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Pain Control in the Peroperative Period

ACUTE PAIN CONTROL AND ACCELERATED POSTOPERATIVE SURGICAL RECOVERY

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The alleviation of postoperative pain is primarily provided for humanitarian reasons but also to reduce nociception-induced responses, which may adversely influence organ functioning and contribute to morbidity. [14] As discussed in this issue, much progress has been made in our understanding of pain physiology and the effectiveness and side effects of various analgesics and techniques of administration. Based on this knowledge, optimal pain relief allowing normal function can usually be obtained following most surgical procedures, especially when using multimodal or balanced analgesia. This approach provides sufficient pain relief through additive or synergistic effects by different analgesics and with a concomitant reduction of side effects because of the requirement of lower doses of individual drugs and differences in side-effect profiles. [13]

In recent years, awareness of pain relief and pain education has been introduced in the surgical literature. [15] The introduction of acute pain services has increased the quality of postoperative pain relief; however, further improvements in perioperative care and outcome require increased attention among surgeons to choices and availability of different analgesics and techniques in different operations because pain relief is a prerequisite to improved outcome.

This article provides an updated review of the differential effects of different analgesics on perioperative pathophysiologic responses and organ dysfunctions, hospital stay, and convalescence. Furthermore, updated

knowledge is provided on the integration of postoperative pain relief in a multimodal approach to hasten recovery, based on recent reviews. [16] [17]

PAIN CONTROL AND THE SURGICAL STRESS RESPONSE

A common feature shared by all surgical patients is the widespread changes in several biologic cascade systems, including a predominance of catabolic hormones, activation of cytokines, complement, arachidonic acid metabolites, nitric oxide, and free oxygen radicals, all of which secondarily may lead to organ dysfunction and morbidity. Pain may obviously be considered as another neurophysiologic response to surgery but with its own secondary effects on biologic functions. Effective treatment of postoperative pain, therefore, results in modification of the biologic responses to surgery, but the extent of modification is dependent on the choice of analgesic technique. [16] [17] [18]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used routinely for postoperative pain treatment. In contrast to studies demonstrating attenuation of endocrine metabolic responses to endotoxin administration in volunteers, most postoperative studies have shown NSAIDs to have no or only a slight inhibitory effect on classic catabolic stress hormones, acute phase protein, and other immunologic responses and protein economy [17] [18] ; however, NSAIDs have consistently been demonstrated to reduce opioid requirements by 20% to 30%. Consequently, improvement in outcome caused by the reduction of opioid-related side effects (i.e., sedation, nausea, ileus, hypoxemia, sleep disturbances, and bladder dysfunction) has also been obtained in approximately 25% of randomized postoperative studies of NSAID treatment. [19]

Systemic and Epidural Opioids

Opioids administered systemically in conventional dosages in patient-controlled analgesia or intermittently have only few or no stressreducing effects, [17] [18] in contrast to high-dose opioid anesthesia, which may reduce intraoperative, but not postoperative, endocrine metabolic changes. [17] The effect of opioid analgesia on immune functions is controversial because both immune-suppressing and immune-enhancing effects have been described. [19] [33] To date, no alteration of infection rates or spread of malignant disease after opioids has been reported in clinical studies. Results of studies on the stress-reducing effects of epidural analgesia with opioids are inconsistent, but in general, the effects on

endocrine metabolic functions and protein economy are relatively small or absent, especially in major operations. [17]

Neural Blockade with Local Anesthetics

Activation of the peripheral nervous system and the CNS plays a key role in initiating pain and the

hormonal and metabolic responses to surgery. [17] Accordingly, large amounts of data have demonstrated that central blockade (spinal or epidural anesthesia) with local anesthetics reduces the classic pituitary, adrenocortical, and sympathetic responses, and decreases glucagon and adrenergic inhibition of insulin secretion. These effects of local anesthetic blockade have led to improvement in postoperative nitrogen economy and reduced glucose intolerance. [17] [18] Relevant to clinical implications, a single-dose neural block has no important effect on protein economy, whereas a 24-hour block improves nitrogen economy, with further improvement by a 48-hour block with continuous epidural analgesia. [17] [18] In contrast to the pronounced effects of neural blockade with local anesthetic on endocrine metabolic changes, only negligible or no effects are seen on various immunologic and inflammatory responses (i.e., cytokines and other cascade systems). [17] Epidural local anesthetic blockade may, however, alter coagulatory-fibrinolytic functioning, [17] thereby reducing thromboembolism.

