Labat Lecture 2005: Surgical Stress and Postoperative Outcome—From Here to Where?

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When I received the invitation to give the 2005 Labat Lecture, it was a great pleasure and honor for several reasons. First of all, to be a surgeon invited to give this most prestigious lecture to the American Society of Regional Anesthesia and Pain Medicine but also because it in some way emphasized and alluded to my previous efforts to increase the collaboration between the 2 specialties in order to improve postoperative outcome. However, it also brought back good memories of my 2 mentors in regional anesthesia, the late Benjamin Covino and Bruce Scott, both personal friends as well as cotravelers to numerous meetings and workshops, which provided me as a surgeon with unique possibilities to learn about the benefits and challenges in regional anesthesia and surgical outcome. Much of what I learned from Benjamin Covino and Bruce Scott and numerous other friends and collaborators within the anesthesiologic profession has influenced my research over the last 3 decades and was synthesized into this lecture.

In the late 1970s and early 1980s, I was influenced by the papers by George Crile[1] that discussed the shockless operation by "anoci-association," suggesting that blockade of the afferent neural input from the surgical area protected the brain and other organs from the undesirable sequelae of surgical injury (Fig 1). However, it took more than 60 years until these fascinating ideas were further developed by David Hume from Boston, among others, who showed in animal experiments that the nervous system was crucial to release the adrenal response to injury and by Philip Bromage who demonstrated that the adrenocortical and hyperglycemic response could be attenuated by epidural anesthesia in surgical patients. My interests in the surgical stress response actually started with studies to demonstrate that the adrenocortical response was not necessary for survival in surgical patients, as previously thought, since studies in glucocorticoid treated patients with various degrees of adrenocortical insufficiency did not show signs of acute postoperative adrenocortical failure.[2] These studies also evaluated a physiological scheme for administering physiological doses for supplementation of cortisol in such patients.[2] Based upon these findings, we questioned the necessity of the surgical stress response in the elective surgical situation and subsequently showed in many studies that various parts of the endocrine metabolic response to surgery could be blocked by regional anesthesia, provided the afferent blockade was sufficient.[3] These findings, supported by many groups with more detailed assessments of catabolism[4,5] demonstrated that continuous epidural analgesic techniques were the most powerful instrument to reduce the catabolic response to surgery and thereby improving protein economy.[3-6] In contrast to the pronounced inhibitory effects on endocrine metabolic responses by regional anesthesia, the effect on inflammatory responses and immune function was limited and probably clinically irrelevant.[3,6]

Based on these pathophysiological studies important questions were raised as to the clinical implications of a reduction of surgical stress responses, including sufficient pain relief, thus leading to ultimate questions such as "can every operation be ambulatory?" and "what are the factors responsible for being hospitalized today?" and finally "what is it that we cannot control?" since apparently many operations are still associated with an undesirable morbidity and mortality, need for hospitalization, and prolonged convalescence.

A careful evaluation of the factors responsible for delayed postoperative recovery[7,8] has shown that the surgical stress responses (endocrine, metabolic, and inflammatory) are most important due to the subsequent induction of various organ dysfunctions (pain, catabolism, impaired pulmonary function, increased cardiac demands, gastrointestinal dysfunction [paralytic ileus], and an unfavorable change in the coagulatory-fibrinolytic ratio). In addition, other

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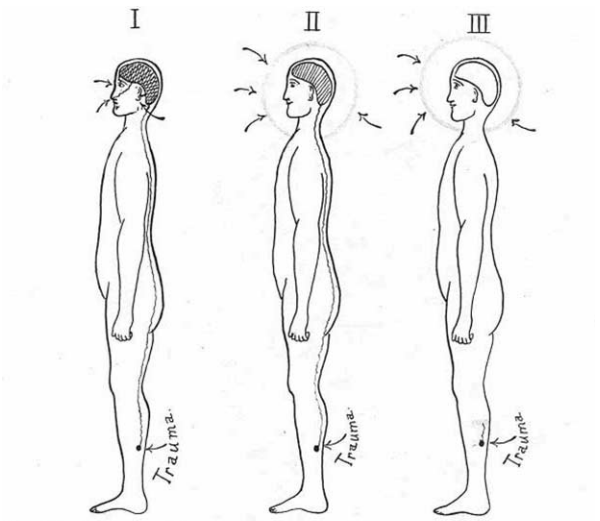

FIG. 24.—SCHEMATIC DRAWING ILLUSTRATING PROTECTIVE EFFECT OF ANOCI-ASSOCIATION.

