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Manipulation of the Metabolic Response in Clinical Practice

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Abstract. Surgical injury is followed by profound changes in endocrine metabolic function and various host defense mechanisms leading to catabolism, immunosuppression, ileus, impaired pulmonary function, and hypoxemia. These physiologic changes are supposed to be involved in the pathogenesis of postoperative morbidity. Effective afferent neural blockade with continuous epidural local anesthetic techniques inhibits a major part of the endocrine metabolic response, leading to improved protein economy but without important effects on inflammatory or immunologic responses. In contrast, pain treatment with other modalities such as nonsteroidal antiinflammatory drugs (NSAIDs) and opioids has only a small inhibitory effect on endocrine metabolic responses. Preoperative high-dose glucocorticoid therapy provides additional pain relief and improves pulmonary function, but it reduces the inflammatory response (acute-phase proteins, cytokines, hyperthermia) and immune function. Minimally invasive surgery leaves the endocrine metabolic responses largely unaltered but reduces the inflammatory response and immune suppression. Thus several techniques are available to modify the stress responses in elective surgery patients. The effect of these techniques to alter endocrine metabolic and inflammatory responses during severe surgical illness has not been established. Neural blockade and minimally invasive surgery have improved outcome following elective surgery, especially when integrated into a multimodal postoperative rehabilitation program. Application of this knowledge from pathophysiologic responses to uncomplicated surgical injury should be explored in patients with severe surgical illness.

Major surgery is still associated with undesirable sequelae such as pain, cardiopulmonary, infectious and thromboembolic complications, cerebral dysfunction, nausea, gastrointestinal paralysis, fatigue, and prolonged convalescence. It has been hypothesized that the surgical stress response and resulting increase in demands on organ functions may be responsible for these sequelae, and that a multimodal approach to controlling postoperative pathophysiology, metabolism, and rehabilitation subsequently may improve surgical outcome [1]. Furthermore, inhibition of the initial response to the surgical stimulus may theoretically be advantageous should a complication occur, based on the "second-hit" theory of multiple organ failure [2].

This article reviews established techniques that manipulate the metabolic response in elective surgical patients, and it is suggested that such changes when combined with those of other techniques may also be useful in severe surgical illness. The chapter focuses on the effect of pain-relieving techniques, the use of high-dose glucocorticoid, and the use of minimally invasive surgery.

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Effect of Pain Relief on Surgical Metabolism

Pain is induced by activation of the peripheral and central nervous systems, which also are involved as one of the major release mechanisms of the metabolic response to surgical injury [1, 3]. Pain relief is a necessary but not sufficient technique to improve surgical outcome [1], and pronounced differences exist between the metabolic effects of the various pain-relieving techniques.

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

NSAIDs are used routinely for acute pain treatment. Although they have been demonstrated to attenuate the endocrine metabolic response to endotoxin administration in human volunteers, most surgical studies have shown NSAIDs to have no or only a slight inhibitory effect on classic catabolic stress hormones, acute-phase protein responses, and protein economy [3]. However, a few studies have shown that ibuprofen reduces adrenocorticotropic hormone (ACTH) and cortisol release as well as interleukin-6 (IL-6) after laparotomy [4] and that it decreases fever, tachycardia, and oxygen consumption in sepsis patients [5]. It has no effect on morbidity or survival. In summary, the well established analgesic effects of NSAIDs may have only a slight or inconsistent inhibitory effect on metabolic responses in surgical patients and may therefore serve only as one of the components in a multimodal effort to reduce catabolism.

Opioids

Opioids administered systemically in low dosages in patient-controlled analgesia or in an intermittent conventional regimen have only slight or no stress-reducing effects [1, 3, 6]. In contrast, high-dose opioid anesthesia may reduce intraoperative, but not postoperative, endocrine metabolic changes [3].

Epidural analgesia with opioids has also only a slight inhibitory effect on catecholamine and cortisol responses to surgery, although the results are not consistent in the literature [3]. In general, the effects are relatively small, especially during major operations. Accordingly, the effect of opioid administration on

Table 1. Effect of epidural and spinal anesthesia and analgesia on postoperative nitrogen economy.