The modifying effects of neural blockade with local anesthetics on surgical stress responses are most pronounced in lower-body procedures and less pronounced in upper-abdominal and thoracic operations because of relatively insufficient afferent blockade in the somatic and visceral nervous system with thoracic epidural analgesia. Nevertheless, appropriate neural blockade with local anesthetic presently represents the most effective technique to reduce surgical stress responses (and to reduce postoperative pain).

PAIN CONTROL AND SURGICAL OUTCOME

Despite extensive data to demonstrate beneficial physiologic effects in specific organ dysfunctions and outcomes (‘Table 1) by efficient analgesia, the anesthetic and surgical literature has shown inconsistent results on overall postoperative morbidity.

Nausea, Vomiting, and Ileus

The pathogenesis of nausea, vomiting, and ileus of anesthesia and surgery is multifactorial, including direct surgical neurogenic stimulation of the vomiting center, various anesthetics, and the use of opioids. [13] [26] [32] Accordingly, the use of NSAIDs, with their well-documented opioid-sparing effects (20-30%), has led to reduced nausea, vomiting, and

TABLE 1 -- EFFECTS OF EPIDURAL OR SPINAL ANESTHESIA WITH LOCAL ANESTHETICS ON PERIOPERATIVE PARAMETERS

	Effect	Magnitude
Blood loss or transfusion requirements (lower body procedures)	.L	**30%**
Pulmonary complications (lower body procedures)	↓	**40%**

Thromboembolic complications (lower body procedures)	↓	50%
Ileus (abdominal procedures)	↓	2 days
Mortality (acute hip surgery)	↓	25%

↓ = reduced.

Data from references [2] [17] [22]

ileus in approximately 25% of randomized postoperative studies. [19] This supports the importance of the use and further development of multimodal, opioid-reduced or opioid-free analgesic regimens to hasten postoperative gastrointestinal recovery. Recent efforts with such an approach in gynecologic laparoscopy [6] or laparotomy [7] support this conclusion because high-dose local anesthetic infiltration or central blockade techniques have reduced nausea and vomiting; however, pain relief was suboptimal with the opioid-free, high-dose central and incisional blockade technique with local anesthetics compared with continuous epidural local anesthetic-opioid combinations. [7] Therefore, the development of optimal opioid-free or opioid-reduced regimens is required if nausea, vomiting, and ileus are to be eliminated. Potential analgesic drug combinations for further study include ketamine, alpha, -agonists, and glucocorticoids.

Because early enteral nutrition is important to improve outcome and reduce infectious complications, [16] the reduction or elimination of ileus in abdominal procedures is of major importance. Extensive experimental data have demonstrated that postlaparotomy ileus predominantly is caused by an inhibitory sympathetic reflex. [17] [30] Several randomized clinical studies of various abdominal procedures have shown that continuous epidural local anesthetic administration reduces paralytic ileus. [17] [22] [30] This advantageous effect of epidural local anesthetic is observed compared with systemic or epidural opioid administration, and epidural local anesthetic-opioid combinations also seem to be effective compared with opioid analgesia systemically or epidurally. [17] [30] To obtain the ileus-reducing effect by continuous epidural local anesthetics, the catheter insertion should be applied at the thoracic level [17] [22] [30] ; however, despite the well-documented ileus-reducing effect of continuous epidural local anesthetics, the overall outcome has not been improved, probably because the advantageous physiologic effects were not used for early enteral nutrition (see subsequent discussion).

Pulmonary Complications

Most physicians assume that postoperative pain may reduce pulmonary function and that postoperative patients who are relatively pain

free have fewer pulmonary complications. Although postoperative pain treatment may improve pulmonary function, especially with the use of continuous local anesthetics, [22] the overall clinical effects on pulmonary outcome have been debatable [17] [22] based on randomized clinical studies; however, one cumulative meta-analysis showed continuous epidural local anesthetics to improve, but not eliminate, pulmonary complications, whereas other analgesic techniques, such as systemic and epidural opioids, intercostal nerve blocks, or wound infiltration with local anesthetics, were not effective. [2] Also, a meta-analysis comparing general versus regional anesthesia (single dose and continuous) demonstrated central neural local anesthetic blockade to reduce postoperative pulmonary

complications (A. Rodgers et al, unpublished observations, 1999). The inability of individual studies to demonstrate that effective pain relief leads to improved pulmonary outcome may be explained by the small size of these studies compared with the low incidence of the outcome and probably by the lack of integration of enforced mobilization in the postoperative care program (see subsequent discussion).