I. Conscious patient in whom auditory, visual, olfactory and traumatic noci-impulses reach the brain.

II. Patient under inhalation anesthesia in whom traumatic noci-impulses only reach the brain.

III. Patient under complete *anoci-association;* auditory, visual, and olfactory impulses are excluded from the brain by the inhalation anesthesia; traumatic impulses from the seat of injury are blocked by novocain.

Fig 1. George Crile's theory, as illustrated in his book *Anoci-Association*, which was published in 1914. (Reprinted with permission.)

factors may contribute to delayed recovery such as hypothermia, fluid excess, hypoxemia, sleep disturbances, immobilization and semistarvation, and traditions within postoperative surgical care (tubes, drains, catheters, restrictions, and so on).[7-9]

Our knowledge on postinjury changes in the nociceptive system has increased tremendously in the last decade, and various concepts to improve postoperative pain management have been tested such as "preemptive analgesia" and "multimodal analgesia," the latter probably being most important.[10] Thus, multimodal analgesia to provide efficient opioid sparing[11] may contribute to enhancement of early postoperative recovery, but additional multicomponent studies are required to strive for total or near-total opioid-free postoperative pain management. In this context, regional anesthetic techniques continue to be demonstrated to be the most efficient postoperative pain-alleviating techniques, whether by continuous central neuraxial blockade, peripheral blocks, or local wound perfusion techniques in appropriate surgical conditions.[9]

Postoperative nausea and vomiting (PONV) and ileus are important factors delaying recovery, and PONV has to be managed according to available multimodal pharmacological interventions.[12] The most efficient technique to alleviate postoperative paralytic ileus is continuous epidural analgesia with local anesthetics, as shown in numerous randomized trials.[13] Such techniques may therefore provide optimal conditions for an enhanced postlaparotomy recovery, since they allow early oral feeding, which otherwise has been demonstrated to reduce infectious morbidity and length of hospital stay without increasing the risk of anastomotic dehiscence.[14]

Fluid Management

In recent years, it has become obvious that perioperative fluid management may have important implications for postoperative recovery for several reasons: first of all appropriate compensation for preoperative dehydration and optimization of cardiovascular function must be made according to available evidence.[15] This also applies to minor surgery where several randomized trials have shown that administration of at least 1 to 1.5 L may improve PONV, dizziness, and so on after minor ambulatory procedures.[16] When it comes to major surgery where large volumes are often administrated, detrimental effects hereof have been demonstrated regarding cardiovascular, pulmonary, and thromboembolic function as well as prolonged paralytic ileus.[17] Furthermore, more recent data have shown that large fluid volumes in colorectal and other major abdominal operations may increase morbidity, ileus, and duration of hospital stay.[18,19] In such operations, the administered volumes often come up to 6 to 7 L, resulting in significant weight gain. Surprisingly, similar large volumes have been administered in peripheral vascular surgery in studies aiming to assess the outcome effects of epidural analgesia.[20] Unfortunately, based upon current knowledge,[17-19] these large volumes may have led to increased cardiopulmonary morbidity, thereby overriding the potential positive effects of the regional anesthetic-analgesic regimen.[20] In other studies in laparoscopic cholecystectomy, a careful investigation of functional recovery and discharge as well as the vasoactive surgical stress responses showed an improvement in functional recovery in many organs following 40 mL/kg compared with 15 mL/kg Ringer lactate intraoperatively.[21] These findings call for more procedure-specific studies to provide recommendations for clinical practice. Perioperative fluid management may be one of the most important research areas for the next coming years, especially during central neuraxial blockade where large volumes often are administered, but where vasopressors probably should be utilized more frequently in order to avoid an undesirable fluid excess when the regional blockade wears off.[17]