Anesthesia	Surgery	Comment	Author
Lumbar epidural local anesthetic	Hysterectomy	24-Hour block with inhibition of corticol and glucose response and improvement in nitrogen balance	Brandt [3][a]
	Colonic	44-Hour block. Postoperative nitrogen balance improved and 3-methylhistidine excretion reduced	Vedrinne [3][a]
	Hip surgery	No effect of single-dose epidural bupivacaine on urinary nitrogen and 3-methylhistidine excretion	Carli [3][a]
	Hip surgery	24-Hour block with reduction of cortisol and glucose response as well as usual 72-hour postoperative shifts in amino acid composition in skeletal muscle	Christensen [3][a]
Thoracic epidural local anesthetic	Colonic	24-Hour block with reduction of urinary excretion of catecholamines but not cortisol; urinary nitrogen excretion and whole body protein turnover (leucine oxidation) reduced	Carli [3][a]
	Gastric	48-Hour block with reduced plasma cortisol and glucagon response and decreased urinary catecholamine excretion; urinary nitrogen excretion reduced compared to pain relief with systemic opioids and epidural opioids	Tsuji [3][a]
	Aortic	24-Hour block with reduced plasma cortisol and urinary catecholamine excretion; no effect on urinary nitrogen and cortisol excretion ($n = 2 \times 5$)	Smeets [3][a]
	Abdominal	Single-dose postoperative block (6 hours duration) with slightly reduced plasma catecholamines, glucagon, and cortisol levels; isotope study with decrease in glucose and urea turnover rates	Shaw [3][a]
	Abdominal and thoracic	24-Hour block with no influence on plasma glucose, free fatty acids, and lactate except at the end of operation; and no effects on postoperative nitrogen urea or 3-methylhistidine excretion	Seeling [3][a]
	Abdominal	Single-dose epidural analgesia; no effect on plasma cortisol, glucose prolactin, or nitrogen balance	De Lalande [3][a]
	Abdominal	24-Hour block; no effects on plasma cortisol, glucose, or prolactin; improved nitrogen balance	De Lalande [3][a]
	Colonic	48-Hour continuous epidural block reduced postoperative protein breakdown more effectively than a 24-hour block	Carli [7]
	Colonic	48-Hour continuous epidural block improved postoperative protein synthesis rate compared with general anesthesia and systemic opioids	Carli [8]
Lumbar epidural opioid	Colonic	48-Hour treatment (epidural meperidine); no effect on nitrogen and 3-methylhistidine excretion	Vedrinne [3][a]
	Gastric	Intraoperative epidural local anesthetic + 72-hour postoperative epidural morphine; reduced plasma cortisol and glucagon and urinary excretion of catecholamines and nitrogen	Tsuji [3][a]
	Abdominal	24-Hour intermittent local anesthesia and 72-hour epidural morphine with insignificant reduction in urinary catecholamines and cortisol; unchanged 4-day nitrogen excretion	Hjortsø [3][a]
	Hysterectomy	24-Hour block with improved glucose homeostasis and insignificant reduction in urinary nitrogen excretion	Licker [3][a]

[a]These studies were referred to in a recent review [3].

protein economy is minor and inferior to that obtained by epidural local anesthetics [3] (Table 1).

Neural Blockade with Local Anesthetics

Because activation of the peripheral and central nervous systems plays a key role in initiating the hormonal and metabolic responses to surgical injury [3], an afferent neural blockade with local anesthetics may profoundly alter these responses. For lower body procedures, where epidural local anesthetics provide an effective afferent blockade [3], these techniques result in inhibition of the classic endocrine metabolic response parameters, such as catecholamines, cortisol, and glucose (Table 2). Subsequently, continuous epidural analgesia with local anesthetics improves postoperative nitrogen economy [3] (Table 1). Similarly, fat metabolism with increased lipolysis is reduced as are the usual increases in lactate and ketones [3]. Of major clinical importance is the fact that a single-dose block has no important prolonged effects on metabolism or protein economy, and a 24-hour block improves nitrogen economy, with further improvement by a 48-hour block (Table 1) [3]. Although neural blockade with local anesthetics modifies several of the classic hormonal responses that may influence renal function (cortisol, catecholamines, aldosterone, renin, antidiuretic hormone), no clinically important effects on postoperative fluid or electrolyte balance have been demonstrated, except for reduced potassium excretion, which parallels the reduced catabolism [3]. Oxygen consumption is reduced in accordance with the sympathetic block and reduced catabolism. No studies are available on the effect of short- or long-term epidural analgesia on the endocrine metabolic response during critical surgical illness, where the characteristics and physiologic effects of hormonal changes are different from the initial acute response [9].

