

COMMENTARY & PERSPECTIVE

Cerebral Fat Microembolism and Its Potential Role in Postoperative Cognitive Dysfunction After Major Orthopaedic Surgery

Commentary on an article by Anna N. Miller, MD, et al.: "Use of the Reamer/Irrigator/Aspirator Decreases Carotid and Cranial Embolic Events in a Canine Model"

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Total joint replacement is one of the most commonly performed elective orthopaedic surgical procedures, with approximately 700,000 patients undergoing total knee replacement and 330,000 undergoing total hip replacement each year in the United States¹. Clinical results for contemporary implants and current-generation surgical techniques are both excellent and enduring, with >90% of implants expected to survive at least 10 years postoperatively for both total hip replacement and total knee replacement^{2,3}. In light of such outstanding clinical outcomes, it is easy to see how total hip and total knee replacement have come to be regarded as routine procedures, and yet as surgeons, we know that they still represent major surgical interventions with the potential for substantial morbidity or mortality.

In recent years, much attention has been paid to the potential for cognitive dysfunction following major surgery. Although the focus of the early work on postoperative cognitive dysfunction (POCD) was on cardiovascular surgery⁴, there is also a growing body of clinical evidence supporting the potential for cognitive dysfunction after major orthopaedic surgery. Several factors have been implicated in the pathogenesis of cognitive dysfunction after major surgery, including advancing age, intraoperative hypotension, preexisting vascular or cerebral pathology, and local or systemic inflammatory responses. However, as with adult respiratory distress syndrome, it is the role of fat or bone/bone marrow microembolism that has attracted the greatest attention in the context of POCD following orthopaedic surgery. Clinical studies of humans undergoing total joint replacement have confirmed that fat emboli are liberated during medullary canal preparation, and that the embolic material can induce changes in pulmonary vascular hemodynamics⁵. These results have subsequently been confirmed in preclinical studies of dogs, sheep, and pigs, allowing for prospective investigations into both pathophysiology and therapeutic interventions.

In the current study by Miller et al., which involved a canine model, the authors evaluated the effects of the use of the combined Reamer/Irrigator/Aspirator (RIA; DePuy Synthes) on cerebral microembolism following femoral nail placement. This work is a logical extension of earlier studies that showed that the use of the RIA resulted in less profound increases in intramedullary pressure during reaming, and a reduced risk of fat embolism to the lung⁶. Given the potential protective effects of use of the RIA with respect to pulmonary embolism, the authors designed an animal study in which they combined real-time quantitative monitoring of the formation and vascular distribution of fat emboli with post-mortem assessment of the ultimate tissue distribution of these emboli. The model that they selected, the dog, has been used extensively as a preclinical model for studying fat embolism following fracture repair and arthroplasty^{7,8}; it is also a clinically relevant model because both total hip and total knee replacement are now routinely performed on dogs with advanced degenerative joint disease.

The authors of the current study investigated changes in blood-brain barrier permeability, the extent of embolus formation within the carotid artery, and the incidence and location of cerebral microembolism following unreamed femoral nailing (UR), reamed femoral nailing using a standard series of sequential reamers (SR), and reamed nailing using the RIA device. In order to better replicate the volume of bone that is reamed during femoral nail placement or total joint replacement in humans, the procedure was performed bilaterally in large-breed dogs. As the goal of the study was to determine the short-term effects of the different procedures on fat embolism, the surgeries were performed as acute (nonsurvival) procedures, with animals being maintained under anesthesia for 4 hours after the nailing procedure, then killed for tissue collection and analysis.

As anticipated from previous work on pulmonary fat microembolism, the use of the RIA device with this canine model was associated with significantly fewer microembolic events, specifically, fewer larger-sized emboli (>200 μm); this is clinically relevant because it is these larger emboli that are most strongly implicated in circulatory problems following cardiac bypass surgery. The RIA group showed less permeability of the blood-brain barrier and a reduction in the overall magnitude of embolic showering, although the latter effect was not statistically significant because of the limited sample size in this experimental study. Immunohistochemical analysis of tissue sections revealed that, irrespective of the surgical procedure, microemboli were associated with the expression of

hypoxia-inducible factor-1 alpha (HIF-1 α) and heat shock protein (HSP)-70, markers that have been implicated as sentinels of neuronal stress. HIF-1 α and HSP-70 levels were similar in the UR and RIA groups, and lower than those in the SR group, suggesting that the use of the RIA may allow surgeons to achieve the clinical benefits of a reamed nail without an increased risk of neuronal injury.

The major strength of this study lies in the use of an animal model in which embolic showering of fat, bone, and/or bone marrow has been documented during clinically relevant procedures such as medullary reaming and cement injection/pressurization. It might be argued that the same study could have been performed in human clinical patients, thereby eliminating the need for using animals, but the use of research animals in this case appears justified because it would not have been possible to confirm the tissue-level localization of embolic material or neuronal stress proteins in clinical patients.

As the authors concede, the main limitation of this study lies in the fact that it was not designed to assess the effects of microemboli on cognitive function per se. From a clinical perspective, this would have been extremely challenging because there are no validated cognitive functional tests for dogs. The limited sample size of this study also made it difficult to interpret some of the negative findings from the statistical tests, especially when making direct group-to-group comparisons.

Animal models will remain relevant as test systems for exploring the cellular and molecular pathways underlying POCD, but ultimately, it will only be through carefully designed, objective clinical trials involving human patients that it will be possible to address the clinical importance of strategies that reduce or prevent the formation and/or systemic distribution of microemboli. It is also critically important to recognize that, although fat microembolism represents an attractive potential target for interventional strategies in orthopaedic surgery, the experience in cardiovascular surgery clearly demonstrates the importance of other factors, such as patient age, response to anesthesia, systemic inflammation, and preexisting blood vessel or cerebral pathology⁴, that are unrelated to the nature of the surgical intervention.

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