Cardiac Complications

A predominant part of postoperative cardiac dysfunction (i.e., tachycardia, arrhythmias, or infarction) may be caused by surgical stress responses and sympathetic activation leading to increased demands on cardiac function. In contrast, substrate availability may be decreased because of postoperative hypoxemia. [28] Although these responses may be abated by neural blockade techniques with local anesthetics, [17] [22] the differential effects of various analgesic techniques on postoperative cardiac outcome remain debatable. [4] [17] [22] One meta-analysis of studies comparing regional anesthesia with intraoperative and early postoperative pain relief compared with general anesthesia showed an approximate 30% reduction in postoperative myocardial infarction, although only marginally significant (A. Rodgers et al, unpublished observations, 1999).

Thromboembolic Complications

The pathogenesis of postoperative thromboembolism is the result of unfavorable changes in all three components of Virchow's triad, with a decrease in lower-extremity blood flow, hypercoagulability, increased thrombocyte aggregation, loss of vessel wall integrity, and impaired fibrinolysis. In accordance with the demonstrated favorable effects of continuous epidural analgesia with local anesthetics on all components of Virchow's triad, [17] [22] several randomized controlled trials in hip and knee replacement, prostatectomy, and peripheral vascular surgery have demonstrated reduced thromboembolic complications, including a reduction of pulmonary embolism [17] [22] ; however, studies of abdominal surgery have been negative. [17] These conclusions are supported by one

meta-analysis of all randomized studies comparing regional anesthesia versus general anesthesia and concluding a significant (≈ 50%) reduction in overall thromboembolic complications by regional anesthesia (A. Rodgers et al, unpublished observations, 1999); however, thromboembolic complications have not been eliminated, and further reductions may be possible combining these techniques with a multimodal rehabilitation approach (see subsequent discussion).

Cerebral Dysfunction

Postoperative delirium and other acute confusional states contribute to morbidity, mortality, and prolonged hospital stay. The pathogenesis is multifactorial, including the use of psychoactive medications (e.g., opioids and benzodiazepines), as well as postoperative hypoxemia and sleep disturbances. [16] [20] [28] The role of various analgesic techniques to reduce postoperative cerebral dysfunction remains debatable, and so far regional anesthetic techniques have not been demonstrated to be effective [17] ; however, in none of the previous studies has an emphasis been placed on a multimodal rehabilitation program combined with a reduction of other risk factors. The reduced use of opioid by the use of nonopioid-containing multimodal analgesia may be promising, and preliminary data from some randomized studies of NSAID-induced opioid sparing suggest decreased sedation and confusion. [19]

Postoperative Fatigue and Convalescence

Postoperative fatigue is a common feature of the recovery phase and is related to the magnitude of surgical injury, which correlates with the postoperative impairment of nutritional status, the loss of muscle mass and functioning, and the impairment in cardiovascular adaption to exercise. [8] [20] Single-modality treatment with effective pain control by different techniques (i.e., systemic and epidural opioids, local anesthetic techniques, or NSAIDs) has not reduced postoperative fatigue. [8] [20] Early resumption of normal activities as another indicator of postoperative convalescence has usually been assumed to be related to pain relief; however, studies with effective continuous epidural analgesia in major orthopedic operations have not demonstrated clinically significant effects on overall convalescence. [25] [29] [35] These and other studies [20] may, therefore, suggest that factors other than pain per se may be important to improve convalescence. To date, studies have not separated the effects of surgery-induced catabolic physiologic effects on muscle mass and function, the reduced cardiovascular adaption to exercise, and the increased catabolism by immobilization on fatigue [8] [20] ; however, future efforts to reduce convalescence should include a multimodal effort with effective dynamic pain relief, nutrition, and enforced mobilization (see subsequent discussion).