In contrast to the pronounced inhibition of endocrine metabolic

Table 2. Effect of neural blockade with local anesthetics on endocrine-metabolic and inflammatory responses to elective surgery.

Type of response	Inhibition or improvement	No important effect	No data
Pituitary	β-Lipotrophin	T_3 and T_4	Gastrointestinal peptides
	Adrenocorticotropin	Calcitonin gene-related peptide	Testosterone
	β-Endorphin	Coagulation and fibrinolysis	Estradiol
	Growth hormone	Acute-phase protein and interleukin-6	Somatomedin
	Arginine vasopressin	Water and sodium balance	Ca^{2+}, Mg^{2+}, Zn^{++}, phosphate balance
	Thyroid-stimulating hormone	Granulocytosis and neutrophil function	Macrophage-derived peptides (interleukins, tumor necrosis factor)
	Luteinizing hormone and follicle-stimulating hormone	Liver enzymes and antipyrin clearance	
	Prolactin	Hyperthermia	
Adrenal, renal, and nervous systems	Cortisol		
	Aldosterone		
	Renin		
	Epinephrine		
	Norepinephrine		
Metabolic	Hyperglycemia and glucose tolerance		
	Insulin resistance		
	Lipolysis		
	Muscle amino acids		
	Nitrogen balance		
	Hepatic urea production		
	Oxygen consumption		
	Urinary potassium excretion		
Immunologic	Complement activation (C3a, C5a)		
	Lymphopenia		
	Natural killer cell suppression		

Modified from Kehlet [3].
T_3: triiodothyronine; T_4: thyroxine.

responses by neural blockade during lower body procedures, a smaller reduction of catabolism and improvement in protein economy is achieved during upper abdominal/thoracic procedures [3] (Table 1). The explanation for this discrepancy between lower and upper body procedures is a less effective afferent blockade with thoracic epidural local anesthetic [3] and unblocked phrenic afferents during sub- or supradiaphragmatic surgery [10]. Another factor may be the unblocked vagal afferents during thoracic epidural analgesia, as experimental studies have demonstrated that vagotomy blocks the hyperthermic response to intraperitoneal IL-1 stimulation [11]. The limited clinical data in humans with intraoperative vagal blockade do not suggest that this nerve is important for the cortisol and hyperglycemic response to abdominal surgery [3]. Nevertheless, continuous thoracic epidural local anesthetic administration improves postoperative catabolism and protein economy, and an advantageous effect is achieved in regard to postoperative ileus [1, 3]. Thus epidural local anesthetics may further improve the anabolic–catabolic balance by allowing early oral nutrition [1]. Epidural local anesthetics are equally effective for reducing the endocrine-metabolic response during normothermic or hypothermic recovery [12], despite the fact that hypothermia usully amplifies the immediate postrecovery stress response.

In contrast to the effects of a neural block on hormonal and metabolic responses, no important effects have been demonstrated on inflammatory responses, that is, postoperative changes in acute-phase protein and cytokines (IL-6) [3]. These responses are thus independent of the neural activation and pain per se. Accordingly, the inflammatory response is mostly independent on endocrine activation, although some studies have shown that etomidate (which selectively inhibits adrenocorticol responses) administration results in higher postoperative IL-6 values [13]; this finding suggests that endogenous glucocorticoids may modulate the IL-6 response to surgery.

