

Non-analgesic effects of thoracic epidural anesthesia

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ÖZET

Torakal epidural anestezinin non-analjezik etkileri

Torakal epidural anestezi postoperatif ağrı kontrolünde etkin bir yöntemdir; ayrıca lokal anesteziklerin epidural mesafeye verilmesi ile segmenter sempatik blok meydana gelir. Bu geçici sempatik blokajın kardiyovasküler, solunum ve diğer sistemler üzerine etkileri, postoperatif morbidite ve mortalite üzerine etkileri nedeniyle, araştırılmaya değer gözükmemektedir. Torakal epidural anestezi kalp, akciğer ve büyük batın cerrahilerinde başarı ile kullanılmaktadır. Hareket halinde de etkinliği süren bir analjezi ile birlikte erken mobilizasyon, stres yanıtı baskılanması, erken ekstübasyon ve akciğere ait komplikasyonlarda azalma ve bağırsak işlevinde hızlı derlenme sağlamaktadır. Torakal sempatik blokun en fazla yararlı olacağı düşünülen yer kalp cerrahisidir, ancak yayınlarda morbidite ve mortalite arasında fark saptanmamıştır. Ağrı kontrolündeki başarısına rağmen, torakal epidural anestezinin meta-analizlerde hasta prognozu açısından etkinliği gösterilememiştir. Öte yandan, farklı organ sistemleri üzerine yapılan yakın tarihli çalışmalar halen olumlu etkilerinden söz etmektedir. Torakal epidural anestezi yakın gelecekte daha fazla kullanım alanı bulacak ve tartışmalarla birlikte, üzerinde daha çok çalışılacak gibi durmaktadır.

SUMMARY

Thoracic epidural anaesthesia is selected usually to provide adequate postoperative analgesia; however with administration of local anaesthetics to epidural space selective sympatolysis ensues. The effects of this transient sympathectomy on cardiovascular, respiratory and other systems deserve certainly some interest as it may influence postoperative morbidity or mortality. Thoracic epidural anaesthesia has successfully been used in cardiac, thoracic and major abdominal surgery. It provides dynamic analgesia, rapid mobilization, blunted stress response, early extubation with reduced pulmonary complications and also rapid recovery of bowel function. In cardiac surgery where thoracic sympathetic blockade is expected to be most useful, there is no difference in morbidity and mortality. Despite the superior quality of pain control, the beneficial aspect of thoracic epidural anaesthesia is not reflected on outcome in meta-analysis. Recent papers has still demonstrated positive effects on each system. So thoracic epidural anaesthesia is increasingly used and it seems that it will be discussed more in near future.

Key words: Thoracic epidural, epidural analgesia, stress response, pulmonary function, outcome

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Introduction

Thoracic epidural anaesthesia is selected usually to provide adequate postoperative analgesia; however with administration of local anaesthetics to epidural space selective sympatholysis ensues. The effects of this transient sympathectomy on cardiovascular, respiratory and other systems deserve certainly some interest as it may influence postoperative morbidity or mortality.

Thoracic epidural anaesthesia has successfully been used in cardiac, thoracic and major abdominal surgery. It provides dynamic analgesia, rapid mobilization, blunted stress response, early extubation with reduced pulmonary complications and also rapid recovery of bowel function. In cardiac surgery where thoracic sympathetic blockade is expected to be most useful, there is no difference in morbidity and mortality.

Despite the superior quality of pain, the beneficial aspect of thoracic epidural anaesthesia is not reflected on outcome in meta-analysis. Recent papers has still demonstrated positive effects on each system. So thoracic epidural anaesthesia is increasingly used and it seems that it will be discussed more in near future.

Though thoracic epidural anaesthesia (TEA) had been first reported in 1950's by Crawford et al. (Crawford 1957); it had been more commonly used after Griffith's study in thoracic surgery at 1970's (Griffith 1975). Local anaesthetic use in thoracic epidural space provides excellent analgesia for thoracic and abdominal surgery and also causes high sympathetic blockade which deserves special interest. Sympathetic block by thoracic epidural anaesthesia affects various organ systems such as heart, lungs, upper gastrointestinal organs, kidneys and adrenals. This transient sympathectomy displays major role on reducing neurohumoral stress response. Blunting stress response is usually with decreased incidence of cardiac and pulmonary complications in high risk patients. Note that thoracic sympathetic blockade is established with epidural use of local anaesthetics; utilization of opioids or other drugs such as ketamine via epidural route can not procure the medical sympathectomy. In this lecture TEA means administration of local anaesthetic to thoracic epidural space.

