EDITORIAL VIEWS

Anesthesiology
79:415–418, 1993

General Versus *Regional Anesthesia for Peripheral Vascular Surgery*

Is the Problem Solved?

For many years, anesthesiologists have debated whether regional anesthesia is better than general anesthesia for patients undergoing peripheral vascular operations. Previous studies of regional *versus* general anesthesia often were weak in experimental design and, therefore, did not produce definitive answers. Some of the weaknesses included: nonstandardized, poorly conducted, and/or poorly described general anesthesia; nonstandardized methods of postoperative analgesia in the general anesthesia groups, including both supra- and infrainguinal vascular operations; and dissimilar preoperative status in the study groups. Furthermore, the majority of studies did not conclusively demonstrate a cause/effect relationship between the proposed mechanism of the beneficial effects of regional anesthesia and outcome. Now, two related articles in this issue of ANESTHESIOLOGY[1,2] reevaluate these issues in patients undergoing peripheral vascular surgery.

Will these studies[1,2] reconcile the differences and provide us with clear-cut recommendations? Not totally. However, they are a serious step forward. For research to have a significant impact on future developments in science or practice, usually three conditions should be satisfied: (1) the community should be ready for such a discovery, (2) the study must demonstrate unequivocally the advantage of the method in question, and (3) there should be a clear relationship between the proposed mechanism and the results. These studies[1,2] satisfy the requirements.

As noted above, some anesthesiologists believe that regional anesthesia is better for peripheral vascular operations, whereas others assert that it has no advantage. The differences in viewpoint provoke the emotions of minor religious fervor, wherein beliefs and feelings are appropriate in places of worship and in matters of love but are not desirable in science and medical practice. Thus, the first condition was satisfied: the void of convincing data being filled by emotion readied the anesthesia community for a clear and definitive study. Second, the authors demonstrated that, though regional anesthesia is not a panacea saving all our patients, it seems to offer some advantage over general anesthesia. This advantage, *i.e.*, the decrease in the incidence of peripheral vascular graft thrombosis, was defined and demonstrated convincingly to be related to the use of regional anesthesia.[1] Finally, that the likely mechanism for the decrease in graft thrombosis involves fibrinolysis also was demonstrated.[2]

Though these are the best designed and performed studies[1,2] on this topic to date, many crucial questions are not answered. For example, the studies lack the power to determine whether regional anesthesia decreases the rate of cardiac, pulmonary, or infectious complications. Furthermore, they do not resolve whether the beneficial effect on the incidence of graft thrombosis is due to intraoperative or postoperative regional anesthesia/analgesia, to regional anesthesia *per se,* or to the systemic effect of absorbed local anesthetics.

Though it seems unlikely, the results of these studies could be misleading. For example, information about native *versus* synthetic grafts is not provided. We assume that the numbers of native and synthetic grafts were approximately equal in both groups, but this assumption may be incorrect. Alternatively, if the investigators continued muscle relaxation, sedation, and controlled ventilation until the body temperature increased to normal in the general anesthesia group, could this have changed the outcome? In other words, had the intensive care provided during the operations under general anesthesia been continued in the early postoperative period, would it have made a difference? A previously published paper from the same institution demonstrated that unintentional hypothermia (lower than 35° C) was associated with a significant (almost threefold) increase in the incidence of postoperative hypoxemia and myocardial ischemia in these patients.[3]

Accepted for publication May 13, 1993.

Key words: Anesthetic techniques: general; regional. Outcome: graft failure. Surgery: peripheral vascular.

Statistical analysis using the multivariate model did not reveal the type of anesthesia as a predictor of ischemia. However, general anesthesia was administered more frequently in the hypothermic group than in the normothermic group (70% *vs.* 46%, $P = 0.03$).[3] Thus, despite the fact that the authors provided well justified, acceptable, and standardized anesthetic care during surgery, a different anesthetic technique during emergence from general anesthesia may have produced different results.

One of the greatest strengths of these studies is that the authors address the mechanism of the beneficial effect of regional anesthesia: the reduction in the graft failure rate. The studies demonstrated that the preoperative plasminogen activator inhibitor-1 (PAI-1) concentrations and the type of anesthesia (general *vs.* regional) predict postoperative arterial thrombosis. An increased PAI-1 concentration pre- or intraoperatively is associated with a higher incidence of thrombosis. An important observation is that regional anesthesia prevents such an increase. The authors infer that the increase in PAI-1 concentration is a component of surgical stress response that is modified more effectively by regional anesthesia. The studies, however, do not demonstrate this association nor show a cause/effect relationship. Furthermore, the studies do not address other potentially important mechanisms of coagulopathy, *e.g.*, platelet function. There are no statistically significant differences in perioperative anticoagulant therapy between the patients who did or did not develop postoperative thrombosis[2] (see table 3 in Rosenfeld *et al.*). However, the trend for some differences is there: the patients who did not develop graft thrombosis possibly received more nonsteroidal antiinflammatory drugs and dipyridamole (Persantine)—both inhibit platelet function—than did patients who developed thrombosis. In this regard, the small sample size in the studies did not allow the difference to reach a level of statistical significance and justify a definite conclusion.

