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Prehospital Care of the Multiply Injured Patient

The Challenge of Figuring Out What Works

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In this issue of The Journal, Cooper and colleagues[1] report the results of a well-designed and well-executed randomized trial comparing 2 fluid resuscitation strategies in the initial prehospital treatment of adults with severe traumatic brain injury and posttraumatic hypotension. Although the results show no evidence of improved neurological outcome with the hypertonic saline (HTS)–based resuscitation strategy, the study is noteworthy for several reasons. First, it is one of relatively few examples of double-blind, randomized controlled studies of therapies for critically ill patients conducted in the prehospital setting.[2,3] Such studies are critically important to determine what works in that setting. Second, the study illustrates several issues regarding obtaining informed consent for participation in research from acutely incapacitated patients in the prehospital setting. Third, the study results, although negative, may be helpful in guiding choices of fluid resuscitation strategies in future investigations.

Determining whether a therapy works in the prehospital setting requires testing the therapy in that setting.[2] Therapies that are effective in the hospital may not work in the prehospital setting and, conversely, therapies may work in the prehospital setting that are ineffective once the patient arrives at the hospital.

The prehospital setting is uncontrolled, even when compared with a busy emergency department. The number of personnel, available equipment and pharmacologic agents, and space and lighting may all be limited. Prehospital care providers often have to intervene while injured patients are still trapped in vehicles or in other potentially dangerous situations and frequently care for multiple patients simultaneously. Practical considerations, such as rescuer safety and crowd control, may affect the ability of prehospital providers to complete interventions successfully and rapidly.

On the other hand, prehospital providers are able to initiate therapies before a hospital-based clinician can. For diseases in which physiologic derangements progress quickly and become irreversible (eg, airway obstruction, cardiopulmonary arrest, posttraumatic shock, brain injury with increased intracranial pressure [ICP]), treatments must be initiated in the prehospital setting to maximize their potential effectiveness.

Hypertonic saline has been shown in several animal and human studies to increase blood pressure and decrease ICP.[4-6] Although the mechanism of action of HTS is likely complex, primary effects include an increase in intravascular volume because of fluid shifts and movement of water away from uninjured regions of brain.[4,6] In the setting of severe traumatic brain injury with its associated increase in ICP, devastating secondary injury often occurs if the patient is allowed to remain hypotensive because of inadequate cerebral perfusion pressure.[6] The use of HTS, both to increase mean arterial pressure and decrease ICP and thus increase cerebral perfusion pressure, is a logical and promising ap-

See also p 1350.

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proach to reduce secondary injury and improve neurological outcome. Because the effects of HTS and the progression of secondary brain injury may both occur rapidly, the effectiveness of HTS for patients with traumatic brain injury and hypotension is best evaluated in the prehospital setting.

When an acute, incapacitating, life-threatening illness or injury occurs and the emergency medical services system is activated, the popular perception is that the treatments rendered by paramedics (as opposed to simple rapid transport to a hospital [ie, "scoop and run"]) are effective in improving outcome. Although this is undoubtedly true in some cases, such as defibrillation for cardiac arrest due to spontaneous ventricular fibrillation, many treatments provided by paramedics are simply "borrowed" from other settings and are of unproven effectiveness and have unknown safety profiles in the prehospital setting.[2] For example, prehospital endotracheal intubation, a widely accepted procedure, may have a much higher complication rate than previously thought[7] and likely has little benefit for children.[8]

There is an ethical and moral obligation to determine which therapies are safe and effective in the prehospital setting, make those therapies available, and eliminate the use of therapies that are ineffective or harmful. Fulfilling this obligation requires the controlled and randomized testing of both unproven current therapies and promising new treatments in the prehospital setting. Such trials will often require enrolling research participants who have been suddenly and unpredictably incapacitated and for whom no appropriate surrogate is available to give consent.[9]

Since 1996, federal regulations in the United States have allowed a narrow exception to the general requirement for prospective written informed consent prior to participation in a research study.[10-13] This narrow exception, which requires review and approval by an applicable institutional review board, requires that the human participants be in a life-threatening situation and that available treatments are unproven or believed to be ineffective, that it is not feasible to obtain informed consent because of the sudden and unpredictable incapacitation of the patient associated with the disease being studied, that the treatment being investigated must be instituted rapidly to be potentially effective, and that participation in the research "holds out the prospect of direct benefit to the subjects."[10] The institutional review board must also determine that the clinical investigation could not be practicably performed without the exception.