General Anesthesia and Sedation

The type of general anesthesia has not been demonstrated to have any long-term clinical relevant metabolic effects into the postoperative period, and only quantitatively minor differences exist among anesthetic agents in terms of the intra- and early postoperative endocrine metabolic responses [3]. The main effort to improve outcome for most types of surgery includes a multimodal approach with early rehabilitation [1]; therefore the effects of sedation techniques on metabolism are not relevant except in special circumstances. Currently, fast-track early recovery programs are under development for cardiac and other procedures but so far without investigating the endocrine-metabolic response.

Continuous sedation with proprofol may reduce urinary and plasma catecholamine and cortisol responses, but only for a 12-hour period of sedation [14]. In another study with more aggressive sedation using high-dose opioids for 24 hours during neonatal cardiac surgery, endocrine metabolic stress responses were reduced, and the outcome was improved [15]. Such a regimen requires extended ventilatory support, however, and has not been evaluated in other procedures.

In summary, long-term sedation and its metabolic effects have been investigated only sporadically in elective surgical patients. Its role in modulating endocrine responses and improving catabolism and outcome is questionable.

Glucocorticoids

Evidence has accumulated that an overaggressive, protracted inflammatory and hormonal host defense (stress) response may be an important factor in impairing the outcome after severe surgical illness. These data, together with the “second-hit” hypothesis [2], support the theory that modulating the initial endocrine metabolic and inflammatory responses to the elective surgical procedure may reduce the risk following a second injury or complication. Although our understanding of the antiinflammatory effects of glucocorticoids has improved [16], the clinical use of glucocorticoids for elective or severe surgical illness remains to be established. The use of glucocorticoids has been controversial, especially in severe surgical illness but with a recent refocusing on the potential positive effects of glucocorticoid therapy [17, 18].

The effects of preinjury glucocorticoid administration on various inflammatory responses are relatively well established. Thus preendotoxin glucocorticoid may attenuate symptoms as well as IL-6, C-reactive protein (CRP), tumor necrosis factor (TNF) and IL-8 responses, but not the IL-1 receptor antagonist response [19, 20]. Similarly, high-dose preoperative methylprednisolone (30 mg/kg) may attenuate catecholamine and arginine vasopression responses; the IL-6, CRP, and prostaglandin E_2 (PGE_2) responses; and activation of the plasma cascade system [21–24]. The hyperthermic response is also inhibited [21, 22], and pain and fatigue are reduced [21]. In contrast, IL-10 responses are increased following methylprednisolone [23], and pulmonary function is improved following glucocorticoids in colonic surgery patients [21, 22]. The postoperative delayed hypersensitivity immunologic response is further reduced, leading to anergy [22]; but collagen accumulation in wounds is not altered [22].

The clinical consequences of a single preoperative dose of methylprednisolone has not been established in small-scale randomized studies, although one of the studies suggests less morbidity and a shorter intensive care unit (ICU) stay [24]. In relatively small-scale procedures the anti-inflammatory effects of a preoperative glucocorticoid administration may be beneficial because it reduces pain and swelling after dental procedures [25]. Also in patients undergoing arthroscopic meniscectomy, combined intraarticular glucocorticoid, bupivacaine, and morphine have a pronounced advantageous effect on postoperative pain, inflammatory response (joint swelling, acute-phase protein), and convalescence (mobilization and sick leave) [26].

In summary, further data are needed for specific procedures on the short- and long-term potential (or risk) of modulation of the inflammatory responses by preinjury glucocorticoid administration. So far, patients with preoperative severely impaired pulmonary function represent a group for whom glucocorticoids improve organ (pulmonary) function.

