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PRACTICE MANAGEMENT AND QUALITY CARE

Hemoglobin-based blood substitutes: increased risk and no clinical benefit

Meta-analysis reveals HBBS products are associated with a 30% increased risk of death.

Hemoglobin-based blood substitutes may increase the risk for myocardial infarction and even death, according to data published in *Journal of the American Medical Association*.

Despite a lack of beneficial evidence and a high rate of increased mortality and MI, hemoglobin-based blood substitutes continue to be analyzed in clinical trials and the use of these substitutes has been approved in South Africa.

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"It is important to continue conducting research in this field, but at this point we should return to the animal laboratory to show definitively that the product has less toxicity," **Charles Natanson, MD,** a study investigator and chief of the Anesthesia Section in the critical care medicine department of the clinical center at the National Institutes of Health, told *Cardiology Today*. "The products being studied now, as a class, increase mortality by 30% and increase the risk of an MI 2.7-fold. None of them have shown a clinically significant beneficial effect."

Researchers from the NIH and the Health Research Group conducted a meta-analysis to analyze the link between hemoglobin-based blood substitutes and the risk of myocardial infarction and death in trauma, surgical and stroke patients. Using data gathered from large databases, FDA meeting materials and company press releases, the researchers identified 16 randomized, controlled trials that met their criteria (patients aged ≥19 years receiving therapeutic hemoglobin-based blood substitutes).

The trials, which the researchers found between 1980 and March 25, 2008, included 3,711 patients and five different hemoglobin-based blood substitute products. The safety and efficacy of hemoglobin-based blood substitutes were analyzed in trauma patients (n=5 trials), stroke patients (n=1 trial) and surgical patients (n=10 trials).

Increased risk for MI, death

The researchers found that MI occurred in 59 patients treated with hemoglobin-based blood substitutes vs. occurrence in 16 controls. Individually, no evidence of heterogeneity was found in any study for the MI endpoint (I^2=0%, *P*=.72). When the studies were combined, researchers found an increased risk of MI in the treatment group (RR=2.71; 95% CI, 1.67-4.40).

In the hemoglobin-based blood substitute-treated group, 164 deaths occurred, compared with 123 deaths in the control groups. As with the MI endpoint, the researchers found no evidence of heterogeneity for the mortality endpoint (I^2=0%, *P*=.60). In general, hemoglobin-based blood substitutes were linked to an increased risk of death (RR=1.30; 95% CI, 1.05-1.61).

Important implications

Based on their findings, the researchers conclude that the toxicities associated with hemoglobin-based blood substitutes in humans should be duplicated in animal models. The researchers argue for a policy to demand such preclinical trials to be conducted before further clinical trials take place. The researchers also show concern over late trial data publication and the lack of a previous meta-analysis of hemoglobin-based blood substitute trials. They conclude that if such an analysis had been conducted by the FDA, MIs and hemoglobin-based blood substitute-related deaths may have been avoided.

Natanson relays the public health implications of this information and states that, most importantly, "there should not be secret science. The results of clinical trials should be reported as promptly as possible, allowing the authors time to publish the results. Scientists need to build on previous results and institutional review boards need to have access to that information in order to protect the public," he told *Cardiology Today*. *– by Stacey L. Adams*

For more information:

Natanson C, Kern SJ, Lurie P et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death. *JAMA*. 2008;doi:10.1001/jama.299.19.jrv80007.

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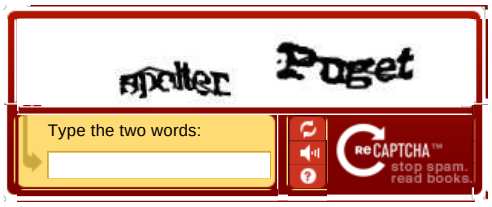

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