The US Food and Drug Administration (FDA) Circulatory System Devices Panel met to discuss the type of data required to effectively evaluate the performance of cardiopulmonary resuscitation (CPR) and hypothermia devices for cardiac arrest patients. Advisory panels make nonbinding recommendations to the FDA.

The era of modern CPR began in the 1960s, when mouth-to-mouth ventilation combined with forceful chest compressions were first used together to attempt to resuscitate victims of cardiopulmonary arrest. Unfortunately, despite the promise of a variety of pharmacological, electrical, and mechanical therapies during and after administration of CPR, meaningful improvements in cardiac arrest survival have been difficult to achieve.

Earlier generations of CPR devices are designed to assist the rescuer in the performance of CPR. These devices, for example, may compress the chest at a fixed rate and compression depth, or they may provide audible or visual indicators to assist the rescuer with compliance with published CPR guidelines. In general, regulatory guidelines do not require clinical data for these devices as long as they are similar in design and technology to previously marketed “predicate” devices. More than 30 devices for external compression and/or timing assistance during CPR have been cleared for marketing by the FDA.

Devices intended to enhance a clinical aspect of CPR, in contrast to devices designed simply to assist the rescuer in the performance of CPR, require clinical data to support approval of the device. These devices, such as those providing interposed abdominal compression, circumferential chest compression, or active compression-decompression, have focused primarily on enhancing hemodynamics during CPR. Despite great interest in improving CPR survival rates, no device intended to enhance hemodynamics during CPR has been approved by the FDA for marketing in the United States. The Circulatory System Devices Panel was asked to discuss and make recommendations about the type of clinical data required to adequately evaluate the performance of CPR devices.

Patient Selection

The Panel recognized that patient selection and specific inclusion/exclusion criteria might be device specific. For example, an intervention designed to aid during the metabolic phase of cardiac arrest may not help, or could even be harmful, if applied during the circulatory phase. Just as a defibrillator trial would require patients with ventricular fibrillation (VF) and a pacing trial would require patients with asystole/bradycardia, so should a device trial designed to improve hemodynamics during CPR enroll patients with compromised hemodynamics. Patient selection may have an important impact on study outcome.

In short, the ideal clinical trial would enroll a well-defined patient population to maximize the chance of observing a treatment effect and minimize the number of patients required. Practically speaking, however, the Panel recognized that performing clinical trials on people experiencing a cardiac arrest is challenging. For example, informed consent, a fundamental element of human subjects research, presents unique difficulties. Clinical studies should follow FDA-published regulations with regard to the ethical conduct of research, the acceptable exceptions to informed consent, and the necessary steps to ensure adequate patient protections.

Even initial rhythm determination can be difficult, and complex patient selection criteria could serve to minimize study enrollment or delay critical therapy. “Casting a broader net” may, therefore, be more effective and more practical in the emergency environment of a cardiac arrest. Clinical trial design should anticipate the potential for important differences in clinical outcome in different patient populations (eg,
in-hospital versus out-of-hospital arrest, witnessed versus unwitnessed arrest) and should prespecify such analyses. Post hoc subgroup analyses are useful for hypothesis generation but generally not for device approval. Data on other known prognostic factors (eg, initial rhythm, time to initiation of CPR) should be recorded whenever possible.

Study End Points

The identification of meaningful study end points for CPR clinical trials also is challenging. There was consensus that survival to hospital discharge and hospital discharge with "intact" neurological function are important and meaningful end points, albeit not necessarily the only acceptable end points. Measurement/assessment of neurological function should be performed by trained personnel blinded whenever possible to the patient’s treatment allocation. The ideal metric of neurological function would be an instrument sensitive enough to detect both physical and cognitive abnormalities that has been validated in the post–cardiac arrest patient population. Although the ideal neurological instrument currently does not exist, a variety of measures have been used in the cardiac arrest setting. A composite neurological end point may be appropriate. Efforts to develop and validate an accurate neurological metric in this patient population (eg, MRI or other brain imaging) may allow for more objective assessment of neurological function in the future.

