SURGICAL STRESS: THE ROLE OF PAIN AND ANALGESIA

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The endocrine, metabolic and inflammatory responses to injury and infection are composed of a variety of physiological changes often grouped together and called the surgical stress response. Over the past few decades, detailed knowledge has accumulated on this response and has allowed consideration and development of therapeutic manoeuvres designed to assist or manipulate the patient's response to a surgical operation in order to improve postoperative morbidity.

Since relief of postoperative pain is supposed to be a prerequisite for improved postoperative outcome, this paper summarizes the effects on the surgical stress response of the available techniques. A short review of the clinical implications of postoperative pain relief will also be given. It is not intended to give a complete bibliography of this vast topic, but primarily to bring recent findings into balance with previous data. The reader is therefore referred to recent reviews of the surgical stress response, including release mechanisms and modifying factors [7, 13, 14, 16, 17, 25].

RELEASE MECHANISMS OF THE SURGICAL STRESS RESPONSE

Although the exact nature and relative importance of the various signals that may initiate, amplify, sustain and complete the stress response remain to be settled, recent studies have shed more light on the relative roles of afferent neural and humoral stimuli.

The nociceptive signal to the central nervous system is transmitted from the site of surgery primarily by small myelinated (A-delta) and unmyelinated (C) sensory afferent fibres [27, 45]. Recent studies with regional anaesthesia producing total pain relief (which was assumed to include block of these fibres) suggest that fast

conducting fibres may also be involved in the initial endocrine and metabolic response [14, 16]. The relative roles of somatosensory and sympathetic afferents has not been specifically addressed, because the available blocking techniques are inadequate and non-specific. However, somatosensory and sympathetic afferents are probably more important in releasing the response than are vagal afferents [14, 16]. The mechanism that sustains the response after injury has not been settled either, but functional changes within the peripheral and central nervous system leading to hypersensitivity in the response to nociceptive stimuli [41] may be of importance.

Although the neural stimulus is a major release mechanism for the surgical stress response, various humoral factors contribute, especially during major procedures and infection. The nature of the substances released at the site of trauma and from macrophages has been studied extensively during recent years, but a clear picture has not yet emerged. Of these, macrophage-derived peptides like interleukins and tumour necrosis factor seem to be most important in releasing various components of the stress response [16, 22, 25]. Although neural and humoral factors may in themselves be responsible for several aspects of the response, both inflammatory and endocrine (predominantly neurally mediated) factors must be activated to produce the full response.

MODIFYING EFFECT OF POSTOPERATIVE PAIN RELIEF

The various techniques available to provide pain relief in surgical patients and thereby eventually modify the surgical stress response are shown in figure 1.

Antagonists of peripheral mediators of pain

Injury leads to release of several endogenous algesic substances (histamine, serotonin, prostaglandins, leukotrienes, substance P, kinins *etc.*) which may facilitate the afferent nociceptive

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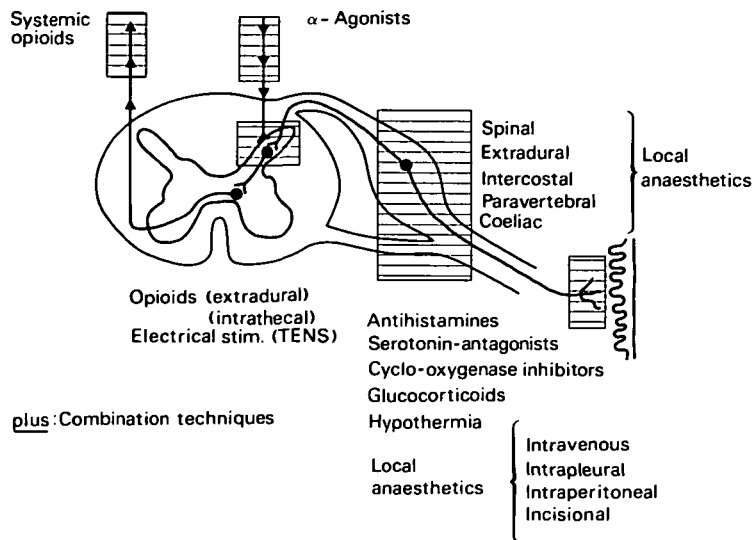
FIG. 1. Postoperative analgesic techniques which may alter the surgical stress response.

neural signal [27,45]. The analgesic effect of treatment with antihistamines or serotonin antagonists has not been settled, but is probably unimportant clinically. Furthermore, the metabolic effect of such an intervention is also negligible with regard to nitrogen turnover [38], temperature, acute phase and leucocytic responses [31].