To qualify for the exception, the study must include processes of community consultation and public disclosure. Community consultation is a 2-way discussion of the proposed research with potential patients or members of the community from which the patients will be drawn; public disclosure is a 1-way dissemination of information regarding the proposed research into the community from which patients will be drawn.[10,13-16] The institutional review board must consider community feedback from community consultation and the adequacy of public disclosure in deciding whether to approve the proposed study. In addition, all studies that use the emergency exception must be overseen by an independent data and safety monitoring board.[10,13,17]

Although these federal regulations allow an avenue through which potentially promising research on therapies for sudden, serious, and acutely incapacitating illnesses may be studied, they have been used relatively rarely. The infrequent use of these regulations may represent the relative rarity of promising therapies for acute and devastating illness, the substantial barriers associated with fulfilling the requirements of these regulations, or both.[15,18] In 2000, the US Food and Drug Administration released a draft guidance aimed at helping investigators and sponsors understand the requirements of these regulations.[19]

Regulations for the protection of human patients in Australia also allow a waiver of the requirement for informed consent in the setting of clinical research investigating potentially beneficial therapies for illnesses that are sudden, life-threatening, and incapacitating.[20] As noted by Cooper et al, the requirement for prehospital informed consent was waived in their study and subsequent permission for continued participation was obtained either from patients, if they recovered sufficiently, or from next of kin. One of the ethics committees apparently required a process of public disclosure, analogous to the requirement included in the US regulations, although no process analogous to community consultation appears to have occurred. Despite the lack of apparent efficacy of the HTS-based strategy, the patients who participated in the study by Cooper et al had the potential to receive a therapy that, according to the knowledge at the time, held out the prospect of improving their outcome. The study by Cooper et al fulfills the spirit of both the Australian and US regulations—namely that patients are enrolled in research trials by using the exception only if the potential exists for direct and individual benefit.

The intervention studied by Cooper et al consisted of initial fluid resuscitation using 250 mL of either HTS or Ringer's lactate solution (control), after which the patient received fluids based on usual practices. This was an evaluation of an initial resuscitation strategy, not a direct comparison of HTS vs Ringer's lactate solution. Patients randomized to HTS could receive a substantial volume of other fluids prior to hospital arrival, as well as additional nonhypertonic fluids in the hospital. However, interpreting trials that use a mixed-fluid strategy may be difficult because it is unclear whether a lack of demonstrated effectiveness is due to a lack of efficacy of HTS or a dilutional effect from the other fluids most patients receive.[6]

Cooper et al did not evaluate HTS-dextran, based on the lack of evidence that the clinical effects of HTS and HTS-dextran are substantially different. Although this choice was reasonable, this is an area of controversy and some studies suggest that the addition of dextran substantially enhances the physiological effects of HTS.[4] This difference might be

particularly important when the hypertonic fluid is used only initially, rather than as the sole and continued form of resuscitation.

Several trends in the data reported by Cooper et al suggest that the HTS strategy may not have been completely ineffective. First, there was a nonsignificant higher rate of survival with HTS corresponding to an odds ratio of 1.26 (95% confidence interval [CI], 0.75-2.11) at hospital discharge and 1.38 (95% CI, 0.82-2.32) at 6 months. The widths of these CIs do not allow clinically important differences in survival to be excluded. In fact, the observed difference in survival at 6 months (55% for the HTS group and 47% for the control group) would correspond to 12.6 as the number needed to treat to save one life.

Furthermore, the relatively sparse data obtained on ICP and cerebral perfusion pressure in the intensive care unit (as shown in Table 3[1]) are consistent with the expected effects of HTS. Although the differences are not statistically significant, the median ICP is lower in the HTS group, as is the duration of time spent with a cerebral perfusion pressure of less than 70 mm Hg. These data must be interpreted with caution, however, because only a select subset of patients undergoes ICP monitoring, raising the possibility of substantial selection bias.

Despite these caveats, the strategy of initial HTS followed by standard fluid resuscitation practices does not appear to substantially improve long-term neurological outcome for patients with severe blunt head injury and posttraumatic hypotension. However, it would be premature to abandon prehospital research with HTS. To build on the work of Cooper et al and others, future studies should be larger in size and should evaluate "pure" HTS-based or HTS-dextran–based strategies, with the goal of determining if a larger or more prolonged effect on ICP and cerebral perfusion pressure can be achieved with an attendant improvement in neurological outcome, and if the small difference in survival noted in the current study can be established as a real treatment effect rather than a random fluctuation of small numbers. Until then, routine use of HTS for resuscitation of patients with hypotension and traumatic brain injury should be reconsidered.

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