In this review we will try to discuss about effects of thoracic sympathetic blockade on each organ systems, focusing specially on cardiovascular and respiratory physiology.

General Anatomy and Physiology

The preganglionic fibers of sympathetic nervous system originate in the intermediolateral gray column of the 12 thoracic and the first three lumbar segments of the spinal cord. The myelinated axons of these nerve cells leave the spinal cord with motor fibers, and then enter one of paravertebral ganglia. As the preganglionic fibers are composed of myelinated and thin fibers, they are more susceptible to local anaesthetics than fibers transmitting sensorial impulses.

The first four or five thoracic spinal segments generate preganglionic fibers to form superior cervical, middle cervical and stellate ganglia which provide sympathetic innervation head, neck, upper extremities, heart and lungs. Afferent pain fibers also travel with these nerves for chest, neck or upper extremity pain with myocardial ischemia. Activation of sympathetic nervous system produces a diffused physiologic response (mass reflex) rather than discrete effects. One preganglionic fiber influences a larger number of postganglionic neurons dispersed to many organs. The sympathetic nervous system response is aggravated by hormonal release of epinephrine. TEA produces a sympathetic blockade at least at same extent to sensorial block.

Cardiac and Circulatory Effects

Sympathetic blockade by high thoracic epidural anaesthesia has the potential for blocking cardiac afferent and efferent fibers, originating from the first to fourth thoracic levels. The perception of cardiac pain and angina is mediated via sympathetic afferent nerves. Sympathetic stimulation results in an increase in heart rate, cardiac output and systemic vascular resistance. Excessive sympathetic activation by surgical stress has been demonstrated to increase myocardial oxygen demand, while inducing coronary arterial vasoconstriction. Clinical features of myocardial ischemia such as ST changes, angina and dysrhythmias may be seen in whole perioperative period. Postoperative hypercoagulable state, another component of stress response which will be discussed later, contributes furthermore to coronary artery thrombosis. However TEA with local anaesthetic blunts these adverse effects of neurohumoral response by blocking selectively cardiac sympathetic fibers.

Coronary blood flow after TEA was investigated in patients with ischemic heart disease (Blomberg

1990). Endocardial to epicardial blood flow was improved, so that regional distribution of perfusion is optimized. TEA also decreases major component of myocardial oxygen demand, as it decreases heart rate. In animal models TEA reduced infarct size during coronary occlusion (Groban 1999).

Moreover TEA has been used in the treatment of refractory angina. In a study by Olausson et al., patients with thoracic epidural anaesthesia had both a lower total number of ischaemic periods and a shorter duration of ischaemic periods, as measured by Holter electrocardiogram (ECG), than the standard intravenous treatment group (Olausson 1997). TEA has gained interest in cardiac surgery as it offers improved analgesia, blunted stress response, optimized coronary blood flow, reduced myocardial oxygen demand, decreased pulmonary complications and faster recovery. Recent studies in open heart surgery- and specially in coronary bypass grafting (CABG)-report improved myocardial structure and left ventricular function after CABG, with lower troponin T and I levels in patients with high TEA is combined to general anesthesia (Berendes 2003, Loick 1999).

Liu et al. in their excellent meta-analysis investigated effects of TEA on outcome in CABG (Liu 2004). They reported early extubation, decreased incidence of postoperative dysrhythmias and significantly decreased pulmonary complications with TEA-general anesthesia combination. However there was no significance on mortality, nor on myocardial infarction (MI); they thought larger randomized-controlled studies were required in order to detect mortality or MI and to completely assess potential benefits of TEA.

Atrial fibrillation and tachycardia are common after cardiac and thoracic surgery. As local anaesthetic use in thoracic epidural level reduces overall sympathetic tone and blocks cardiac accelerator fibers, risk of dysrhythmia is decreased with general anesthesia-TEA combination (Berendes 2003). Thus significantly reduced incidence of supraventricular tachycardias after both cardiac surgery and pulmonary resection (Liu 2004, Oka 2001).

