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Overview

Effect of postoperative pain therapy on surgical outcome

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Abstract

Although efficient treatment of post-surgical pain is considered to be a pre-condition for a normal course of the post-surgical period, epidemiological and clinical research show that a significant number of patients still suffer intense pain after major surgery. Intense nociceptive somatic and visceral post-surgical pain has in the last ten years been considered the most important development of endocrine and neurohumoral disorders in the immediate post-surgical period, (the vital organ functional disorders, occurence of serious postoperative complications and prolonged hospitalisation.) The effects of successful perioperative analgesia on the course and outcome of surgical patients remains disputable, particularly because there is no consensus on the optimal procedure for specific pain therapy. The multimodal analgesia (defined as use of NSAIDs, COX –2 inhibitors or paracetamol in combination with i.v. opioid PCA) results in an opioid sparing effect. However, this opioid reduction does not consistently result in decreased opioid side effects. The overall negative outcome effects by i.v. opioids PCA correspond well with minor effects on postoperative dynamic pain, stress response and organ dysfunctions. At present the entire role of perioperative epidural technique on patient outcome is unclear. Also, the advantages of epidural analgesia have to be balanced against their risk and cost. The concept of multi-modal analgesia is an area of most importance and where future research efforts should focus on the combination of several techniques such as continuous peripheral nerve-blocks, continuous wound-infusion of local anaesthetics, NSAIDs/COX-2 inhibitors, paracetamol, α-2 agonists, ketamine, dextromethorphane, gabapentin/pregabalin, glucocorticoids etc.

INTRODUCTION

Intense nociceptive somatic and visceral post-surgical pain has in the last ten years been considered the most important development of endocrine and neurohumoral disorders in the immediate post-surgical period. That period is therefore characterized by increased catabolism, increased secretion of stress hormones, increased burdening of the cardiovascular system, lung function disorder, occurrence of hypercoagulability, fybrinolysis decline, immunological suppression, paralytic ileus and post-surgical nausea and vomiting. A disorder of glucose homeostasis and lipid and protein metabolism is the consequence of the above mentioned events *(1)*.

The intensity and duration of the stated disorders depend on the intensity of surgical injury, efficient treatment of post-surgical pain and the

application of a number of measures leading to fast rehabilitation of the patient.

The occurrence of central and peripheral sensitization and the development of a chronic pain syndrom are a particular problem of inadequate suppression of the dynamic and static pain in surgery performed on the thorax in the upper abdomen. The frequency of chronic post-surgical pain occurrence with significant influence on the patient's life quality is high and affects up to 40% of patients *(2)*.

There is scientific evidence which demonstrates that the immunological system, connected to the nervous system by cytokines and opioid pepsins, also participates in forming painful sensation.

During peripheral sensitization, immunological cells release pro-inflammatory cytokines TNF, IL6 and IL8, which lead to additional stimuli of the nociceptors and have the same analgesic effect *(3)*.

A number of clinical investigations in recent years have comfirmed better efficiency of the epidural analgesia in suppressing stress response and treating dynamic pain. Although so far there is no scientific evidence with regard to the favourable effect of epidural analgesia on the length of treatment, reduction of vitally threatening complications and the overall treatment results.

The main reason for this lies in insufficient understanding and use of principles of multimodal balanced analgesia and adjusting the medicines and doses to patients on an individual basis.

Apart from the above mentioned, special emphasis lies in the fact that the analgesic system must be optimally integrated in the function of complete procedures of post-surgical treatment and fast rehabilitation («fast track»), which implies applying minimum doses of the opioid analgesics *(4)*.

Types of analgesia

Acetaminophen and NSAID

Acetaminophen (paracetamol) is devoid of anti-inflammatory activity, but is an effective analgesia that has minimal side effects in clinical doses. This drug is the foundation of many analgesic regimes and should be used routinely as part of the basic treatment of acute pain.

Nonsteroidal anti-inflammatory drugs (NSAID) are also a standard treatment for postoperative pain. Drugs in this group are also very effective but suffer from the drawback of having numerous side-effect profiles. These agents may have significant central actions in addition to their recognized peripheral activity *(5)*. Acethaminophen and NSAIDs do not appear to have any effect upon the surgical stress response or upon organ dysfunction. Their main benefit appears to lie in providing moderate pain relief that will reduce opioid requirements by 20%–30% *(6)*.