How can regional anesthesia decrease inhibition of fibrinolysis and rate of graft thrombosis? It has been demonstrated that surgical stress is associated with enhanced coagulation because of an increase in the concentrations of factor VIII,[4,5] von Willebrand factor,[5] fibrinogen,[6] and inhibition of fibrinolysis.[2,6] Evidence suggests that the hypercoagulative state and inhibition of fibrinolysis is associated closely with many components of stress response to surgical trauma. For example, corticosteroids and epinephrine may influence the coagulation process and fibrinolytic activity.[7–10] An increase in factor VIII concentration is related partially to activation of β-adrenergic receptors because infusion of adrenergic agonists[9,11–13] increases the concentration of factor VIII, whereas β-adrenergic antagonists modify such an increase.[10,12,13] Increased corticosteroid concentrations (*e.g.*, in Cushing syndrome[14] or during treatment with corticosteroids[7,8]) also increase concentrations of factor VIII.

Another stress hormone, pituitary arginine vasopressin (aVP), has been invoked to explain the rapid response of endothelial proteins involved in fibrinolysis.[15] Fibrinogen is one of the acute phase proteins produced by the liver in response to injury.[16] The increase in fibrinogen concentration can be mediated by several cytokines, especially interleukin-6 and tumor necrosis factor.[17] Cross talk between inflammatory injury and coagulation has been demonstrated recently.[18]

If we assume cause/effect relationships between stress response to surgical trauma and hypercoagulation (*i.e.*, the stress response to surgical insult leads to hypercoagulation and inhibition of fibrinolysis), in this case, we may accept the notion that regional anesthesia decreases the incidence of thrombosis by modifying the stress response. In fact, it has been demonstrated that epidural anesthesia, particularly for lower abdominal and lower extremity surgical procedures, is effective in preventing a great part of the endocrine-metabolic changes following surgery.[19–26] Thus, it seems conceivable that regional anesthesia may be more effective than general anesthesia in decreasing or preventing neural-hormonal-metabolic stress response, shifting coagulative and fibrinolytic processes toward normalization.

There are many different components of stress response to surgical insult, including hypercoagulation (*i.e.*, inhibition of fibrinolysis). We can treat postoperative pain with analgesics, but we also can decrease it with preemptive analgesia. We can treat pain-induced tachycardia and hypertension with β-adrenergic antagonists and vasodilators, but we also can decrease the incidence and degree of such hemodynamic responses by protecting the brain from afferent pain stimuli. We probably can treat another component of stress response, disturbances in coagulative and fibrinolytic processes, with a certain drug. However, would it be more logical to prevent stress rather than modify stress response? The idea is not new. It was mentioned 80 yr ago[27] by Dr. George W. Crile, who wrote in 1913, "By

blocking nerve conduction, local anesthetics protect the brain from . . . operative injury. . . ." There is a serious controversy concerning the risk/benefit ratio of some components of stress response. There is not much doubt regarding the benefit of protecting the central nervous system from stimuli caused by surgical trauma and avoiding stress response altogether. Therefore, the papers in this issue of ANESTHESIOLOGY suggest that another particular component of stress response, *i.e.*, inhibition of fibrinolysis, can be prevented not by a specific drug but by a regional anesthesia-induced decrease in nociceptive stimulation and overall stress response.

Before I read the results of these studies, the risk (*e.g.*, possible development of epidural hematoma) / benefit ratio was large enough for me to routinely avoid regional anesthesia in these patients. However, the present studies,[1,2] by increasing the possible benefits, improved the risk/benefit ratio and converted me into a believer in the advantages of regional anesthesia.

The greatest contribution that a clinical researcher can make is to change the way his/her peers practice medicine. Though these studies provide evidence of at least one advantage of regional anesthesia for patients undergoing peripheral vascular surgery, I also agree with the authors when they state, "A clinical recommendation of epidural or general anesthesia for patients at high risk for cardiac morbidity cannot be made based on our results." These studies open exciting avenues for research in this area and beg us to continue our efforts to identify and scientifically justify the best anesthetic management for this group of seriously ill patients.

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