Minimally Invasive Surgery

Classic open operations are, as mentioned above, followed by profound changes in endocrine metabolic function and host defense mechanisms, thereby increasing the risk of subsequent organ dysfunction. Following the introduction of various minimally invasive surgery techniques to reduce wound size, a large body of data has shown that laparoscopic surgery leads to a reduced inflammatory response (predominantly cytokine and acute-phase proteins), reduced immunomodulatory response, improved pulmonary function, and less hypoxemia and pain [27–29]. In contrast, relatively little effect has been found in the classic endocrine metabolic responses for laparoscopic versus open operations [27–29]. Most studies have been performed for cholecystectomy or herniorrhaphy, however, and the few studies on major colonic operations suggest a smaller catabolic hormonal response with subsequent improvement in protein economy [27, 29]. The overall effects on endocrine metabolic and inflammatory responses during minimally invasive surgery are listed in Table 3. The clinical implications of the modified inflammatory response during minimally invasive surgery have been considered obvious because of reduced pain, organ dysfunction, need for hospital stay, and convalescence. These findings have also questioned the role of the endocrine metabolic responses in the determination of outcome; studies therefore have focused on the inflammatory response [27–29]. Although these data clearly suggest that altering the initial injury response may be beneficial for minimally invasive surgery, the amount of tissue injury is reduced, not only the pathophysiologic response. The final therapeutic advantage of the more costly minimally invasive surgical technique compared to open operation remains to be established, as treatment bias may have been introduced in the laparoscopic studies with insufficient blinding, and the "open" groups in most studies have not been appropriately treated with optimal pain relief, early oral feeding, and mobilization [1, 29]. However, preliminary observations for colonic surgery support that combined use of neural blockade and minimally invasive surgery may hasten recovery and reduce morbidity [1].

In conclusion, data on the effect of minimally invasive surgery on the endocrine metabolic and inflammatory response suggest that reduction of the wound size (and thereby the inflammatory response) may be beneficial on outcome and the risk of developing a second severe surgical illness. These data also suggest that a short-lasting endocrine-metabolic response may not be as important for determining outcome. The minimally invasive surgery data should stimulate the development of other interventional techniques to modify the inflammatory responses and to apply them in surgical patients in whom minimally invasive surgery cannot be used.

Table 3. Effect of laparoscopic versus open surgery on endocrine-metabolic and inflammatory-immunologic responses.

Endocrine-metabolic responses	
Cortisol	$\rightarrow$
ACTH	$\rightarrow$
Catecholamines	$\rightarrow$
GH, prolactin	$\rightarrow$
Glucagon	$\rightarrow$
Insulin sensitivity	$\uparrow$
Nitrogen balance	$\rightarrow\uparrow$
Inflammatory and immunologic responses	
CRP	$\downarrow$
IL-6	$\downarrow$
Leukocytosis	$\downarrow$
Neutrophil elastase	$\downarrow\rightarrow$
PHA response	$\uparrow$
Monocyte HLA-DR expression	$\downarrow\rightarrow$
Pulmonary function	
PaO_2 or SpO_2	$\uparrow$
Pulmonary function (FVC, FEV_1)	$\uparrow$

Data are from published reviews [27–29].

$\uparrow$: increased response/function in laparoscopy group; $\rightarrow$: no difference between laparoscopy and open surgery; $\downarrow$: decreased response/function in laparoscopy group; ACTH: adrenocorticotropic hormone; GH: growth hormone; CRP: C-reactive protein; IL-6: interleukin-6; PHA: phytohemagglutinin; HLA-DR: class II human leukocyte antigen; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; PaO_2: partial oxygen pressure in arterial blood; SpO_2: pulse oximetry.