The analgesic effect of cyclo-oxygenase inhibitors (indomethacin, ibuprofen etc.) is moderate [15,32], but the metabolic modification produced by these compounds is interesting because various inflammatory and cardiovascular responses may be attenuated. Thus after endotoxin, ibuprofen decreased pyrexia, tachycardia, increased metabolic rate and stress hormone release, while leucocytosis and acute phase protein changes were unaffected [29]. Other studies suggested that indomethacin could decrease postoperative nitrogen excretion [1], and pyrexia [32,33], while the effects on leucocytosis and acute phase proteins are probably negligible [32,33]. No systematic study has been performed to compare the modifying effect of various non-steroid anti-inflammatory agents on the surgical stress response. Neither is any clinical study available on pain relief produced by substance P antagonist administration or its eventual modification of the stress response.

The analgesia produced by hypothermia is well known in patients with burn injury, but this has not been utilized in surgical patients. Nevertheless, recent observations during hypothermic anaesthesia in experimental and clinical studies suggest that postoperative proteolysis may be attenuated [12]. Further studies, also addressing a possible modification of the inflammatory reaction, should be performed.

Glucocorticoids are potent inhibitors of all the metabolites of the arachidonic acid cascade as well as of several of the metabolically active macrophage-derived peptides. Although glucocorticoids may have potential side effects on wound healing and immunofunction, it is most interesting that a single, large preoperative dose of methylprednisolone led to improved pain relief and reduced need for extradural analgesics. In addition, the hyperthermic response was blocked and postoperative impairment in pulmonary function and fatigue decreased [Schulze and colleagues, in preparation]. Obviously, further studies are necessary, but it should be emphasized that glucocorticoids remain the only therapeutic agents with potential multi-inhibitory effects on the various components of the stress response.

Local anaesthetics may be applied directly to the nociceptors by a number of routes—i.v., intrapleural, i.p. and incisional—with varying degress of pain relief [15]. The effect of i.v. administration of local anaesthetics on postoperative pain is controversial, but probably does not significantly affect the postoperative stress

TABLE I. *Effect of extradural or intrathecal local anaesthetics on the endocrine-metabolic response to lower abdominal (gynaeco-logical) surgery, prostatectomy and procedures on the lower extremities. (Data from [14] and [16])*

Type of response	Inhibition or improvement	No important effect	No data

Pituitary	ACTH
	β-endorphin
	GH
	AVP
	TSH
	LH and FSH
	Prolactin
		T_3 and T_4
		Coagulation and
		  fibrinolysis
		Acute-phase proteins
		Water and sodium balance
			Gastrointestinal
			  peptides
			Testosterone
			Estradiol

Adrenal/Renal/ Nervous system	Cortisol Aldosterone Adrenaline Renin Noradrenaline		
Metabolic	Hyperglycemia and glucose tolerance Lipolysis Muscle amino acids Nitrogen balance Oxygen consumption Urinary potassium excretion		

response [3,4,43]. Intrapleural administration of bupivacaine may provide reasonable pain relief after cholecystectomy, kidney surgery, *etc.* [5], but the modifying effect on the stress response and pulmonary function is negligible [35]. I.p. instillation of large doses of bupivacaine has probably no analgesic effect [37,42], and the effect on the stress response is probably insignificant [30,37,42]. Incisional application of local anaesthetics may provide some pain relief [15,40], and preliminary studies of the minor injury produced by inguinal herniotomy suggest some modification of the stress response [40]. However, one should *not expect any important modification after major surgical injury.*

