversee the training and implementation of rapid defibrillation and prehospital ALS (OPALS Implementation Committee) and the research study (OPALS Steering Committee).

Consensus was reached on all aspects of the OPALS Study methodology including: (1) the use of a three-phase before-after design and the nonfeasibility of a randomized controlled design; (2) definition of the study communities as the core urban/suburban areas representing at least two thirds of the cardiac arrest cases; (3) inclusion of cardiac arrest, trauma, and other critically ill patients; (4) isolation of rapid defibrillation as a study intervention; (5) use of a target rapid defibrillation time interval of call received by dispatch to arrival at scene by provider with defibrillator within 8 minutes or less in 90% of cases; (6) combination of endotracheal intubation and intravenous drug therapy as a study intervention phase; (7) the clinically relevant improvements in survival rates to be tested from phase I to II to III; (8) the sample size estimates; and (9) the timeline.

Several investigators conducted a review to determine the feasibility of collecting data for the OPALS Study. A research nurse visited each base hospital program and central ambulance communication center (CACC) and interviewed local 911 and fire department representatives. The review determined that all potential participating base hospital programs had adequate records for at least 36 months of cardiac arrest cases. None of the base hospital regions was currently achieving the target rapid defibrillation response time interval. Most local fire departments were willing to implement first-responder defibrillation with the assistance of the base hospital programs.

On the basis of this review, it was concluded that the most appropriate eligibility criteria for cardiac arrest patients was "all cases for which resuscitation was attempted" because "witnessed ventricular fibrillation" cases could not always be reliably identified. Also, the most appropriate response interval for the rapid defibrillation phase was "call received to arrived scene" because "time interval to defibrillation" was not reliably measured in most centers. It was found that the number of eligible cardiac arrest cases seen annually in the urban/suburban study communities was 1,766, and the baseline survival to discharge rate for these cases was 4.0%.

The research protocol outlining the rationale and methodology for all aspects of the OPALS Study was approved by the Ontario Ministry of Health Emergency Health Services Research Advisory Committee. The approval process involved internal and external peer review. The annual budget is approximately $Can 200,000 for research and $Can 2,000,000 for training, equipment, and salary adjustments.

Thus the approximate total funding for the entire project is $Can 15,000,000.

Objectives

The objectives of the OPALS Study with regard to cardiac arrest patients are to assess the incremental benefit in survival and morbidity that results from the sequential introduction of the following prehospital programs to multiple Ontario communities: (1) rapid defibrillation (system optimization and first-responder), and (2) full ALS measures (intubation and intravenous drug therapy).

Design

The OPALS Study incorporates a multiphase before-after design with the unit of study being all eligible cardiac arrest patients seen during each of three distinct phases.

Phase I represents the baseline survival status after the introduction of the ambulance automatic defibrillation program in each study community and is based on retrospective data for the most recent 36 months before Phase II.

Phase II assesses survival in a 12-month period after introduction of "rapid defibrillation" (as defined below).

Phase III assesses survival in a 36-month period after introduction of "full ALS programs" (as described below).

Data will be pooled across communities, but the start date for the phases will vary for each community because each will require different periods of time to prepare for Phases II and III. The data collection phases within each community will be separated by intervening and overlapping training and run-in periods.

The preferred design for studying any intervention is the randomized controlled trial, which decreases the likelihood of allocation bias between the intervention and the control groups. The investigators examined options for using randomized controls in this study and believed that none was feasible. Both study interventions, rapid defibrillation in Phase II and full ALS in Phase III, represent systemwide programs. These programs require extensive training of hundreds of prehospital personnel. Randomly allocating individual patients to receive or not receive the benefit of a systemwide program such as first-responder defibrillation or paramedic services would be very difficult. Prehospital personnel have made it clear that, because of ethical concerns for patient care, they would not participate in a study that required them to randomly use or withhold ALS skills such as intubation or intravenous drug therapy. For the same reason, randomization by use of a crossover design would not be acceptable to prehospital personnel. Randomization by community may be feasible but is likely subject to more confounding than the proposed before-after design because of inherent differences between communities. Examples of differences between communities might include age, prevalence of coronary disease, rates of citizen CPR, traffic congestion, proportion of high-rise buildings, and distribution of ambulances.