Based upon data from the many outcome studies where unimodal intervention has been instituted to improve recovery such as regional anesthesia, pain

management, and nutrition, it has been obvious that additional, less sophisticated factors of perioperative care must be revised and adjusted to current scientific evidence from randomized clinical studies.[7-9] This especially applies to unnecessary use of nasogastric tubes, drains, and urinary catheters and various restrictions on feeding and mobilization, all of which may retard recovery and thereby counteract the effect of other techniques to facilitate recovery, including regional anesthetic-analgesic techniques.[7-9,22,23]

Finally, over the last decade, it has become apparent that the effects of multimodal analgesia and continuous epidural analgesic techniques on postoperative outcome in major operations have been disappointing in that there is only agreement that pulmonary morbidity is somewhat reduced and possibly cardiac morbidity but with no positive effects on hospital stay.[24-27] This also applies to recent major randomized studies,[25-27] all of which unfortunately are of insufficient design in being predominantly opioid-based analgesia, provide too little local anesthetic, or do not provide any information on the level of insertion of the epidural catheter. Furthermore, general principles of care (drains, tubes, catheters, feeding, and so on) have not been described or modified to take advantage of the physiological effects of the regional anesthetic technique.[24-27] When it comes to future outcome studies in regional anesthesia, we therefore need to have clear definitions of what a perioperative epidural technique is regarding level, dose of local anesthetic and opioid, duration of analgesia, and efficacy.[28]

Pharmacological Modification of the Stress Response

The use of beta-blockers may inhibit the sympathetic response, which subsequently may provide anticatabolic effects[29] and may improve cardiac outcome due to reduction of the stress-induced increased cardiac demands.[30] Use of anabolic agents such as growth hormone or anabolic steroids and insulin may also reduce catabolism.[29,31,32]

Modification of inflammatory responses may have major clinical implications since interleukin 6 contributes to postoperative sleep disturbances and fatigue; also, other cytokine and humeral responses may lead to impaired immune function with subsequent increase in infectious complications and wound dysfunction.[8,9] In this context, insulin has also been shown to have anti-inflammatory effects.[31] Glucocorticoids may reduce PONV and inflammatory sequelae such as pain and fatigue.[33,34] More recently, perioperative use of statins has been demonstrated to improve cardiovascular outcome probably mediated by preservation of endothelial function.[35]

Minimally Invasive Surgery

Because of the reduced trauma and length of incision, minimally invasive surgery reduces surgical stress, predominantly inflammatory responses and less so endocrine metabolic changes.[36,37] Subsequently, minimally invasive abdominal surgery has been shown to reduce other stress-induced responses such as postoperative pulmonary dysfunction, sleep disturbances, postoperative hypoxemia, and paralytic ileus.[36,37] However, the precise role of minimally invasive surgical techniques to improve outcome compared with other multimodal rehabilitation techniques requires further study.[38]

Nutrition

It is well established that early oral nutrition will have stress-reducing effects by minimizing catabolism and reducing infectious complications and hospital stay.[14] In addition, recent data have demonstrated that preoperative administration of oral or intravenous carbohydrate may reduce postoperative endocrine metabolic responses and catabolism and preserve muscle mass and glycogen.[39-41] However, further studies are needed to define the clinical implications of this approach regarding recovery and hospital stay.[39,42,43]

The Concept of Multimodal Rehabilitation (Fast-Track Surgery)

From the above, it is obvious that no single technique may solve the postoperative morbidity problem since major operations initiate a multifactorial cascade leading to dependency on the health care system due to surgical stress responses, pain, increased organ demands, ileus, pulmonary dysfunction, and sleep disturbances. A logical approach to achieve major improvements in postoperative outcome has therefore been the concept of multimodal rehabilitation where all pathogenic factors involved in postoperative recovery are combined and modified in order to achieve a "pain- and risk-free" surgical patient.[7-9] The main aim of these programs has been to reduce postoperative morbidity, need for hospitalization and convalescence, and thereby, if successful, to reduce costs. Although this approach is rational and with initial extremely positive results, there has been some resistance to the approach and unwillingness to change traditional practice until more data are available from randomized studies. In this context, it is important to understand that fast-track surgery is a concept where