Despite the well demonstrated opioid-sparing effects the effects of NSAIDs, specific COX – 2 inhibitors and paracetamol on postoperative outcome is debatable. Most previous studies included different types of surgery and only simple assesment of opioid related side effects, suchas PONV, duration of ileus, sedation etc. Recent studies, with a more detailed assessment of opioid related side effects suggest benefits in some procedures, such as knee surgery and cholecystecomy *(5, 6, 7)*. An improved outcome by opioid sparing combination would be in minor or moderate surgical procedures, where the stress responses and organ dysfunctions are slight.

On the basis of evidence from 4 meta analyses and one systematic review it appears that multimodal analgesia (defined as use of NSAIDs, COX – 2 inhibitors or paracetamol in combination with i.v. opioid PCA), results in an opioid sparing effect, although this opioid reduction does not consistently result in decreased opioid side effects. Based on current literature Rathmell *et al.* concluded that »Despite much rhetoric about combining multiple analgesic technique to provide multimodal analgesia, only limited evidence suggests that this approach will improve pain control or perioperative outcomes» *(8)*.

Opioids

Opioids are the main method for controlling acute postoperative pain. Morphine and its derivates and synthetic compounds are capable of very good pain relief. Nevertheless, there are still a significant number of patients who do not receive adequate pain relief. The reason for this includes poor understanding of the drugs by the patients and medical staff. Clinicians may fail to assess and compensate for interpatient variability, the length of action may be overestimated and the dosage prescribed inadequate.

Patient- controlled analgesia (PCA) has been compared to conventional methods in several studies *(9)*. Most studies favour PCA, and the general belief seems to be that patient satisfaction is improved.

The effect of PCA on postoperative outcome is debatable since morbidity and hospitalisation have not shown improvement in randomised trials *(10)*. The overall negative outcome effects by PCA correspond well with the minor effects on postoperative dynamic pain, stress response and organ dysfunction.

A meta analysis of 15 randomized trial controls (RTCs) with 787 patients showed greater analgesic efficacy with PCA without increase in side effects. However, the length of hospitalisation was not reduced *(11)*. A meta analysis of 32 RCTs and 2072 patients showed that PCA was associated with analgesia and reduced risk of pulmonary complications *(12)*.

Regional analgesic tehniques

Epidural anaesthesia and analgesia

As afferent neural stimuli and activation of the autonomic nervous system by pain may release endocrine metabolic responses, it has been hypothesised that a reduction in surgical stress response (endocrine, metabolic and inflammatory) will lead to a reduced incidence of

postoperative organ dysfunction and to an improved surgical outcome.

Regional continuous techniques with local anaesthetic may lead to a substantial reduction in the surgical stress response *(13)*.

Studies investigating lower extremity surgery have shown continuous lumbar epidural local anaesthetic techniques to be most effective, probably because of a more effective afferent blokade *(14)*.

A systematic overview of the available randomised controlled trials –141 with more than 10,000 patients over 30 years – showed that the use of epidural and spinal block resulted in a statistically and clinically significant reduction in morbidity and mortality after surgery. Furthermore, perioperative anaesthesia and analgesia decreased the risk of deep venous thrombosis, pulmonary embolism and pneumonia by 39%–55% *(15)*.

The effect of postoperative epidural analgesia on the incidence of myocardial ischemia or infarction in controlled trials has shown that the use of thoracic, but not lumbar, epidural analgesia significantly decreases the incidence of postoperative myocardial infarction *(16)*.

Kehlet 1997 has also provided evidence that continuous thoracic epidural local anaesthetic techniques reduce postoperative paralytic ileus. It is important to emphasise that location of the catheter tip and choice of analgesia drug can independently influence postoperative morbidity. A review of 9 randomized and observational studiesshowed that when the epidural catheter tip corresponds to the dermatomes of the surgical incision, there is an earlier return of gastrointestinal function *(17)*.

However, several recent large, randomized controlled trials have failed to show any major advantages of perioperative epidural technique *(18, 19)*.

In a study of 915 patients, identified as high risk patients undergoing major abdominal surgery, Rigg *et al.* concluded that the most adverse morbid outcomes are not reduced by use of combined epidural and general anaesthesia and postoperative epidural analgesia, but that the improvement in analgesia, reduction in respiratory failure, and low risk of serious adverse consequences suggest that many high-risk patients undergoing major intra-abdominal surgery will receive substantial benefit from combined general and epidural anaesthesia intraoperatively with continuous postoperative epidural analgesia.