Conclusions and Future Directions

The catabolic endocrine metabolic and inflammatory response may have important consequences for outcome in major elective surgical procedures due to the profound changes in body composition with loss of weight and muscle mass and resistance to infection. Other sequelae of the surgical stress response are pain, sleep disturbance, ileus, and pulmonary and cardiac dysfunction, all of which may contribute to convalescence and fatigue [1]. Recent advances in perioperative care have included optimization of pain relief, nutrition, fluid management, anesthesia and surgical techniques, and antimicrobial prophylaxis. Despite the fact that many unimodal intervention studies have reported a positive effect on outcome, the pathogenesis of common postoperative sequelae is multifactorial. Subsequently, a rational strategy to demonstrate substantial reduction of perioperative morbidity and shortened convalescence most be multimodal to modify all pathogenic mechanisms leading to the conventional postoperative cascade to dependence [1]. Such efforts include intensified preoperative information, stress reduction with neural blockade or humoral mediator modification, and sufficient pain relief, allowing early mobilization and facilitating recovery of gastrointestinal function to allow early restoration of oral intake. Based on such multimodal intervention studies [1], it is hypothesized that modification of catabolism and sympathetic responses to surgery may be advantageous [1]. Inhibition of the endocrine metabolic response may reduce catabolic consequences on muscle mass and function. Furthermore, modification of these responses by a neural blockade has obvious secondary advantageous effects in reducing nausea, vomiting, and ileus, thereby facilitating oral intake, which otherwise has been shown to reduce postoperative morbidity and risk of infectious complications. The inflammatory responses are not influenced by optimal pain relief or reduction of catabolism by afferent neural blockade but are reduced by glucocorticoids and minimally invasive surgery. The clinical advantageous effects of minimally invasive surgical techniques are well established and easy to understand because they reduce the amount of wound trauma. In contrast, modification of inflammatory responses by pharmacologic intervention with glucocorticoids or other antiinflammatory/anticytokine agents is controversial, as a certain magnitude of response obviously is necessary for sufficient immune function and resistance to infection and wound healing, but an exaggerated inflammatory response is undesirable and contributes to the development of multiple organ failure.

Based on the data derived from elective surgical procedures, it is concluded that surgically induced neural reflex responses and endocrine metabolic catabolic responses should be alleviated by effective pain-relieving techniques and neural blockade. Modification of other (inflammatory/immunologic) responses remains to be evaluated and explored regarding the clinical significance on outcome. Such knowledge should serve as a scientific basis for potential applications in patients with severe surgical illness, but so far this has not been sufficiently evaluated to allow any recommendations for clinical practice.

Résumé

L'agression chirurgicale est suivie de changements profonds de la fonction endocrine métabolique et des mécanismes de défense de l'hôte, responsables d'un état catabolique, d'une immunosuppression, d'un iléus, d'une fonction pulmonaire diminuée et d'une hypoxémie. Ces changements physiologiques ont probablement une part dans la pathogenèse de la morbidité postopératoire. Lorsque fait de façon effectif, le blocage neuronal afférent par une technique d'anésthésie épidurale continue, inhibe en partie la résponse métabolique endocrine, améliorant ainsi l'épargne protéinique, mais sans effet notable sur les résponses inflammatoire ou immunitaires. En contraste, le traitement de la douleur par les AINS ou les opiacés a un effet inhibiteur minime sur les résponses métaboliques endocrines. Une glycocorticothérapie préopératoire à haute dose soulage la douleur et améliore la fonction pulmonaire, mais réduit la réponse inflammatoire (protéines de la phase aiguë, cytokines, hyperthermie) et la fonction immune. La chirurgie mini-invasive produit des réponses métaboliques endocrines non modifiées, mais réduit la réponse inflammatoire et l'immunosuppression. Ainsi plusieurs techniques sont disponibles pour modifier la réponse au stress des patients en chirurgie élective. L'effet de ces techniques sur la modification des réponses métaboliques et inflammatoires endocrines dans l'agression chirurgicale sévère n'est pas établi. Le blocage neuronal et la chirurgie mini-invasive ont certes amélioré l'évolution après la chirurgie élective, surtout lorsqu'ils sont intégrés dans un programme de réhabilitation postopératoire multimodale. L'application de ces connaissances, allant depuis les réponses physiopathologiques à la lésion chirurgicale non compliquée, devrait être explorée chez le patient ayant une maladie chirurgicale, sévère.