Although the Panel agreed on the utility of longer-term end points, there was no consensus on the usefulness of surrogate end points. The ideal surrogate would be a short-term outcome or measurement that correlated perfectly with a more "meaningful" end point such as improved survival without neurological impairment. Potential surrogates, such as demonstration of improved hemodynamics during CPR, return of spontaneous circulation (ROSC) after cardiac arrest, survival to hospital admission, or survival for 24 hours do not reliably predict overall survival. Some CPR device studies, such as those involving active compression-decompression and inspiratory impedance threshold devices, have demonstrated improvement in 24-hour survival rates without improvement in survival to hospital discharge. Although a reliable short-term surrogate end point may be acceptable, none exists for cardiac arrest patients. As such, a device that demonstrates improvement for one link in the chain of survival would need to be evaluated on the basis of how the entire chain is affected.

Study Design

Because of important advances along the entire chain of survival (eg, potential for earlier defibrillation), there was consensus that single-arm studies with "historical" controls may not provide an adequate control group. Similarly, important differences in emergency medical services within and outside the United States preclude easy comparison of these 2 groups. Although prospective, randomized trials are ideal, in some cases, prospective nonrandomized studies may be appropriate. Blinding whenever possible (ie, for assessment of neurological outcomes) and assessing for bias when blinding is not possible (eg, third-party observation of CPR quality in the device-versus-control group) should be considered.

The development of an acceptable historical control database and the development of uniform definitions of effectiveness and adverse event end points would facilitate CPR device research. Some cardiac arrest databases exist; however, they often are limited because of their small size, biased referral base, and complex issues of patient privacy/reporting.

Hypothermia Devices for CPR

The Panel also discussed the type of data that would be necessary to evaluate hypothermia devices for the treatment of cardiac arrest. There has been a great deal of interest in hypothermia as an adjunct therapy for cardiac arrest patients, particularly in the wake of 2 randomized, controlled clinical studies that suggested hypothermia may be of clinical benefit. The Hypothermia After Cardiac Arrest Study Group studied 275 patients in Europe who experienced a witnessed VF or “nonperfusing” ventricular tachycardia cardiac arrest and remained unconscious after collapse despite ROSC within 60 minutes of the arrest. A higher rate of survival and a higher rate of “favorable” neurological outcome (Pittsburgh cerebral-performance category 1 [good recovery] or 2 [moderate disability]) were reported among patients randomized to hypothermia as compared with those who received conventional (normothermic) care. Cooling was performed with an external cooling device and ice packs if necessary to reach a target temperature of 32°C to 34°C within 4 hours of the ROSC. Hypothermia was maintained for 24 hours. A second trial reported on 77 patients in Australia who had persistent coma despite ROSC after VF arrest. Improved survival “with a good outcome” (ie, discharged home or to a rehabilitation facility) was reported for patients randomized to hypothermia as compared with normothermia. Cooling was initiated in the ambulance and continued in the emergency department by means of ice packs placed around the head, neck, torso, and limbs. The target core temperature was 33°C for 12 hours.

On the basis of these 2 studies, the International Liaison Committee on Resuscitation recommended in 2003 that unconscious adult patients with ROSC after resuscitation from out-of-hospital VF arrest should be cooled to 32°C to 34°C for 12 to 24 hours and that such cooling may be beneficial for other rhythms or in-hospital arrests. Unfortunately, neither study was powered to detect differences in adverse event rates between the treatment and control groups. It is noteworthy that studies that used an inferior vena cava balloon catheter to cool patients with myocardial infarction have demonstrated nonsignificant increases in the incidence of shock, pulmonary edema, deep vein thrombosis, and vascular and bleeding complications.

The Panel recognized that a number of issues present challenges to the evaluation of devices designed to induce hypothermia. The rapidity with which hypothermia is induced and with which normothermia returns after cessation of cooling may have both therapeutic and safety implications. Optimal degree and duration of cooling remain uncertain. Although cooling as used in the narrowly defined recommendation of the International Liaison Committee on Resuscitation may be acceptable, the Panel concurred that it was not
Conclusions

Cardiac arrest remains an important public health concern that affects hundreds of thousands of patients annually. Scientifically well-conducted clinical studies can and should be performed to support the approval of devices designed to improve clinical outcomes of cardiac arrest victims.

Key Words: United States Food and Drug Administration ■ cardiopulmonary resuscitation ■ hypothermia ■ device approval ■ heart arrest
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