Selection bias will be decreased by the inclusion of all eligible cardiac arrest patients seen during each of the three study phases. The same inclusion and exclusion criteria will be carefully applied to all cases throughout the study phases to ensure comparability of the study populations. Possible confounding factors such as improved citizen CPR rates and changing ambulance response intervals will be noted and controlled for by data analysis.

Setting

Eleven Ontario EMS base hospital programs have agreed to participate in the OPALS Study (Burlington, Cambridge, Kingston, London, Niagara, Ottawa-Carleton, Peterborough, Sarnia, Sudbury, Thunder Bay, and Windsor). Each of these base hospital programs share common characteristics: (1) 911 emergency telephone system, (2) ambulance defibrillation program, and (3) ability to provide at least 3 years' retrospective data for cardiac arrest patients.

Within the base hospital regions are 21 urban/suburban communities that will be the setting for the OPALS Study. These study communities are clearly defined and separate geographic areas (usually based on municipal boundaries), which together include at least two thirds of cardiac arrest cases for that base hospital defibrillation program. The communities must be served by ambulance services with an annual call volume of at least 1,000 dispatched code 3 (prompt) or 4 (life-threatening) calls. The populations of the study communities range from 16,000 to 750,000.

Each study community will be eligible to participate in Phase III of the OPALS Study if they are able to achieve the target rapid defibrillation response time interval and provide 12 months' data from Phase II. The target rapid defibrillation time interval is defined as call received by dispatch to arrival at scene by a responder with defibrillator in 8 minutes (and 0 seconds) or less for 90% of cardiac arrest cases in the study area.

Times will be based on those provided by the local Central Ambulance Communication Centers (CACC) and the local fire departments, and the clocks for these agencies will be synchronized with each other. Communities can only begin

to organize training for Phase III after the OPALS Steering Committee judges that 3 months of Phase II data are complete and meet the target response interval based on reports from the data coordinating center at the University of Ottawa. Each community will have 24 months after the approval of the OPALS Study within which to meet the target rapid defibrillation response interval criteria. Communities will be assisted by the Implementation Committee (described below) in the optimization of their defibrillation response system. Failure to meet the response interval criteria will preclude a community from proceeding to Phase III.

Study population

The primary study population will be all patients with cardiac arrest (absence of a detectable pulse, unresponsiveness, and apnea) (1) of presumed cardiac origin, (b) out-of-hospital in the study communities, and (2) for which resuscitation is attempted by emergency responders. Case definitions will follow the Utstein Style guidelines for reporting cardiac arrest data.[7]

The following will be excluded: (1) patients younger than 16 years; (2) patients who are "obviously dead" as defined by the Ambulance Act of Ontario (decomposition, rigor mortis, or other); (3) trauma victims, including hanging and burns; and (4) patients with cardiac arrests clearly of other noncardiac origin including drug overdose, carbon monoxide poisoning, drowning, exsanguination, electrocution, asphyxia, hypoxia related to respiratory disease, cerebrovascular accident, and documented terminal illness.

Ethical considerations

The OPALS Study has full Research Ethics Committee approval. Informed consent need not be obtained because patients will not be randomly allocated to receive different therapies. All patients within each phase will be offered the same intervention program. Patients will be subjected to therapy and procedures already provided either inside or outside the hospital and will not be exposed to undue risk or discomfort. Strict patient confidentiality will be assured.

INTERVENTION PHASE II: RAPID DEFIBRILLATION

Each study community will optimize the local prehospital response system to achieve the target rapid defibrillation interval of call received by dispatch to arrival at scene by responder with defibrillator within 8 minutes (and 8 seconds) or less for 90% of cases. Time interval from collapse to actual defibrillation is the most clinically important parameter but was not consistently and accurately measured in all centers during Phase I. This Phase II optimization process may include any or all of the following: (1) reduction of dispatch time intervals within CACC centers, (2) more efficient deployment of existing ambulances, or (3) first-responder (firefighter or police) defibrillation.