Major concern in widespread use of TEA was severe hypotension due to extensive vasodilation with subsequent functional hypovolemia. Intravascular volume resuscitation and vasopressors can be preferred in the treatment of TEA-induced hypotension. On the other hand fluid

overload must be avoided in pulmonary resection surgery such as pneumonectomy. Casalino used TEA in CABG surgery, hypotension incidence was less than 20 % with 0.5 % bupivacaine and was easily corrected with low dose vasopressor. He stated that female sex, use of calcium channel blockers and body mass index were associated risk factors (Casalino 2006). Neal investigated effects of TEA on outcome in esophagus surgery and concluded that utilization of vasopressor was not needed despite of fluid restriction (Neal 2003).

In conclusion, the selective blockade of cardiac sympathetic innervation by TEA may improve the balance of oxygen supply and demand in the ischaemic myocardium with heart rate control, dilation of stenotic coronary arteries and also improving left ventricular function.

Pulmonary Effects

Reduction in functional residual capacity (FRC) after major abdominal and thoracic surgery is a well known change with general anaesthesia, and lasting for a week. Adequate analgesia is not only contributing factor to prevent respiratory complications, other factors like preservation of diaphragmatic function, early extubation, reducing risk of atelectasis and pneumonia, early mobilization must be considered.

Impairment of pulmonary function is most often investigated in thoracic surgery. Cranial movement of diaphragm, alterations of the shape of the thorax, development of atelectasis and redistribution of intrathoracic blood volume are accepted mechanisms of postoperative respiratory dysfunction. One lung ventilation (OLV) during surgery may potentially worsen clinical course.

The role of epidural anaesthesia on diaphragmatic function is explained by blocking inhibitory reflexes; thoracic epidural block causes also increased FRC due to caudad motion of diaphragm (Warner 1996). Use of iv or epidural opioids has no effect on diaphragm function. In addition, an increase in chest wall tone and decreased chest wall compliance secondary to spinal reflex arc and pain are both blunted by TEA (Moraca 2003).

In large meta-analysis with unhomogenous surgery population, adding epidural anesthesia to general anaesthesia results always in a decreased extubation time (Guay 2006, Moraca 2003, Ballantyne 1998) and usually reduced pulmonary complications (Guay 2006, Moraca 2003). Another

meta-analysis including only CABG patients reported faster extubation and less respiratory complication with thoracic epidural blockade (Liu 2004).

TEA may change lung volumes owing to its effect on intrathoracic blood volume. The filling of pulmonary vessels is passive and is not influenced by sympathetic efferents. Experimental and clinical studies have demonstrated an increased FRC and decreased intrathoracic blood volume (Hachenberg 1999). The experimental studies investigating effects of TEA on hypoxic pulmonary vasoconstriction have contradictory results (Kozian 2005). Prospective clinical observation demonstrated that TEA-general anaesthesia combination did not affect arterial oxygenation and shunt fraction during OLV (Kozian 2005). Corresponding to previous clinical reports, we did not observe an increased shunt in patients with TEA comparing to general anaesthesia group during OLV (Ozcan 2007).

Some anaesthesiologists worry about motor blockade of intercostal muscles after TEA in patients with limited pulmonary reserve. A decline in vital capacity (VC) can be seen after TEA in the presence of extensive epidural blockade with the use of higher concentration of local anaesthetic. Looking at overall lung function, concerns about ventilation/perfusion mismatch with TEA has still not been proven (Groeben 2006). TEA with sensory blockade up to midcervical level causes significant reduction in VC and forced expiratory volume. However thoracic epidural block with relatively low concentration of local anaesthetic has been found safe even in patients with severe chronic obstructive pulmonary disease (Gruber 2001). In subjects with bronchial hyperreactivity who constitutes another risk population for high thoracic epidural blockade, TEA seemed to attenuate bronchial reactivity rather than to increase it, probably due to systemic effects of local anaesthetics (Groeben 2006).

Effects on Stress Response

The stress response to surgery initiates a cascade of physiologic and metabolic events. This response begins with initiation of general anaesthesia and lasts for days postoperatively. The release of cytokines and neuroendocrine mediators, catabolic state, immunocompromise, fever, increased oxygen consumption, hypermetabolism, altered carbohydrate metabolism are well known components of this survival process.

However long-lasting and inadequate perioperative stress may easily increase postoperative cardiac, vascular and infectious morbidities. The modulation of neurohumoral response is essential in high risk patients to decrease these morbidities (Waurick 2005).

