Controversies in resuscitation: to infuse or not to infuse (2)

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The German poet, Goethe, once said, "When facts are scarce, words soon take their place". This appears to be the problem with our evolving exploration into the proper treatment of post-traumatic hemorrhage, and particularly with respect to the specific discussion of our more recent publication in the New England Journal of Medicine entitled, "Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries" [1].

One of the frustrations of a researcher who has conducted a large scale clinical trial (with hundreds of data points involving hundreds of patients) is the inability to transcribe many additional findings of a particular study. This limitation is partly imposed by editors because of limited space in a scientific journal and it is also partly imposed by a good author who does not want not to lose sight of the forest for the trees in a scientific communication. I hope, in the following discussion, to better explain our findings and to address some of the recurring questions concerning our study.

First, the general concept imparted by the study was that aggressive blood pressure elevation prior to the control of internal hemorrhage may actually be detrimental. This evolving paradigm has now been well-demonstrated in multiple new animal models [2-5], giving it reasonable experimental credibility as a valid concern.

However, whether or not resuscitative efforts, specifically those using intravenous infusion of isotonic crystalloid fluids, is of benefit or detriment in any individual patient is still debatable. In other words, one could argue that for a particular patient (e.g., one with a systolic blood pressure of 40 mmHg or less) benefit might be derived from limited resuscitative efforts. Meanwhile, another patient may clearly be compromised by such resuscitation if it leads to hydraulic disruption of clot formation and accelerated secondary hemorrhage (as it does in animals) [2-5]. Unfortunately, such delineations of patients cannot be very well predicted clinically, even by the best of experienced practitioners. From a clinician's point of view, it would be difficult to guess which particular patient would benefit (if such is the case) from such resuscitative efforts because most patients present in a similar fashion (e.g., gunshot or stab wound and low blood pressure). Blood pressure is a poor predictor of clinical status and its accurate measurement is barely possible in those with a systolic pressure of 70 mmHg or less (under emergent circumstances). In our study of hypotensive patients with penetrating injuries to the torso, we found that, on balance, patients fared much better by limitation of fluid resuscitation where the test intervention was aggressive prehospital and emergency department infusions of isotonic crystalloids, regardless of the initial clinical presentation.

Perhaps one could look, in retrospect, and try to find the most seriously injured patients (e.g., In-
jury Severity Score > 25) and see if they benefitted from fluid resuscitation. Indeed, we did such 'data-dredging' and found even more of an accentuation of the mortality rate for those receiving aggressive preoperative resuscitation [1]. Throughout all aspects of the study, the amount of preoperative fluid resuscitation correlated inversely with survival. On balance, it seems that the risks outweigh the benefits and clinical judgment would not truly be applicable to predicting the value for preoperative fluid in this particular study population of penetrating injury patients.

That, of course raises another issue. Some have said that since our patients were stabbing and shooting patients, the study is irrelevant to their own practices (which primarily involve blunt injuries). However, we were the first to point out that studies should also be performed in that particular sub-population of patients [1]. Blunt trauma patients certainly can have a risk for uncontrolled internal bleeding and this risk must be balanced against the risk of cerebral hypoperfusion in cases of accompanying serious head injury. Yes, blunt trauma may be a different case, but this issue needs to be worked out in a scientific fashion, not in a rhetorical fashion [6].

Indeed, aside from our study, data from prospective controlled clinical trials are clearly lacking. Therefore, the burden of proof for the intervention of pre-operative fluid resuscitation should now be placed on those who think it may be of value. In other words, they should produce well-designed clinical trials that prove the efficacy of preoperative fluid resuscitation. Our viewpoint regarding the potential detriment of preoperative fluid resuscitation in penetrating trauma is substantiated by many recent animal studies which provide a logical explanation for our findings [2–5]. It seems that every few months, a new experimental study is published that validates the evolving paradigm that aggressive fluid resuscitation (to elevate blood pressure) prior to control of vascular hemorrhage is actually detrimental. Therefore, recognizing that blunt trauma, and particularly cases with accompanying long bone fractures and head injury, may be different, we are the first to suggest scientific evaluation of the proposed therapy of preoperative fluid infusion. Unfortunately, our study has come under question by others who have reacted by looking for inconsistencies between our patient populations and their own practices or by looking for possible inconsistencies within the limited data presented in the New England Journal paper [1].