First-responder defibrillation

Each municipality will be encouraged to develop first-responder defibrillation based on the Guidelines for Rapid Defibrillation Programs Delivered by Public Safety Agencies in Ontario. These guidelines have been developed and approved by the Ontario Ministry of Health and Ministry of the Solicitor General and Correctional Services (responsible for firefighters).

The base hospital medical directors or physician delegates will train instructors and will oversee training and certification of all providers through use of certified instructors. The medical directors will also oversee quality assurance by ensuring adequate review of documentation of each case of first-responder defibrillation. Finally, the medical directors will oversee programs of skills maintenance and continuing medical education.

INTERVENTION PHASE III: FULL ADVANCED LIFE SUPPORT

Each base hospital program will oversee the implementation of a program of prehospital ALS provided by ambulance services operating in the study communities. The minimum essential elements of this program are (1) endotracheal intubation, (2) intravenous therapy, and (3) administration of intravenous drugs.

Basic operational standards for conducting an ALS program were proposed at the consensus retreats. The proposed ambulance configuration is one ALS and one basic life support–defibrillation (BLS-D) attendant per vehicle. During the initial 3-month run-in period at the start of the program (not to be included in the data analysis of Phase III), the configuration will be two ALS attendants per ALS vehicle. Where possible, the dispatch center will send both a BLS-D and an ALS vehicle to "potential ALS calls" (dual-vehicle response). Each 24-hour ambulance will require up to 6 ALS attendants to provide constant ALS coverage throughout the year. An acceptable ALS program must ensure that all cardiac arrests in a community are attended by an ALS-capable vehicle with a response interval of call received to arrival at scene of 11 minutes or less for 90% of cases.

Experienced ambulance officers will be selected for ALS training according to criteria proposed at the consensus retreats. In the province of Ontario, certified ambulance officers have undergone 1,600 hours of classroom and practical teaching through a 10-month community college program. The additional ALS training will be based on the Canadian Medical Association competency requirements for Emergency Medical Technology Level III. This additional training will include didactic (6 weeks), clinical (6 weeks), and preceptorship (12 weeks) components. The base hospital medical directors will be responsible for ongoing quality assurance, which will include review of case documentation and regular continuing education of ALS skills.

OUTCOME MEASURES

Primary outcome

The primary outcome measure for the cardiac arrest component of the OPALS Study will be survival to hospital discharge, which is defined as the patient leaving the hospital alive. This must be verified by either a review of hospital chart or an interview of the patient's family physician.

Secondary outcomes

The neurologic function of survivors will be assessed at discharge and at 1 year according to a 5-point scale of Cerebral Performance Category (CPC).[63] These data are not available for Phase I patients.

Other survival measures according to the Utstein (ROSC) style will be collected: return of spontaneous circulation (all phases), admission to hospital (Phases II and III), and survival to 1 year (Phases II and III).

Quality of life of survivors will be measured (Phases II and III) at 1 year by means of the Health Utility Index, which provides an estimate of health utility between 0 and 1.0.[64]

Time from "call received" to "arrival at scene" with defibrillator as well as to "defibrillation" will be measured in a consistent fashion in Phases II and III by ensuring regular synchronization of ambulance and first-responder defibrillator clocks with CACC clocks. Time intervals to "ALS procedures" will be documented in Phase III.

Performance of ALS measures (intubation, intravenous therapy, drug administration) will be documented in terms of rates of success, and complications as judged by the medical directors.

The direct costs (training, salary, administration, and equipment) for implementing and maintaining the rapid defibrillation and ALS programs will be documented for each base hospital region. A formal health economic analysis of the study interventions will be conducted separately for Phases II and III.

DATA COLLECTION

Phase I: Baseline

Data will be collected for cardiac arrest patients by having data elements abstracted directly into a database from the Ambulance Call Reports (ACR), initial rhythm records, CACC reports, and survival records. Each base hospital will submit to the data coordinating center photocopies of these records for the retrospective 36-month period.