Resumen

El trauma quirúrgico produce profundos cambios en la función metabólica y en una variedad de mecanismos de defensa que resultan en catabolismo, inmunosupresión, íleo, alteración de la función pulmonar e hipoxemia. Tales cambios físiológicos supuestamente están involucrados en la morbilidad postoperatoria. Un control efectivo del bloqueo neural aferente mediante anestesia epidural inhibe una parte mayor de la respuesta metabólica endocrina con mejoramiento de la economía proteica, aunque sin efecto importante sobre las respuestas inflamatoria o inmunitaria. Por el contrario, el manejo del dolor con otros métodos tales como AINES u opiáceos apenas ejerce un efecto inhibitorio mínimo sobre las respuestas metabólicas endocrinas. La terapia preoperatoria con altas dosis de glucocorticoides provee control adicional del dolor y mejora la función pulmonar, pero reduce la respuesta inflamatoria (proteínas de fase aguda, citocinas, hipertermia) y la función inmunitaria. La cirugía mínimamente invasora produce mínima alteración en la respuesta metabólica endocrina, pero reduce la reacción inflamatoria y el grado de inmunosupresión. Se puede ver que existen diversos métodos para modificar las respuestas de estrés en los pacientes sometidos a cirugía electiva. El efecto de tales métodos, en cuanto a la alteración de las respuestas metabólicas endocrinas inflamatorias en la enfermedad quirúrgica severa, aún no ha sido bien definido. El bloqueo neural y la cirugía mínimamente invasora han mejorado los resultados de la cirugía electiva, especialmente cuando se integran a un programa multinodal de rehabilitación postoperatoria. La aplicación de todo este conocimiento sobre las respuestas fisiopatológicas al trauma quirúrgico no complicado debe ser investigada en los pacientes con enfermedad quirúrgica grave.