Epidural opioid techniques are less effective on the stress response, and are comparable with systemic opioid techniques and the use of NSAIDs. High – dose opioid anaesthesia suppresses intra- but not postoperative stress responses *(13)*.

On the basis of evidence from 7 meta-analyses and 3 large randomized trials the investigators concluded that there is a beneficial effect of epidural anaesthesia and analgesia in terms of some measures of cardiac and pulmonary function and evidence of superior analgesic efficacy, although a reduction in the duration of hospitalisation was not observed.

At present the entire role of perioperative epidural technique on patient outcome is unclear.

In addition, the advantages of epidural analgesia have to be balanced against their risk and cost.

The regional catheter techniques

The use of regional perineural anaesthetic techniques for any suitable surgery may offer many advantages. Patients can be discharged early with effective pain control, the requirement for opioids will be reduced, and the side effects associated with the use of these agents such as nausea, vomiting, sedation and pruritus will be reduced *(20)*. There is even evidence that long-term outcome can be influenced positively by the use of regional anaesthetic technique for a short time postoperatively *(21)*. However, there are no randomized control studies on the effects of these techniques on major morbidity and mortality. Also the general applicability of perineural catheter technigues is uncertain because of the required level of technical skill and infrastructure to manage the catheters.

In a recent controlled comparison of the perfusion of local anaesthetic through an incisional catheter and more invasive epidural technique the same analgesic effect was demonstrated. A meta- analysis of 45 randomized controlled studies with 203 patients of continuous wound catheter technique for postoperative analgesia showed reduced pain scores (32%) and opioid consumption (25%), decreased risk of postoperative nausea and vomiting and a 30% increase in patient satisfaction in 5 studies of abdominal surgery, 13 studies of cardiothoracic surgery, 6 studies of gynaecologic surgery, and 12 studies of orthopaedic surgery *(22)*. For a limited number of patients there was a reduction in hospitalization of one day *(23)*.

Multimodal fast-track rehabilitation and outcome

The concept of multi-modal analgesia is an area of most importance, where future research efforts should focus on a combination of several techniques, such as continuous peripheral nerve-blocks, continuous wound-infusion of local anaesthetics, NSAIDs/COX-2 inhibitors, paracetamol, α-2 agonists, ketamine, dextromethorphane, gabapentin/pregabalin , glucocorticoids etc. Each medication and technique component has already been demonstrated to provide analgesia and opioid sparing. However, multiple combinations to enhance analgesia, reduce stress response and dynamic pain and prevent chronic pain are required *(23, 24, 25, 26)*.

The concept of a multimodal postoperative rehabilitation programme in which pain relief is a key factor is a major task for the future.

The main goal of the our research project is to define the value and meaning of the concept of multimodal balanced analgesia in regard to:

Efficiency of removing postoperative pain.

Reducing the level of specific markers of endocrinic, metabolic and stress re psponse.

Modulation of immunological response.

Frequency of occurrence of postoperative complications.

Prolonged morbidity of patients.

Length of hospitalization.

Treatment outcome.

Frequency of chronicostoperative pain development.

By investigating and comparing two basic modalities of postoperative analgesia in our project, i.e.

1. patient-controlled continuous epidural application of medication, and
2. patient-controlled continuous intravenous application of medication

on a large number of patients subjected to major thoracic and abdomenal operations, and patients undergoing major urological operative procedures two homogenous and comparative groups were classified, and the advantages and disadvantages of individual modalities will be identified with regard to the above mentioned research goals.

Specific research goals in the project are:

In the group of thoracosurgical patients, to examine the effect of thoracic epidural analgesia on the function of the lungs, the patient's oxygenation, frequency of occurrence of atelectasis, frequency of occurrence of inflammation complications.

To examine the effects of thoracic epidural analgesia on cardiac function, particularly on the occurrence of arrhythmia and coronary ischemia episodes.

To examine the influence and importance of thoracic epidural analgesia and the effect of opiates and opioids in an analgesic mixture on gastrointestinal motility.

To examine the importance and influence of individual analgesia modalities on the perseverance of normoglycemia in the immediate post-surgical period.

To examine the importance and influence of opiate and opioid saving concept on the course of fast track concept of surgical treatment in abdominal surgery

To examine possible advantages and disadvantages of analgesia modalities controlled by patients compared to the usual continuous programme techniques.

To examine the specific factors that could influence the development of chronic pain syndrome.

To examine the specifics of physical and emotional experience of pain, optimal manner of evaluating pain intensity and adjustment of dose for senior patients.

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