Regional anaesthesia

The effects of regional anaesthesia (extradural or intrathecal) on the endocrine metabolic response have been reviewed in detail recently [14, 16] and will only be summarized here (table I). Most studies in which a pronounced inhibitory effect has been observed involved operations such as hysterectomy, vaginal surgery, inguinal herniotomy, minor orthopaedic procedures, prostatectomy and hip replacement. In contrast to these studies of operations on the *lower* part of the body, more than 20 studies of extradural analgesia and the stress response to procedures in the upper abdomen and thorax have failed to show a similarly pronounced inhibitory effect. However,

a large variation has been found in the effect of regional anaesthesia on specific endocrine and metabolic changes after upper laparotomy. Unfortunately, interpretation is hindered by lack of control of the degree of sensory block, information on the amount of local anaesthetic administered, degree of pain relief *etc.* [14,16]. Despite these flaws in methodology, it seems valid to conclude that neural block, as produced by extradural analgesia, is less efficient in decreasing the surgical stress response to upper abdominal and thoracic procedures than in decreasing the response to lower body operations. Possible explanations for this are:

(1) Unblocked vagal afferents (but experimental and clinical studies suggest that these are unimportant [14]).

(2) Unblocked phrenic afferents. No information is available.

(3) Insufficient afferent and efferent sympathetic blockade. The addition of a coeliac plexus block has been shown to decrease the stress response further during extradural analgesia [14], and intraoperative splanchnic nerve block decreased several responses during gastrectomy [39]. However, the degree of sympathetic block during regional anaesthesia is under debate [8], and interpretation of the available studies therefore becomes difficult.

(4) Insufficient afferent somatic block. This is probably the main explanation for the lack of

important effects of extradural local anaesthetics on the stress response to upper abdominal surgery. Studies using evoked potentials have demonstrated that the afferent block is insufficient during thoracic extradural analgesia with conventional doses of bupivacaine [20]. This discrepancy in efficacy between a thoracic extradural and lumbar extradural block is easily understandable, since the amount of local anaesthetic administered during a thoracic extradural technique is less than 50 % of that used during a lumbar technique.

(5) The role of unblocked pelvic parasympathetic afferents is unknown.

(6) Potentiating humoral release mechanisms and increased heat loss may also contribute to the decreased effect of regional anaesthesia during major (and long) operations.

The effect of continuous intrathecal block during major procedures has not been studied, but such a block may be expected to be more efficient in decreasing the surgical stress response.

The effect of a pure somatic block with bilateral intercostal nerve block has been addressed in one study. There was no effect on the plasma cortisol response and only a slight inhibitory effect on the glucose response [24]. The effect of continuous paravertebral block on the surgical stress response to upper laparotomy has not been studied, but no major effect would be expected. The administration of 0.5 % bupivacaine 5 ml h^{-1} only provided a moderate degree of pain relief [2].

Thus studies published during the past 2 years have not provided much new information on the inhibitory effect of different regimens of central neural block on the surgical stress response, and further studies should focus on the effect of a more intense block by continuous intrathecal local anaesthetic administration or even combined extradural and intrathecal administration.

Spinal opioids

The effect of extradural or intrathecal opioid administration on the surgical stress response has been reviewed in detail [14,16]. There is general agreement that, despite reasonably good postoperative pain relief, these techniques have no major effect on the surgical stress response, although occasionally an inhibition of some stress parameters has been demonstrated. These studies have therefore emphasized that pain relief *per se* does not necessarily lead to a decrease in the surgical stress response.

Spinal α-adrenergic agonists

The intrathecal or extradural administration of α-adrenergic agonists has been shown experimentally to modulate spinal nociceptive processing [44] and some preliminary clinical studies have shown a small or moderate effect on postoperative pain, or a potentiating effect on local anaesthetic action [21,26]. In a study comparing extradural clonidine 150 μg with extradural morphine 4 mg after hysterectomy, an almost similar, moderate effect on postoperative pain was obtained, but only a slight modulatory effect on the surgical stress response [21]. No studies are available on the combined effect of extradural clonidine and morphine.

