

Suicide bombing: how to prevent death in civilians?

In their Article (Sept 3, p 906),¹ Madelyn Hicks and colleagues describe casualties from suicide bombs in Iraq during 2003–10. During the studied period, lethality was significantly higher for Iraqi civilians than for coalition soldiers. Hicks and colleagues speculate that difficult access to adequate hospital treatment for Iraqi civilians could mainly explain this difference in mortality.

We would like to underline that, at the beginning of the Iraqi conflict, despite the growing use of body protection and the deployment of many high-quality medical facilities, around 90% of military combat-related deaths occurred before the casualty reached a medical treatment facility.² The early control of extremity haemorrhage was identified as the top priority after autopsy data showed a significant portion of deaths from compressible haemorrhage.

Simple and safe tools were implemented directly on the battlefield to prevent exsanguinations due to extremity haemorrhage. And in military practice, it is now common and expected for non-medical personnel to manage life-threatening extremity haemorrhage rapidly and accurately: a tourniquet can be applied by either the casualty himself or any brother in arms.³ Moreover, on the basis of military findings,⁴ recent civilian guidelines on management of bleeding after major trauma recommend adjunct tourniquet use to stop life-threatening bleeding from open extremity injuries in the presurgical setting.⁵

Hence, focusing on civilians after bombing, we wonder whether simple tools such as the tourniquet, applied by the man in the street, could be a more efficient approach to improving survival than the hypothetical deployment of “high-quality treatment” facilities.

We declare that we have no conflicts of interest.

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Authors' reply

Pierre Pasquier and colleagues make the valuable point that coalition soldiers' use of tourniquets in the field might have contributed to our study's finding that fewer coalition soldiers than Iraqi civilians were killed per lethal suicide bombing in Iraq,¹ and to the lower lethality of armed violence generally to US soldiers² than to Iraqi civilians.

Military field packs provisioned with haemostatics and tourniquets are effective in controlling catastrophic bleeding from extremity wounds.³ Extremity wounds accounted for 70% of US and UK military wounds from improvised explosive devices (which include suicide bombs), with torso wounds present in less than 10% of these military casualties, partly owing to use of body armour.³ Pasquier and colleagues' suggestion that civilians use such tourniquets to improve survival from suicide bombs might not be feasible on a population-wide level due to problems of distribution and training. Tourniquet provision might feasibly be located near areas of civilian concentration that are suicide bomb targets: checkpoints,

police stations, mosques, and markets. To establish the feasibility and efficacy of such an intervention would require investigation.

It is essential to point out that, to whatever degree civilian-administered tourniquets might improve immediate rates of survival from extremity wounds caused by suicide bombs, a tourniquet is a temporary measure that does not replace the adequate health care required by victims for their continued survival. If a civilian-applied tourniquet is required temporarily to stanch severe bleeding from an extremity, to survive in the long term, that civilian will require effective emergency and surgical treatment to the limb once arriving at hospital.

Moreover, a study of victims of civilian suicide bombs arriving at hospitals in Israel⁴ suggests that substantial proportions of victims arrive not only with extremity injuries (44%), but also with internal injuries (32%), head injuries (22%), chest injuries (21%), abdominal injuries (16%), and burns (17%). Survival of these wounds would not be affected by tourniquets. 30% had three or more body regions injured, 29% had severe-to-critical injuries, 52% required surgery, and 27% required intensive care—all indicators of the need for high-quality, complex treatment of injuries caused by suicide bombs in civilians,⁴ as in soldiers.^{3,5}

Although all forms of prevention and intervention should be considered, what is known so far suggests that the provision of adequate medical treatment and facilities is one necessary component for improved survival from suicide bombs, for both military and civilian victims.^{3–5}

We declare that we have no conflicts of interest.

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Exon-skipping therapy for Duchenne muscular dystrophy

Sebahattin Cirak and colleagues (Aug 13, p 595)¹ report impressive results with systemic exon-skipping therapy for patients with Duchenne muscular dystrophy. However, reliance on immunohistochemistry and western blots alone could be very misleading.^{2,3} Of other factors, non-specific, false-positive signals from muscle membrane and inaccurate immunoblot quantitation because of biopsy sample variations are difficult to eliminate.

The exon-skipping strategy intervenes at the level of mutant pre-mRNA. A more direct way to show efficacy would therefore be to do so at the RNA level. However, this cannot be done on the basis of reverse-transcriptase PCR (RT-PCR) alone. The shorter skipped fragment might be amplified preferentially and a positive result, after about 40–50 cycles of PCR amplification, might reflect successful oligomer-mediated exon skipping but only very infrequently—in a rare transcript, perhaps even in one cell. This finding would not be of any therapeutic significance.

In the muscle of patients with Duchenne muscular dystrophy, full-length dystrophin mRNA is usually absent⁴ because of nonsense-mediated mRNA decay⁵—a process by which mRNAs containing premature stop

codons are degraded. The premise of exon-skipping therapy is restoration of the reading frame and near-full-length dystrophin transcripts. Therefore, comparison of muscles before and after exon-skipping therapy, with either a quantitative RNase protection assay using a probe 3' to the exon-skipped site, or, although technically challenging, northern blot analysis to show restoration of near-full-length dystrophin mRNA, are definitive ways to validate the therapeutic potential of this approach.

Such validation is necessary to establish the credibility of treatment for Duchenne muscular dystrophy by the exon-skipping approach. Clinical efficacy trials are not yet justified.

I declare that I have no conflicts of interest.

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Authors' reply

Satyakam Bhagavati questions the choice of biochemical outcome measures in our systemic phase 2 exon-skipping study of Duchenne muscular dystrophy. He suggests two RNA-based assays (quantitative RNase protection and northern-blot analysis), which are theoretically feasible but difficult to do and limited in their scope. To assess exon skipping at the RNA level, we used the standard methods that are regularly used on

both animal and human tissue, and in all the published clinical trials to date.^{1–3} We detailed the RNA results in the original webappendix and, although we acknowledge that the methods of RNA detection used are not fully quantitative, the main aim of the study was that of increasing protein expression in these boys.

Indeed, the assessment of dystrophin protein expression has several advantages over the RNA studies suggested. First, protein analysis by the techniques we used allows verification of the correct localisation of the restored protein in situ; its capacity to interact with its sarcolemmal partners increases their expression at this location. Second, protein analysis allows assessment of the uniformity of expression in different fibres, and how many fibres have been targeted by the treatment. Finally, western blot allows us to assess the molecular weight of the different truncated proteins and ensure that a single product was present in each patient after forcing exon skipping. None of this crucial information would have been available after the suggested RNA studies.

Bhagavati is correct in reminding us that care should be used when interpreting protein expression data. However, we assessed the treated versus non-treated samples blindly, and were able to correctly assign the treated samples independently from the RNA data.

In our study, we used antibodies that are sensitive, highly dystrophin-specific, and show no cross-reaction to negative fibres, and a quantitative immunohistochemistry technique that is now widely accepted and used in the field.⁴ We showed that the protein restoration was statistically associated with the dose of the AVI-4658 used, further indicating that our findings are genuine.

Since dystrophin levels of 30–50% give rise to much milder dystrophinopathy phenotypes,⁵ we are cautiously optimistic about the outcome of