Phase II: Rapid defibrillation

The same records for all eligible cases of cardiac arrest will be submitted to the data coordinating center. In addition, 1-year information will be provided for survivors: survival, CPC scores, and Health Utilities Index scores (administered by telephone). In addition, the base hospitals will provide first-responder defibrillation documentation of defibrillation attempts, procedural problems, and fire department dispatch times for "arrival at scene." Accurate and synchronized times will be provided for "defibrillation" by both the ambulance officers and the first-responders.

Phase III: Full Advanced Life Support

The same data will be submitted as in Phase II for the cardiac arrest patients. In addition, the base hospitals will also provide data on the use of ALS procedures and drugs in terms of success and complications.

SAMPLE SIZE

Sample size is estimated on the basis of these assumptions: (1) two-sided α level of .05, (2) β error of .2, (3) baseline survival rates of 4.0%, (4) 3:1 ratio of phase I to phase II patients to minimize duration of Phase II, (5) 1:3 ratio of phase II to phase III patients, and (6) demonstration of relative differences in survival of 50% from phase I to II (4.0% to 6.0%) and 40% from phase II to III (6.0% to 8.4%). Table 1 outlines the number of patients required for each phase. With approximately 1,770 patients available annually, only two thirds of eligible cases need be entered into the study to meet the sample size requirements. This affords a margin of security should some communities fail to meet the requirements for Phase II or III.

The Phase II sample size affords the following degrees of power to show various relative improvements from Phase I to Phase II: .72 power for 45% improvement, .63 power for 40%, .53 power for 35%, .43 power for 30%, and .33 power for 25%. The phase III sample size will afford the following degrees of power to show various relative improvements from phase II to phase III: .71 power for 35%, .59 power for 30%, and .45 power for 25%. These sample size figures will also afford power of .80 to demonstrate a relative improvement, from Phase I to Phase III, as small as 35% (4.0% to 5.4%).

Timeline for training and implementation

Each study community will proceed from phase to phase regardless of the progress of the others. System optimization for Phase II may take from 0 to 24 months in individual communities. Preceptor training and run-in assumes four groups of 3 months each but some communities may require less time. The estimated activity schedule for each community is outlined in Table 2.

STUDY HYPOTHESES

Primary hypotheses

The primary hypotheses are as follows:

1. That there will be an improvement in survival to hospital discharge from Phase I (baseline) to II (rapid defibrillation).

2. That there will be improvement in survival to hospital discharge from Phase II (rapid defibrillation) to III (full ALS).

Secondary hypotheses

The secondary hypotheses are as follows:

1. That there will be no decrease in neurologic function of survivors from Phase II to III.

2. That there will be an improvement in other survival measures (ROSC, admission, 1-year outcome) from Phase II to III.

3. That there will be no decrease in quality of life of survivors from Phase II to III.

DATA ANALYSIS

Phase I

Multivariate logistic regression analyses will be performed to assess predictors of survival from among these variables: community size, ambulance service, age, gender, winter season, witnessed status, initial rhythm, CPR initiated by citizen, CPR initiated by fire/police, time intervals "call receipt-arrival at scene," "arrival at scene–arrival at patient's side," "patient's side–depart scene," "depart scene–arrival hospital." This will allow calculation of odds ratios, with 95% confidence intervals, of those variables significantly associated with survival. This in turn will provide further insight into the relative importance of system factors that may be amenable to modification in a BLS-D EMS system.

Phases II and III

All other analyses, besides the interim analysis in Phase III, refer to comparisons between Phases I and II and to comparisons between Phases II and III (ie, the same statistical techniques will be used at the conclusion of Phase II and Phase III).

The primary hypothesis of improved survival rates between Phases I and II and between Phases II and III will be tested by χ^2 analysis techniques. All *P* values will be two-tailed. Ninety-five percent confidence intervals will be calculated for the absolute difference in survival rates between

Table 1.
Sample size for study phases.

Study Phase	Survival (%)	Patients	Months
I: Baseline	4	3,756	36
II: Rapid defibrillation	6.0	1,192	12
III: Full ALS	8.4	3,522	36

Table 2.
Estimated activity scheduled for each community.