Hospital Stay and Overall Outcome

Despite significant beneficial physiologic effects on various organ systems and in some selected postoperative morbidity parameters obtained by neural blockade techniques with local anesthetics [2] [17] (Table 1) , the overall effects on postoperative morbidity and hospital stay remain debatable. [14] [17] [22] This especially applies to major procedures, such as abdominal and thoracic procedures. The extensive use of patient-controlled analgesia has increased patient satisfaction but not overall outcome, morbidity, and hospital stay. [1] [14]

Obviously, these mostly negative outcome studies by provision of different types of postoperative analgesia have been both unexpected and disappointing, even more so because much effort and many resources have been used to introduce acute pain services. In addition, these findings were surprising because various analgesic techniques, and especially the neural blockade techniques, have demonstrated advantageous effects on various postoperative organ dysfunctions. [17] [22] Therefore, explanations for the disappointing lack of clinically significant reductions of postoperative morbidity parameters by pain relief should be sought. In this context, physicians should realize that (1) effective analgesic regimens allowing normal function (dynamic pain relief) have been used only in relatively few studies, (2) the provided pain relief often is too short to produce the expected effects on outcome, (3) the postoperative care program has not been adjusted to take advantage of the physiologic effects of the provided pain relief, and (4) the studies have not integrated the provided pain relief into an active rehabilitation program.

THE MULTIMODAL APPROACH TO ACCELERATE POSTOPERATIVE RECOVERY

The pathogenesis to postoperative morbidity, need for hospitalization, and convalescence involves

several factors (Fig. 1) . [16] Pain relief per se has not represented a major breakthrough to improve surgical outcome, as discussed earlier. Nevertheless, effective functional postoperative pain relief has a great potential to improve postoperative outcome, because pain-relieving techniques have beneficial physiologic effects on different organ systems in the postoperative period. To enhance progress and document the potential advantageous effects on analgesic techniques on postoperative outcome, a detailed analysis must be made of the various factors that may limit early recovery after surgery (Fig. 1) . This procedure includes an answer to the simple question, Why is the patient in hospital today? This question must be asked each day after the procedure to define those factors responsible for postoperative organ dysfunction and continued hospitalization.

As is apparent from Figure 1 , the most common factors responsible for hospitalization may be counteracted if the entire perioperative care program is revised and adjusted to take advantage of recent advances

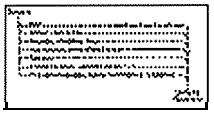

Figure I. Factors that may influence morbidity and recovery following otherwise successful anesthesia and surgery.

in the knowledge of perioperative pathophysiology and interventional techniques. Thus:

1. Pain can be treated effectively to achieve the goal of dynamic pain relief, that is, allowing normal function (as discussed elsewhere in this issue).
2. Stress responses may to some extent be abated by the use of neural blockade techniques with local anesthetics.
3. Nausea, vomiting, and ileus may be reduced with effective pain alleviation with neural blockade techniques, opioid-reduced multimodal analgesia, and the additional use of antiemetics.
4. Hypoxemia may be reduced by routine oxygen administration in high-risk patients, or more simply to mobilize patients to subsequently improve pulmonary mechanics and increase oxygenation. [28]
5. Sleep disturbances and episodic desaturation during the night may be improved by minimally invasive surgical techniques, reduced use of opioids and benzodiazepines, and reduction of noise. [28]
6. Early fatigue may be reduced by improvement of sleep and reduction of stress responses (cytokines). Late fatigue may be reduced by the reduction of the catabolic stress response by neural blockade techniques, combined with early enforced mobilization, enteral nutrition, facilitated by appropriate pain alleviation techniques (neural blockade). [20]
7. Immobilization-induced undesirable sequelae may be avoided by the provision of dynamic pain relief and subsequent enforced mobilization. Conventional postoperative semistarvation caused by traditions in perioperative and postoperative care, as well as

nausea, vomiting, and ileus, may be counteracted by effective opioid-reduced analgesia.
8. Non-pain-related and non-analgesic-related factors that may delay recovery and that are included in traditional postoperative care systems, such as unnecessary routine use of drains and nasogastric tubes, need revision. [16] Most often, the scientific literature from randomized

trials does not support such routine use. [16] Other recovery-delaying factors involve an "observation period" and inappropriate administration of perioperative fluids, leading to overhydration. This especially applies during the use of intraoperative and postoperative neural blockade techniques, in which the sympathetic block and subsequent hypotension may be followed by the administration of large amounts of fluids, leaving patients physiologically overhydrated when the block regresses, thereby overriding the advantageous effects of the nociceptive block on cardiopulmonary function.

