

SIGNA VITAE 2010; 5 (Suppl 1): 60 - 62

Clinical Trials

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ABSTRACT

The clinical practice of resuscitation science is dependent on discoveries generated in the basic science and animal laboratory and then translated into clinical trials for application in humans. The successful implementation of prospective, randomized, controlled, clinical trials in the field of cardiac arrest remains challenging and continues to evolve. Funding for clinical trials of cardiac arrest is limited, and there are significant obstacles to performing such studies because of the inability to obtain informed consent under these emergency circumstances. The absence of reliable national statistics on cardiac arrest, evaluation of neurological outcome, and potential confounders such as post-resuscitation hospital-based care and quality of cardiopulmonary resuscitation (CPR) continue to challenge cardiac arrest clinical trials. Nonetheless, the immense public health burden of cardiac arrest is being recognized, appropriate public health initiatives to address the problem are being implemented, and the resuscitation research community is meeting this challenge.

Keywords: resuscitation, clinical trials, funding, informed consent, neurological and functional assessments, standards

Introduction

The national and international recommendations that guide the treatment of cardiac arrest throughout the world are developed through a careful evidence evaluation process that formally assesses the effectiveness of various resuscitation therapies reported in the literature. The clinical practice of resuscitation science is dependent on discoveries generated in the basic science and animal laboratory and then translated into clinical trials for application in humans. The successful implementation of prospective, randomized, controlled, clinical trials in the field of cardiac arrest remains challenging and continues to evolve. Recent data suggest that survival rates for cardiac arrest vary by nearly 500%, depending on location. (1) This systematic bias could obscure the validity of a new intervention that

could produce significant improvement in survival rates. Funding for clinical trials of cardiac arrest is limited, and there are significant obstacles to performing such studies because of the inability to obtain informed consent under these emergency circumstances. The absence of reliable national statistics on cardiac arrest, evaluation of neurological outcome, and potential confounders continue to challenge cardiac arrest clinical trials. Nonetheless, the immense public health burden of cardiac arrest is being recognized, appropriate public health initiatives to address the problem are being implemented, and the resuscitation research community is meeting this challenge.

The Need for Clinical Trials

In a large North American study involving 10 geographic locations covering a catchment of 21.4 million people with 20,520 cardiac arrests, the incidence of cardiac arrest was 50.1 per 100,000 population. (1) Survival ranged from 3.0% to 16.3% in these 10 centers with

a median of 8.4%. (1) This represents a huge health burden from cardiac arrest. In addition, the number of years of life lost due to sudden cardiac arrest, appears to be at least 1,000,000 years annually in the United States. (2) At a very conservative valuation of \$50 000 per life-year, this places the cost of sudden cardiac death at about \$50 trillion annually. On the basis of this number, the net present value of research that could produce a 10% reduction in mortality from sudden cardiac arrest would be about \$75 billion. (2)

Exception from Informed Consent

Despite the need for clinical trials to improve outcome from cardiac arrest, the inability to obtain informed consent from victims of cardiac arrest represents a challenge for resuscitation scientists. The goal of any cardiac arrest clinical trial is to evaluate a promising clinical intervention that holds potential for direct benefit to the patient, while doing everything possible to maintain

the welfare, safety, and rights of human subjects. Each country implementing cardiac arrest clinical trials has approached this ethical dilemma differently. In the United States, the Food and Drug Administration implemented its Final Rule (21 CFR 50.24) in November, 1996. (3) This regulation makes cardiac arrest clinical research feasible, while, at the same time, mandating an extensive process of Federal Wide Assurance, multiple Institutions Research Committee oversight and approval, community consultation and public notification prior to protocol initiation. One multi-center clinical research consortium reported approval from 58 Institutions Research Committees requiring about 6 months of time with an equal amount of time for completion of community consultation and public notification. (4) While allowing clinical cardiac arrest research to be implemented, current regulations make this a time consuming, work-intensive, and ultimately very expensive process. Significant funding for such trials is now required, which can limit investigation to the few, most highly promising research questions.