Study Phase	Month	Activity	Duration (mo)
I: Baseline	0–8	Retrospective data collection	8
II: Rapid defibrillation	0–6	Optimization of system	6
	7–18	Data collection	12
III: Full ALS	16–18	Didactic/clinical training ACLS	3
	19–30	Preceptor training and run-in	12
	31–66	Data collection	36

phases. χ^2 Procedures will be used to evaluate the homogeneity of survival rates across the study communities. If the differences in survival are homogeneous, then a pooled estimate of survival will be calculated. If the differences are not homogeneous, then communities with like results will be combined and reasons for the differences will be evaluated. These subgroups will be compared between phases by χ^2 analysis. In addition, a random effects model will be considered to provide an overall survival rate across all communities.

We have attempted to capture all the indicators of changes in the system that could affect survival (potential confounders): community, ambulance service, age, gender, witnessed status, initial rhythm, CPR initiated by citizen, CPR initiated by fire/police, time intervals "call receipt–arrived scene," "arrived scene–arrived patient's side," "patient's side–depart scene," "depart scene–arrival hospital." Logistic regression analysis will be performed to control for the possible confounding effects of these indicators and to assess the effect of phases on survival.

The variables "rate of survival" and "call receipt–arrived scene" will be displayed descriptively in a graph per month over time and will be evaluated by time-series analysis. In particular, by using interrupted time-series analysis procedures we will evaluate the effect of intervention (study phases) on survival. Time-series analysis will also be used to evaluate any other unexpected changes in survival over time. Run-in data will be included in time-series analyses only.

Differences between phases for other outcomes, patient characteristics, and treatment and system characteristics will be tested with the Wilcoxon rank-sum, χ^2, Fisher's exact or Student's *t* test analyses, as appropriate. Other characteristics such as costs and performance of ALS procedures will be presented descriptively.

One interim analysis will be performed on the primary outcome (survival) when 50% of Phase III patients have been accrued according to the O'Brien-Fleming technique of grouped sequential analysis.[65] To retain the overall α level of .05, the α levels will be .0053 for the interim analysis and .0488 for the final analysis. This analysis will be reviewed by the Steering Committee. Demonstration of significant benefit at the time of the interim analysis would permit early termination of the study and, consequently, considerable savings in time and resources.

Outcome comparisons will be made between phases for the following a priori subgroups: initial rhythm, witnessed status (bystander and EMS), community, and community size by quartiles.

STUDY RELEVANCE

Cardiac disease is the most common cause of death in Canada and the US and sudden cardiac arrest frequently claims the lives of men and women during their most productive years. Survival for out-of-hospital cardiac arrest in most Ontario communities is among the lowest reported in Western countries. Ontario emergency health care providers believe that much better survival rates can be achieved for victims of cardiac arrest through optimizing the "chain of survival" as described by the American Heart Association. Particularly weak in most Ontario communities are the third and fourth links of the chain, early defibrillation, and early advanced cardiac life support. Widespread implementation throughout Ontario of full prehospital advanced cardiac life support, as practiced in many US communities, would cost many millions of dollars. In this era of severely limited resources and competition to maintain or develop health care programs, the Ontario Ministry of Health is obligated to justify expenditures for new initiatives.

The objective of the OPALS Study is to determine the relative benefits of the third and fourth links in the "chain of survival" in Ontario communities. Neither the existing medical literature nor previous studies clearly indicate the relative effectiveness of early defibrillation and early ALS for cardiac arrest victims. The OPALS study should provide clear answers to these questions and thereby help the Ministry of Health and Ontario communities determine their priorities for providing the most cost-effective prehospital care to their citizens.

We expect the results of the OPALS Study to be fully applicable to prehospital care in most other Western countries. This is an era when providers of health care services, whether government, health maintenance organization, or private insurance company, are reexamining the effectiveness and costs of medical services for their constituents. In an age of evidence-based medicine and severe fiscal restraint, it is only natural that providers question the value of full ALS for out-of-hospital patients. We believe that the OPALS Study will clearly demonstrate to health care providers the cost-effectiveness of rapid defibrillation programs for cardiac arrest and of full ALS programs for cardiac arrest, trauma, and critically ill patients. The results of this study, therefore, have the potential to significantly affect policies and funding for prehospital care throughout the world.

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