Medical Xpress

Use of hemoglobin-based blood substitutes associated with increased risk of death, heart attack

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An analysis of studies involving the use of hemoglobin-based blood substitutes indicates their use is associated with an increased risk of death and heart attack, according to a JAMA study being released early online, and will appear in print in the May 21 issue of JAMA.

The development of a blood substitute—a liquid that has a long shelf-life, does not need refrigeration and does not cause infection—would provide a potentially lifesaving option for surgical and trauma patients with shock from loss of blood, especially in rural areas and military settings. “To date, a large proportion of blood substitutes in development have been hemoglobin-based products [hemoglobin is the oxygen-carrying protein in the red blood cells]. Yet randomized controlled trials completed as early as 1996 have raised questions about the safety of these products and have failed to demonstrate clinical benefit. Nonetheless, at least 1 of these products is approved for use outside the United States and new clinical trials are being conducted or planned worldwide,” the authors write.

Charles Natanson, M.D., of the National Institutes of Health, Bethesda, Md., and colleagues conducted an analysis of previous studies to examine the association between hemoglobin-based blood substitutes (HBBSs) and the risk of heart attack and death in trials using these products in surgical, trauma and stroke patients. The authors searched databases and other sources for randomized controlled trials that

included patients age 19 years and older who received HBBSs therapeutically. Sixteen trials that met the authors' criteria were identified, involving five different products and 3,711 patients.

There were a total of 164 deaths among HBBS-treated patients and 123 deaths among patients in the control groups. Overall, the HBBS products were associated with a 30 percent increased risk of death. There were a total of 59 heart attacks among HBBS-treated patients and 16 heart attacks among patients in the control groups. For these studies combined, there was a 2.7 times increased risk of heart attack among patients receiving HBBSs.

Subgroup analysis of these trials indicated the increased risk was not restricted to a particular HBBS or clinical indication. "The pattern of increased risk demonstrated by a variety of HBBSs across an array of clinical settings argues for a policy whereby any new or existing HBBSs should be subjected to pre-clinical studies in animal models that replicate the known toxicities of HBBSs demonstrated in humans before further clinical trials of this class of product are allowed to proceed," the authors write.

The researchers also discussed the regulatory process that permitted repeated trials with these agents despite persistent safety concerns.

"Sponsors are required by law to report their results to the Food and Drug Administration (FDA) in a timely fashion after studies are completed, even if they do not publish their findings. However, the data reported by sponsors to the FDA are not made public by the FDA unless the product is approved or an advisory committee is convened to discuss the product. The cumulative mortality analysis … indicates that prompt meta-analyses of the HBBS trials by the FDA most likely would have demonstrated significant risks by 2000. Had the agency placed a moratorium on trials at that point, product-related deaths and [heart

attacks] in subsequent trials most likely would have been prevented. However, such data were not available to scientists, the public, institutional review boards, or competing HBBS manufacturers," the authors write.

Five trials of HBBSs reportedly are ongoing in eight different countries outside the United States and at least one trial is being planned for the U.S.

"The results of all trials of experimental agents conducted in human beings—from phase 1 to phase 4—should be fully and expeditiously disclosed to the scientific and medical communities. The case study detailed here underscores both the scientific inefficiency and the real risks to patients of the current failure to report data promptly."

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