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Prehospital Care of the Multiply Injured Patient
The Challenge of Figuring Out What Works

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I n this issue of The Journal, Cooper and colleagues1 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 the 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 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 cerebrovascular perfusion pressure.5 The use of HTS, both to increase mean arterial pressure and decrease ICP and thus increase cerebral perfusion pressure, is a logical and promising approach.
proach to reduce secondary injury and improve neurologi-
cal outcome. Because the effects of HTS and the progress-
ion of secondary brain injury may both occur rapidly, the
effectiveness of HTS for patients with traumatic brain in-
jury 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 trans-
port to a hospital [ie, “scoop and run”]) are effective in im-
proving outcome. Although this is undoubtedly true in some
cases, such as defibrillation for cardiac arrest due to spon-
taneous 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. For example, prehos-
pital endotracheal intubation, a widely accepted proce-
dure, may have a much higher complication rate than previ-
ously thought and likely has little benefit for children.

There is an ethical and moral obligation to determine
which therapies are safe and effective in the prehospital set-
ing, 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 treat-
ments in the prehospital setting. Such trials will often re-
quire enrolling research participants who have been sud-
denly and unpredictably incapacitated and for whom no
appropriate surrogate is available to give consent.

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. 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 unpre-
dictable 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 par-
ticipation in the research “holds out the prospect of direct
benefit to the subjects.” The institutional review board must
e also determine that the clinical investigation could be
practically performed without the exception.

To qualify for the exception, the study must include pro-
cesses of community consultation and public disclosure. Com-
munity consultation is a 2-way discussion of the pro-
posed 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 regard-
ing the proposed research into the community from which
patients will be drawn. The institutional review board must
consider community feedback from community con-
sultation and the adequacy of public disclosure in deciding
whether to approve the proposed study. In addition, all stud-
ies that use the emergency exception must be overseen by
an independent data and safety monitoring board.

Although these federal regulations allow an avenue through which potentially promising research on thera-
pies for sudden, serious, and acutely incapacitating ill-
nesses 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 devas-
tating illness, the substantial barriers associated with ful-
filling the requirements of these regulations, or both. In
2000, the US Food and Drug Administration released a draft
guidance aimed at helping investigators and sponsors un-
derstand the requirements of these regulations.

Regulations for the protection of human patients in Aus-
tralia also allow a waiver of the requirement for informed
consent in the setting of clinical research investigating po-
tentially beneficial therapies for illnesses that are sudden,
life-threatening, and incapacitating. As noted by Cooper
et al, the requirement for prehospital informed consent was
waived in their study and subsequent permission for con-
tinued participation was obtained either from patients, if they
recovered sufficiently, or from next of kin. One of the eth-
ics committees apparently required a process of public dis-
closure, 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 Austra-
lian 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 ini-
tial fluid resuscitation using 250 mL of either HTS or Ringer’s
lactate solution (control), after which the patient re-
ceived 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 flu-
ids 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 flu-
ids most patients receive.

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. This difference might be

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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) 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 postrummatraumatic 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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