Systemic opioids

The moderate degree of pain relief produced after major procedures by conventional doses of intermittent or continuous opioids has only a negligible effect on the surgical stress response [14,16]. In a study using patient-controlled administration of fentanyl after cholecystectomy, no important effect could be demonstrated on plasma catecholamine or glucose response while postoperative cortisol concentrations were moderately diminished, despite very good pain relief [23]. Thus although there are few available data, optimal pain relief by systemic opioid administration cannot be expected to have an important modulatory effect on the surgical stress response. Very large doses of systemic opioids are necessary if a pronounced decrease in the stress response is required [14,17].

Combined analgesic regimens

Since total postoperative pain relief cannot be achieved by a single agent or method without major expenditure on equipment and surveillance systems, or without significant side effects, recent efforts have focused on improving pain relief by combinations of agents. Thus combining extradural local anaesthetics (0.5 % bupivacaine 5–8 ml h^{-1}) with morphine 0.5 mg h^{-1} provides total pain relief even after upper abdominal surgery [9,36]. However, this is at the cost of either lower extremity paralysis [9] or potential respiratory side effects [36]. The use of lower concentrations of local anaesthetics and morphine leads to less good pain relief [2,6,18,19].

Despite total pain relief after upper abdominal surgery with the combined technique, no sig-

nificant effect was observed on the surgical stress response or the impairment in pulmonary function [36]. Similarly, a combination of extradural bupivacaine with morphine and systemic indomethacin led to total pain relief after cholecystectomy [32], but no clinically significant effect on the impairment in pulmonary function, convalescence or the stress response. These studies, therefore, clearly indicate that total pain relief after major surgery does not necessarily lead to an important decrease in the surgical stress response. Again, this is probably the result of incomplete afferent neural block with several fast conducting neural pathways functioning, despite sufficient block of the slow conducting and pain mediating C-fibres [16,20].

Although a combination of analgesic regimens will have a major place in the future treatment of postoperative pain [15], measures to provide concomitant modification of humorally mediated responses and techniques to improve afferent neural block should be explored. In this context the role of the addition of high dose glucocorticoid therapy should be investigated further. The use of intense intraoperative block by a combination of continuous intrathecal and extradural block may be clinically advantageous (Kehlet and colleagues, unpublished observations), probably because of a decrease in the peripheral and central hypersensitivity to pain that occurs after injury [41].

CLINICAL IMPLICATIONS AND SUMMARY

The clinical implications of pain relief and the variable decrease this produces in the surgical stress response are largely unknown. This is because there are surprisingly few data and those that exist only demonstrate minimal beneficial clinical effects on postoperative morbidity parameters other than pain relief. Thus no controlled study has been performed to evaluate the clinical effect of pain relief by inhibition of endogenous algesic substances. This also applies to the systemic administration of opioids, even when sufficient pain relief is obtained by patient-controlled analgesia.

Postoperative pain relief by extradural opioid administration after conventional extradural block with local anaesthetics probably has no major effect on postoperative morbidity (or the stress response) after major abdominal procedures [10,11,28], although one study in high risk patients has suggested a major decrease in several complications [46]. In contrast, a vast amount of data exist from controlled studies comparing regional anaesthesia with local anaesthetics and general anaesthesia [34]. Cumulated data, mostly from procedures in the lower abdomen, orthopaedic or urological surgery, demonstrate a beneficial effect of regional anaesthesia on postoperative morbidity parameters such as blood loss, thromboembolic complications, pulmonary infection, gastrointestinal motility and postoperative hospital stay [34]. Interestingly, the most pronounced effect on morbidity occurred in procedures where regional anaesthesia with local anaesthetics also most effectively reduced the stress response. However, the important question whether this represents a causal relationship or an incidental event has not been finally answered.

To summarize, analgesia per se may not necessarily have an important effect on the surgical stress response, but is highly dependent on the technique used to provide postoperative pain relief. Furthermore, the effect of pain relief per se on postoperative morbidity is probably not a major one, unless the technique also concomitantly decreases the surgical stress response. Future studies should continue to describe the role of the various release mechanisms of the surgical stress response and to evaluate modifying techniques, in the hope of further decreasing postoperative morbidity.

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