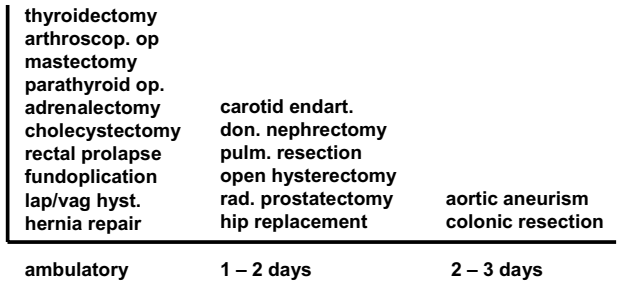

Fig 2. Recent data on duration of postoperative hospital stay with multimodal rehabilitation (fast-track surgery). (Data from Kehlet et al.[7-9])

unimodal, evidence-based interventions are combined in a multimodal effort to reduce pain and organ dysfunctions and subsequently morbidity, hospital stay, and convalescence. Furthermore, discharge criteria from traditional practice have not been changed but are achieved much earlier due to improved pain relief and reduced organ dysfunctions. Examples from the results of multimodal rehabilitation (fast-track surgery) are shown in Figure 2. Some of these results are based on simple principles of fast-track surgery by improving pain relief and organizing anesthetic and early recovery care. Major procedures (pulmonary resection, surgery for aortic aneurysm, and colonic resection) are more complex and require a complete multimodal rehabilitation program. Especially the results from colonic surgery in elderly and high-risk patients have received much interest and supported the concept.[44] The results from fast-track colonic surgery from several international institutions have been uniform to demonstrate increased mobilization; early, sufficient oral energy and protein intake; improved postoperative pulmonary, cardiac, and muscle function; preservation of lean body mass; and reduced fatigue and need for sleep after discharge, without increased health care support after discharge compared with standard care.[9,44] These data also suggest that the risk of medical (cardiopulmonary) complications is reduced.

Surgical Stress and Postoperative Outcome—From Here to Where?

In order to achieve a major improvement in postoperative outcome toward the "pain- and risk-free operation," an intensified multidisciplinary collaboration between anesthesiologists and surgeons will be required in the forthcoming years.[9] Thus, the 2 specialties together will cover expertise within all the factors involved in postoperative recovery. In this process, it will be unfortunate if an interprofessional disagreement takes place on which specialty is to lead in the process of "perioperative medicine." Based upon the nature of the underlying problems, it needs to be a truly multidisciplinary effort where leaders can be selected from both specialties, depending on availability of local expertise and interest.

The key topics for improvements will include more detailed clinical studies on the cellular mechanisms of stress responses to injury[45] including the endocrine metabolic changes,[46] followed by detailed clinical studies on which responses to modify and which to preserve or support. Other key topics will be improvement of multimodal, opioid-sparing pain treatment; integration of minimal invasive surgery with the principles of fast-track surgery[38]; and assessment of the relative role of combination therapies of pharmacological modification of the stress responses by beta-blockers,[29,30] insulin,[31] anabolic agents,[32] glucocorticoids,[33,34] and statins.[35] Also, the stress-reducing effect of preoperative glucose administration needs to be evaluated regarding outcome aspects.[39-43] For the anesthesiologists, this will be a fascinating time to develop "minimally invasive" anesthetic techniques. Although regional anesthetic and analgesic techniques undoubtedly will continue to have an important role, future studies with multimodal pharmacological modification of pain and stress may have the potential to replace more invasive central neuraxial blockade for postoperative management.[47]

In summary, although more than 90 years have passed since George Crile launched the hypothesis of "anoci-association," many studies are still required to optimize postoperative recovery, especially in acute and trauma surgery where preexisting stress responses and organ dysfunctions are apparent before hospitalization and therefore may be more difficult to modify. We have also learned during the last 10 years that, despite much progress in anesthesia and surgery, no easy answers will be achieved and that the future approach must be multidisciplinary and multimodal within the concept of "fast-track surgery." The future is now for us to collaborate.

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