Since the major initiation of the endocrine activation comes from afferent stimuli, blocking these impulses may modify endocrine responses. Single-dose neural blockade, applied as either intraoperative epidural or spinal anaesthesia has only a transient stress reducing effect without prolonged endocrine or metabolic effects. Thus it is preferable to continue epidural blockade for 24-48 hours postoperatively (Holte 2002).

Generally lumbar epidural block is sufficient in lower body procedures to blunt stress response. TEA is needed in abdominal surgery and may still be partially effective in upper body procedures in the presence of contribution of other reflexes (usually phrenic nerve) or concomitant hypothalamic stimulation (Segawa 1996). Furthermore appropriate blockade is only achieved by local anaesthetics.

TEA improved successfully tissue perfusion and subcutaneous oxygen tension even outside of the sympathetic block in abdominal surgery patients (Kabon 2003, Buggy 2002). TEA has also been shown to attenuate stress response by a suppressive effect on whole-body lipolysis after colorectal surgery (Lattermann 2002). Maximal catecholamine and cortisol levels were found to be lower in patients with neuroaxial blockade in a very recent meta-analysis; maximal blood glucose levels were similarly well controlled with epidural block indicating successful modulation of neurohumoral response (Ballantyne 1998).

Coagulation

Thromboembolic events in the postoperative period have been linked to the hypercoagulable state initiated during surgery. The primary contributors to this pro-thrombotic state are a reduction in venous blood flow secondary to positive pressure ventilation, neuromuscular blockade, and activation of the sympathetic system. Effects of sympathetic stimulation on coagulation has been demonstrated many years ago; it produces significant increases in factor VIII, von Willebrand factor; and also inhibits fibrinolysis through PAI-1, decreases antithrombin III and initiates platelet aggregation (Bredbacka 1986). Epidural anaesthe-

sia attenuates the hypercoagulable perioperative state and decreases thromboembolic complications by blunting the neurohormonal response and improving lower extremity blood flow (Modig 1983). In addition, the systemic absorption of local anaesthetics, improved pain control, and early mobilization likely decrease the incidence of clot formation. Blunting the sympathetic response is associated with demonstrable effects on the coagulation cascade, with normalization of both factor VIII and von Willebrand factor and also with decreases in PAI-1, and an increased antithrombin III (Moracca 2003).

This hypercoagulable process has more severe risk for patients with coronary artery disease. The normal arterial smooth muscle responds to sympathetic stimulation with vasodilatation, however atherosclerotic coronary bed responds with vasoconstriction. The loss of endothelial cell integrity is important in aetiology, similarly loss of vasodilatory capacity and abnormal release of mediators have their role in pathogenesis. The release of serotonin originating from platelet activation sites (at high turbulence areas), is also associated with atherosclerotic coronary bed. The successful ablation of sympathetic constriction is accomplished mostly by TEA (Williams 1999).

In a recent meta-analysis with very large population, neuroaxial blockade was found to improve patients survival (Rodgers 2000). Altered coagulation was accepted as one of major benefits of central neural blocks. This led to reduced deep venous thrombosis, pulmonary embolism, myocardial infarction. Kehlet stated in his large meta-analysis significant decrease in thromboembolic complications in lower abdominal and lower extremity surgeries with epidural analgesia-general anaesthesia combination. Interestingly in lower abdominal surgery neuraxial analgesia failed to decrease incidence of thromboembolic events. TEA had less significant effect on lower extremity and deep pelvis blood flow, local anaesthetics were not used in some of studies and early mobilization –one of major advantage of epidural analgesia- was not obtained (Kehlet 2001).

Adding central neural blockade to general anaesthesia is an attractive alternative in patients undergoing major operations -and specially for vascular surgery- as it provides improvement in venous blood flow, attenuation of the sympathetic response to surgery, anticoagulant properties of local anaesthetics, early mobilisation and ability to lower blood pressure values.

Gastrointestinal Function

In high-risk surgical patients, gastrointestinal hypoperfusion is associated with increased morbidity and mortality. Hypoperfusion causes a redirection of blood flow away from the splanchnic organs because of increased sympathetic activity or impaired blood flow distribution within the microvascular networks. Splanchnic hypoperfusion often leads to increased mucosal permeability, endotoxaemia and multiple organ failure. To achieve splanchnic sympathetic blockade high lumbar or thoracic epidural anesthesia is needed.

In numerous recent studies, the epidural infusion of regional anaesthetic agents during and after major surgery has been shown to protect the gut from decreased microvascular perfusion and to decrease the time to the return of gastrointestinal function (Neal 2003, Carli 2002).