Funding

Funding for cardiac arrest clinical trials is limited, and continues to impede rapid progress in the field. One exception has been the development of the National Heart, Lung, and Blood Institute's Resuscitation Outcomes Consortium in the United States. (5) The Resuscitation Outcomes Consortium (ROC) was created to conduct clinical research in the areas of cardiopulmonary resuscitation and traumatic injury. ROC consists of 10 Regional Clinical Centers and a Data and Coordinating Center that provide the necessary infrastructure to conduct multiple collaborative clinical trials to aid rapid translation of promising scientific and clinical advances to improve resuscitation outcomes. Recognizing the need to stimulate progress within the field, the National Institutes of Health will have invested approximately \$120 million over 12 years in this initiative by 2016. If the results of the ROC clinical

trials significantly improve outcome from cardiac arrest, continued funding for cardiac arrest clinical trials will be promising.

Clinical Trial Issues

Cardiac arrest clinical trial study designs will be impacted by the true denominator of the disease. Significant challenges remain in knowing the true statistics for incidence, epidemiology, and surveillance of sudden cardiac arrest. The absence of a national mandate for reporting all cardiac arrests and the resulting absence of reliable national statistics creates a challenge to the conduct of future clinical studies. (6) This deficiency in understanding the epidemiology of cardiac arrest is a result of the lack of a consistent, standardized definition of sudden cardiac arrest and the use of surrogate data for epidemiological purposes, marked variation in the reported incidence of pediatric cardiac arrest, and limitations in the use of death certificates, such as misdiagnosis of underlying etiology, misreporting of diagnosis, and miscoding. As a result, comparisons of cardiac arrest outcomes have potential for significant bias. Therefore, any study evaluating and reporting cardiac arrest outcomes must account for these potential reporting biases and adhere to established or uniform end points such as those proposed under the Utstein guidelines. (7,8)

As resuscitation science has evolved, interventions have become more successful in resuscitating, reviving, and discharging patients, and there is an increasing need to reconsider outcomes such as length of survival, preservation of neurologic function, and quality of survival. Immediate restoration of spontaneous and adequate circulation is the highest priority of cardiac arrest resuscitation. However, progress in resuscitation science will not be measured by improved survival rate, but by neurologically intact survival rate. Previous clinical trials have failed to provide significant neurological protection to patients resuscitated from cardiac arrest. (9) This is changing

rapidly with the advent of therapeutic hypothermia as a standard of post-resuscitation care, which improves neurological and functional outcome. (10) The Cerebral Performance Categories (CPCs), previously used as the primary outcome measure in cardiac arrest clinical trials, is increasingly regarded as insufficient to adequately and sensitively assess cardiac arrest survivors. (11) Furthermore, discontinuing evaluation of cardiac arrest survivors at hospital discharge is increasingly regarded as an insufficient time period for follow up. More sensitive neurological and functional assessments for cardiac arrest survivors that are feasible to implement in large, costly clinical trials need to be developed. Standards for neurological evaluation and appropriate time periods of assessment need to be defined and universally applied. Improving neurological outcome for victims of cardiac arrest first requires measuring dysfunction.

Although randomized controlled clinical cardiac arrest trials continue to have face validity and remain a "gold standard", the significant potential for intrinsic (and sometimes subtle) confounders in cardiac arrest trials is an important issue to recognize. Hospital-based post-resuscitation care (e.g. establishing Resuscitation Centers in the community) is one of the most significant recent advances in treatment of cardiac arrest. One-year neurologically intact survival more than doubled (from 26% to 56%) after implementing such an approach. (12) The services provided by such centers vary by institution and often by patient. Clinical trials measuring cardiac arrest outcome without standardizing hospital-based care for all study patients are subject to significant bias. Variability in post-resuscitation care remains a significant threat to clinical trial validity. Similarly, the recognition of the importance of the quality of cardiopulmonary resuscitation (CPR) provided at the scene of cardiac arrest is a source of potential bias in clinical trials. (13-15) Like post-resuscitation care, quality of CPR varies by emergency medical services system, hospital,

and patient. Non-blinded clinical trials risk differential quality of CPR in study groups. Without measurement, this potential bias will remain undetected. Electronic CPR monitoring with real-time voice-prompted feedback, now widely available, represents a potential solution but is not universally applied. Clinical cardiac arrest trials should electronically measure quality of CPR,

compare, and report performance in all patient groups.

Conclusion

The public health burden of cardiac arrest is enormous. Combined with the development of new, promising clinical interventions, the need for high quality translational research in the field of cardiac arrest has never been greater.

Challenges to implementing clinical cardiac arrest clinical trials include funding, inability to obtain informed consent, unreliable national statistics on cardiac arrest, selection of outcome variables, and potential confounders. Irrespective, public health initiatives to address cardiac arrest are being implemented, and the resuscitation research community is meeting this challenge.

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