For example, a typical 'criticism' of our study has been the relatively short out-of-hospital intervals provided by the Houston EMS system. In fact, we argue that the results would have been more impressive if there had been more time to infuse more fluids. Also, it is said that the fact that the study was not 'blinded' (as it could not be) may have 'biased' the study. Indeed, such biases did occur toward the end of the study when practitioners began to give lesser fluid infusions in-hospital. However, this 'bias' would make the study and control groups look more alike and yet we still found a significant difference. During the first 6 months of the study, the differences in survival were 69 versus 55% for the delayed vs. immediate fluid resuscitation groups, respectively. By the study's end it was only 70 versus 62%. Less study bias would have strengthened our case.

Another question frequently raised about the study has been that mean blood pressures were higher and fairly well-matched between study groups by the time patients got to the operating room. Again, a superficial interpretation would make one question our findings. However, one must keep in mind that mean blood pressures are affected by several dynamics. First, while mean blood pressures are somewhat useful in helping to show initial comparability of study groups as a whole, they are poor measures of clinical status. Mean pressures are skewed by the large numbers of patients presenting with 'unmeasurable' pressures. Those with the worst pressures (no pressures) fall out of the cohort being measured as time passes (they die), leaving an 'elevated' mean pressure. Furthermore, the study did involve some fluid infusions for both groups (e.g., antibiotics, multiple intravenous catheters kept at a 'keep open' rate, and some red blood cell transfusion). Also, if bleeding is uncontrolled, blood pressure for a given patient in the fluid group could go up, stay the same (goes out as fast as it comes in) or even fall lower (if slowing hemorrhage is accelerated). Therefore, mean blood pressures are subject
to misinterpretation. Indeed, the original manuscript reviewers recognized and understood these dynamics.

There have been other critiques and questions, but the fact remains that no one else has performed such a head-to-head trial of fluid versus ‘no fluid’. Again, the burden of proof for preoperative fluid resuscitation is now on those questioning our findings, and not on us. Indeed, the study results indicate that the two groups were extremely well-matched and there are few other confounding variables to explain the differences in outcome. And even if the differences had not been found to be statistically significant, the data clearly do not support any efficacy from early aggressive fluid resuscitation for penetrating torso injury.

As Goethe also said, “There is nothing more terrifying than ignorance in action”. Therefore, we still encourage scientific studies that will validate our work as well as other investigations that will examine patients with blunt trauma. Hopefully such studies will be performed with stratifications of patients with (and without) serious head injury.

Before I finish, I also want to address the question of paramedics performing the clinical care and, most importantly, executing the study. It is true that, in many venues, paramedics are often task-oriented and that they often follow ‘cookbook’ protocols. However, that observation is more an issue of local medical direction. The better the training and mentorship, the fewer protocols paramedics seem to need. Very often ‘cookbook’ protocols are used as substitutes for education, leaving paramedics with little room to make appropriate clinical judgements or even question dogma. In cities where I’ve practiced (Seattle and Houston), protocols are generally limited to scientific protocols. Training and physician supervision are intensive. Such training includes on-going literature reviews and group discussions of scientific studies. In fact, the paramedics who conducted our study are now very familiar with scientific study design and they actually help us to develop methodology. Indeed, their practical suggestions help us to ensure study compliance and better clinical care. By such active participation, the study becomes their property as well. The wide acclaim and congratulations that we received on the success of this latest project is a source of quiet pride for them. It is no surprise then that several of the formal reviewers for this study subsequently commented on the outstanding performance of the paramedics, both clinically and investigationally.

In closing, I would state that, in some venues, there has been an almost emotional reaction to the conclusions drawn from our recent study because the results seemed to go against traditional training. But when we began to ask such clinicians what the scientific bases for their concerns were, we found that many were unfamiliar with the actual studies that formed the basis for our traditional fluid resuscitation practices [7–9]. Few were familiar with the animal models and study designs of those classic studies. In turn, after careful explanation of those studies and pointing out the results of the more recent models of uncontrolled hemorrhage, most have begun to appreciate our point of view. We explain that we are clearly in support of fluid resuscitation after control of hemorrhage, but that aggressive fluid infusions prior to surgical control can be risky. We also emphasize that this position is primarily directed at patients with presumed vascular injuries such as those typically occurring after penetrating trauma. But the study also challenges others to re-examine our traditional approaches and pave the way for future resuscitation research for other trauma patients.

References

[5] Owens TM, Watson WC, Prough DS, Uchida T, Kramer GC. Limiting initial resuscitation of uncontrolled hemorrh-