The time to the first bowel movement after surgery was significantly shortened by using TEA combined with general anaesthesia (Kozian 2005, Moracca 2003). The main mechanism seems to be a block of the nociceptive afferent fibres and the thoracolumbar sympathetic efferent fibres, with unopposed parasympathetic efferent fibres. TEA can enhance bowel motility not only by producing pain relief and lessening the systemic stress response, but also by creating a sympathectomy, resulting in unopposed parasympathetic innervations to the gut. Sympathetic stimulation, pain, opioids, nitrous oxide, inhalation anaesthetics, and increased endogenous catecholamines all contribute to postoperative ileus, and all are blunted or blocked in patients treated with perioperative TEA.

To optimize recovery of gastrointestinal system the epidural must be placed and activated prior to the surgical stress and nociceptive afferent stimulation, the epidural catheter should include the T5-L2 dermatomes, and the solution administered into the catheter should include local anaesthetics to affect a sympathetic blockade of the gut, the epidural local anaesthetics need to be administered postoperatively until bowel function returns (usually 2-3 days) to achieve the full benefits of the technique (Moracca 2003).

Immune Response

Immunocompromise after surgery is a well known and frequently seen in practice as increased tendency to infection or progression of malignancies (de Leon-Casasola 1996). The aetiology has still

not been elucidated but stress response with inhalation anaesthetics and iv opioids have been considered to have major part in the process. Reports about postoperative immunity investigated usually lymphocyte function or cytokine release. Recent papers declared that comparing with iv opioid neuroaxial block was a better alternative to preserve lymphocyte activity and to block to some extent an increase in cytokines such as interleukins even in trauma patients (Volk 2004, Beilin 2003, Moon 1999). Authors stated in consensus that effects of central blocks on immune system could be explained by successfully blunted surgical stress response.

It is certainly difficult to assess postoperative immune system function, but few reports are promising and deserve more interest for anesthesiologists in near future.

Outcome

TEA is considered to be gold standard after major thoracic surgery and recommended for major abdominal procedures. The synergistic effect of local anaesthetic and opioids combination is well known and it provides better analgesia during activity. The use of combination may reduce the dose related adverse effects of either agent alone. Epidural anaesthesia is particularly effective at providing dynamic analgesia, early mobilization and rapid functional recovery. The probable benefits of TEA include the attenuation of cardiac complications, an earlier return of gastrointestinal function and decreased respiratory dysfunction with early extubation.

Although faster extubation with reduced pulmonary function, modulation of stress response with control of hypercoagulable state, decreased incidence of dysrhythmias are common in recent metaanalysis, significant decrease in mortality and hospital stay has still not shown (Guay 2006, Liu 2004). Waurick and Liu pretended larger meta-analysis were needed to detect any major morbidity and to comment significant benefits (Waurick 2005, Liu 2004). The standardization of studies in terms of timing of blockade, drugs applied, endpoints, etc. It is essential to use adequate dose or level for appropriate surgery and patient, to define "pre-emptive" analgesia, to decide when to stop postoperative analgesia and to select a multimodal strategy according to patient.

Conclusion

In a very recent metaanalysis, Liu and Wu reported that -in contrast to common considerations and also to the findings reviewed above- there was no current evidence that any method of postoperative analgesia, including the epidural analgesia, has any clinically significant beneficial effect on postoperative complications (Liu 2007). They concluded, however, that this was primarily due to typically insufficient subject numbers to detect any differences, or due to a "proven insufficiency" of any analgesic method on postoperative complications. As a matter of fact, anesthesiologists still tend to focus "only" on the effect on pain control of different analgesic methods, which leads to a much less number of studies investigating the "other" beneficial effects of analgesia. In this manner, TEA is a method which has been examined relatively more, compared to other analgesic methods. As reviewed in this lecture, TEA actually serves much more than "just pain control". Some of these non-analgesic effects are analgesia-associated, as some are totally independent of analgesia. Most of the findings have been reported with the application of pure local anaesthetics or their combination with other drugs (opioids, alpha agonist, etc). Whether applications containing no local anaesthetic have also similar non-analgesic beneficial effects, needs also to be investigated.

TEA (with local anesthetics), performed alone or combined with general anesthesia, is not only the method of choice for postoperative analgesia in many operations, it also obtains a large number of other, non-analgesic advantageous effects.

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