As observed in many other medical conditions, unimodal treatment of such a complex problem as perioperative morbidity cannot be expected to provide major steps toward accelerated postoperative recovery. Therefore, some physicians have proposed that the effective control of perioperative pain, pathophysiology, and rehabilitation can be achieved only by a multimodal intervention, including dynamic pain relief, stress reduction, patient information, and then integration into a program with enhanced early mobilization and oral nutrition [16] (Fig. 2) . In addition, the administration of various growth factors may be indicated in certain high-risk patients, although further documentation is needed. [16]

Although the multimodal rehabilitation approach seems simple,

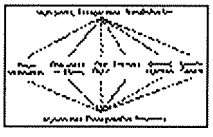

Figure 2. Components of a multimodal effort to control perioperative pathophysiology and recovery. preop = preoperative.

obvious, and without significant additional cost, limited data on its application are available, and those data are predominantly of a relatively small scale, from single centers, and from nonrandomized observations that merely serve as hypotheses. Further research in this promising and important field is needed. A summary of such preliminary observational studies is provided in Table 2 . The acceleration of postoperative rehabilitation by the multimodal concept primarily has been focused on reducing morbidity and enhancing recovery, but obvious secondary advantages include a decreased need for hospitalization and reduced costs. In recent years, perioperative pain treatment has been optimized, especially after introduction of "acute pain services." Therefore, why the implementation of an accelerated surgical recovery program has been so difficult may be questioned. In the author's experience, patients have not been the limiting factor because preoperative patient information and education are essential and have been involved in several published programs (Table 2) . In contrast, insufficient understanding and knowledge of perioperative pathophysiology and rehabilitation may have limited progress and, therefore, need more attention, with revision of traditional perioperative care programs. The economic constraints and administrative pressures to reduce costs may also represent

TABLE 2 -- RESULTS FROM MULTIMODAL INTERVENTION AND OPTIMIZATION OF PAIN RELIEF ON POSTOPERATIVE RECOVERY

Study	Operation	Multimodal Components	Hospital Stay/Outcome

Callesen et al [5], Kark et al [12]	Hemiorrhaphy	Preoperative education, infiltration anesthesia, care specialization	Short-stay--ambulatory, reduced morbidity
Michaloliakou et al [24]	Laparoscopic cholecystectomy	Multimodal analgesia	Ambulatory, reduced pain and nausea
Rasmussen et al [27]	Meniscectomy	Multimodal analgesia+enforced mobilization	Ambulatory, reduced pain and convalescence
Collier [9]	Carotic endarterectomy	Preoperative education infiltration, anesthesia care specialization	l-2 d, reduced morbidity
Coveney [10]	Mastectomy	Paravertebral block	Reduced pain, 96% ≤ 24-h stay
Tovar et al [31]	Lung lobectomy	Preoperative education, multimodal analgesia	l-2 d
Worwag and Chodak [36]	Prostatectomy	Multimodal analgesia, preoperative education	1.3 d
Bardram et al [3]	Laparoscopic colonic resection	Preoperative education, enforced mobilization+nutrition, multimodal analgesia	2d
Kehlet and Mogensen [21]	Open colonic resection	Preoperative education, enforced mobilization+nutrition, multimodal analgesia	2d
Weingarten et al, [34] Macario et al [23]	Knee and hip replacement	Revised clinical pathway, epidural analgesia	4-5 d, reduced costs

a barrier for improvement. Interestingly, the need for additional resources to introduce the multimodal rehabilitation approach is probably limited, except for expenses, to necessary acute pain services and physiotherapy in certain specialties (e.g., orthopedics). A common feature for the success of the so-far-introduced programs (Table 2) is the multidisciplinary effort with extensive collaboration between anesthesiologists (i.e., pain services), surgeons, surgical nurses, and physiotherapists to achieve positive initial results. Intensive preoperative patient information and education, nurse specialization, and the use of optimal analgesic treatment combined with multimodal rehabilitation techniques have also been essential.

SUMMARY

Postoperative pain relief continues to demand our awareness, and surgeons should be fully aware of

the potential physiologic benefits of effective dynamic pain relief regimens and the great potential to improve postoperative outcome if such analgesia is used for rehabilitation. To achieve advantageous effects, accelerated multimodal postoperative recovery programs should be developed as a multidisciplinary effort, with integration of postoperative pain management into a postoperative rehabilitation program. This requires revision of traditional care programs, which should be adjusted according to recent knowledge within surgical pathophysiology. Such efforts must be expected to lead to improved quality of care for patients, with less pain and reduced morbidity leading to cost efficiency.

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