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References

1. Kehlet, H.: Multimodal approach to control postoperative pathophysiology and rehabilitation. Br. J. Anaesth. *78*:606, 1997
2. Garison, R.N., Spain, D.A., Wilson, M.A., Keelen, P.A., and Harris, P.D.: Microvascular changes explain the "two-hit" theory of multiple organ failure. Ann. Surg. *227*:851, 1998
3. Kehlet, H.: Modification of responses to surgery by neural blockade: clinical implications. In Neural Blockade in Clinical Anesthesia and Management of Pain, Cousins, M.J., and Bridenbaugh, P.O., editors, Philadelphia, Lippincott-Raven, 1998, pp. 129–175
4. Chambrier, C., Shassard, D., Bienvenu, J., Saudin, F., Paturel, B., Garrique, C., Barbier, Y., and Bulletreau, P.: Cytokine and hormonal changes after cholecystectomy: effect of ibuprofen pretreatment. Ann. Surg. *224*:178, 1996
5. Bernard, G.R., Wheeler, A.P., Russell, J.A., Shein, R., Summer, V.R., Steinberg, K.B., Fulkoson, W.J., Wright, P.E., Christman, B.W., Dupont, W.D., Heaggins, S.B., and Swindell, B.: The effects of ibuprofen on the physiology and survival of patients with sepsis. N. Engl. J. Med. *336*:912, 1997
6. Mangano, D.T., Ciliciano, D., Hollenberg, M., Leum, J.M., Browner, W.S., Goehner, P., Merrick, S., and Verrier, E.: Postoperative myocardial ischemia; therapeutic trials using intensive analgesia following surgery. Anesthesiology *76*:342, 1992
7. Carli, F., and Halliday, D.: Modulation of protein metabolism in the surgical patient: effects of 48-hours continuous epidural block with local anesthetics on leucine kinetics. Reg. Anesth. *21*:430, 1996
8. Carli, F., Phil, M., and Halliday, D.: Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthetic rate in surgical patients. Anesthesiology *86*:1033, 1997
9. Van den Berghe, G., Dezegher, F., and Boullion, R.: Acute and prolonged critical illness as different neuroendocrine paradigms. J. Clin. Endocrinol. Metab. *83*:1827, 1998
10. Segawa, H., Mori, K., Kasai, K., Fukata, J., and Nakao, K.: The role of the phrenic nerves in stress response in upper abdominal surgery. Anesth. Analg. *82*:1215, 1996
11. Watkins, L.R., Goehler, L.E., Relton, J.K., Tartaglin, N., Silbert, L., Martin, D., and Maier, S.F.: Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci. Lett. *183*:27, 1995
12. Motamed, S., Klubien, K., Edwardes, M., Mazza, L., and Carli, F.: Metabolic changes during recovery in the normothermic versus hypothermic patients undergoing surgery and receiving general anesthesia and epidural local anesthetic agents. Anesthesiology *88*:1211, 1998
13. Jameson, P., Desborough, J.P., Bryant, A.E., and Hall, G.M.: The effect of cortisol suppression on interleukin-6 and white blood cells responses to surgery. Acta Anaesthesiol. Scand. *41*:304, 1997
14. Plunkett, J.J., Reeves, J.D., Ngo, L., Bellows, W., Shafer, S.L., Roach, G., Howse, J., Herskowitz, A., and Mangano, D.T.: Urine and plasma catecholamine and cortisol concentrations after myocardial revascularisation: modulation by continuous sedation. Anesthesiology *86*:785, 1997
15. Anand, K.J.S., and Hickey, P.R.: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N. Engl. J. Med. *326*:1, 1992
16. Barnes, P.J.: Antiinflammatory action of glucocorticoids: molecular mechanisms. Clin. Sci. *94*:557, 1998
17. Meduri, G.U., and Kanangat, S.: Glucocorticoid treatment of sepsis and acute respiratory distress syndrome: time for a critical re-appraisal. Crit. Care Med. *26*:630, 1998
18. Matot, I., and Sprung, C.L.: Corticosteroids in septic shock: resurrection of the last rites? Crit. Care Med. *26*:627, 1998
19. Santos, A.A., Scheltinga, M.R., Lynch, E., Brown, E.F., Lawton, P., Chambers, E., Browing, J., Dinarello, C.A., Wolff, S.M., and Wilmore, D.W.: Elaboration of interleukin-1-receptor antagonist is not attenuated by glucocorticoids after endotoxemia. Arch. Surg. *128*:138, 1993
20. Rock, C.S., Coyle, S.M., Keogh, C.V., Lazarus, D.D., Hawes, A.S., Leskiw, M., Moldawer, L.L., Stein, T.P., and Lowry, S.F.: Influence of hypercortisolemia on the acute phase protein response to endotoxin in humans. Surgery *112*:467, 1992
21. Schulze, S., Sommer, P., Bigler, D., Honnens, M., Shenkin, A., Cruickshank, A.N., Bukhave, K., and Kehlet, H.: Effect of combined prednisolone, epidural analgesia and indomethacin on the systemic response after colonic surgery. Arch. Surg. *127*:325, 1992
22. Schulze, S., Andersen, J., Overgaard, H., Nørgaard, P., Nielsen, H.J., Aasen, A., Gottrup, F., and Kehlet, H.: Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch. Surg. *132*:129, 1997
23. Tapardel, Y., Duchatteau, J., Schmartz, D., Marecaux, G., Shala, M., Barvais, L., le Clerc, J-L., and Vincent, J-L.: Corticosteroids increase blood interleukin-10 levels during cardiopulmonary bypass in men. Surgery *119*:76, 1996
24. Taketa, S., Ogawa, W.R., Nakanishi, K., Kim, C., Miyashita, M., Sasajima, K., Unda, M., and Takano, T.: The effect of preoperative high-dose methylprednisolone in attenuating the metabolic response after oesophageal resection. Eur. J. Surg. *163*:511, 1997
25. Skjelbred, P., and Løkken, P.: Reduction of pain and swelling by corticosteriod injected 3 hours after surgery. Eur. J. Clin. Pharmacol. *23*:141, 1982
26. Rasmussen, S., Larsen, A.S., Thomsen, S.T., and Kehlet, H.: Intraarticular glucocorticoid, bupivacaine and morphine reduces pain, inflammatory response and convalescence after arthroscopic meniscectomy. Pain *78*:131, 1998
27. Kehlet, H., and Nielsen, H.J.: Impact of laparoscopic surgery on stress responses, immunofunction and risk of infectious complications. New Horiz. *6*:s80, 1998
28. Vittimberga, F.J., Foley, D.P., Meyers, W.C., and Callery, M.P.: Laparoscopic surgery and the systemic immune response. Ann. Surg. *227*: 326, 1998
29. Kehlet, H.: The surgical stress response: does endoscopic surgery confer an advantage? World J. Surg. *23*:801, 1999