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Review / Derleme

Neuraxial Regional Anaesthesia in Patients with Active Infection and Sepsis: A Clinical Narrative Review

Aktif Enfeksiyon ve Sepsisli Hastalarda Nöraksiyal Rejyonal Anestezi: Klinik Derleme

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Abstract / Öz

Infection is considered to be a relative contraindication for regional anaesthesia. However, there is a paucity of articles addressing the topic of regional anaesthesia in patients with an active infectious process. Recent publications show a low incidence of infection (0.007% to 0.6%) of the central nervous system after neuraxial punctures in patients at risk of, or with ongoing bacteraemia, and a low incidence of infection after performing regional anaesthesia techniques in immunosuppressed patients, or patients with an actual infection. Therefore, some authors conclude that it seems that there is little justification to set strict contraindications regarding this indication and that the risk–benefit ratio should prevail. In addition, a low incidence of meningitis or abscesses after the lumbar puncture has been observed in patients with unsuspected and ongoing bacteraemia, or who were at risk of bacteraemia, when antibiotic therapy has been previously started. For viral infections, regional techniques seem to be safe, being applied in patients with HIV infection. The only established absolute contraindication for any type of regional anaesthesia technique is the infection at the puncture site. Debate persists if a neuraxial anaesthesia technique is to be performed in the course of sepsis with the origin away from the puncture site. In case of thoracic epidural anaesthesia and analgesia, experimental and clinical studies highlight their potential benefits in the systemic inflammatory response syndromes and founded sepsis, both in surgical and non-surgical patients. Finally, the anti-inflammatory and anti-infective effects of local anaesthetics and the basis of excessive inflammatory response are described, as the latter might be involved, in part, in the clinical outcomes.

Keywords: Regional anaesthesia, neuraxial anaesthesia, epidural anaesthesia, sepsis, intensive care

Enfeksiyon rejyonal anestezi için ilgili bir kontraendikasyon olarak kabul edilmektedir. Ancak, aktif bir enfeksiyöz süreci olan hastalarda rejyonal anestezi konusuna değinen az sayıda çalışma bulunmaktadır. Son yıllarda yayınlanan çalışmalar, risk altındaki veya devam eden bakteriyemisi olan hastalarda nöraksiyal ponksiyon sonrasında santral sinir sistemi enfeksiyonu insidansının düşük (%0,007-%0,6) olduğunu göstermektedir. Aynı şekilde, immünsüprese hastalarda veya mevcut enfeksiyonu olan hastalarda da, rejyonal anestezi tekniklerinin uygulanması sonrasında enfeksiyon insidansı düşük bulunmuştur. Bu nedenle bazı yazarlar, bu endikasyonla ilgili katı kontraendikasyonlar oluşturulması için az sayıda gerekçe olduğu ve risk-yarar oranının dikkate alınması gerektiği çıkarımını yapmışlardır. Ek olarak, şüpheli ve devam eden bakteriyemisi olan ya da bakteriyemi riski olan hastalarda antibiyotik tedavisi daha önceden başlatıldığında, lomber ponksiyon sonrasında menenjit veya apse insidansı düşük olarak gözlenmiştir. Viral enfeksiyonlar için, HIV enfeksiyonu olan hastalara uygulanan rejyonal teknikler güvenli görünmektedir. Herhangi bir rejyonal anestezi tekniği için tek kesin kontraindikasyon ponksiyon yerindeki enfeksiyondur. Ponksiyon yeri dışındaki bir orijinden kaynaklanan sepsis vakasında, nöroaksiyal anestezi tekniklerinin uygulanması konusunda tartışmalar devam etmektedir. Deneysel ve klinik çalışmalar, sistemik inflamatuvar yanıt sendromlarında ve sepsiste, hem cerrahi hem de cerrahi olmayan hastalarda, torasik epidural anestezi ve analjezinin potansiyel faydalarını vurgulamaktadırlar. Son olarak, lokal anesteziklerin anti-inflamatuvar ve anti-infektif etkileri ve klinik sonuçlarda da etkili olabilecek olan aşırı inflamatuvar yanıtın temeli de tanımlanmaktadır.

Anahtar Sözcükler: Rejyonal anestezi, nöraksiyal anestezi, epidural anestezi, sepsis, yoğun bakım

Introduction

Severe sepsis accounts for 2.26 cases per 100 hospital admissions and 3 cases per 1.000 inhabitants in developed countries, requiring a high dependency unit care (including intensive care) for more than half of patients, thus leading to growing health care costs (1). Overall, mortality reaches 28% (1).

There is a paucity of studies addressing the use of regional anaesthesia in patients with an active infectious process, including sepsis. However, two indirect aspects might support the choice of neuraxial regional anaesthesia (NRA) in these patients.

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First, there is evidence that NRA reduces the incidence of postoperative infection, both in single organs or systems (2). In addition, the surgical trauma patients and patients who have experienced moderate or severe trauma and who need surgery are at risk of suffering systemic inflammatory response syndrome (SIRS), but they subsequently showed a decreased response to perioperative infection; these patients could benefit from NRA.

Infection may be a relative contraindication for NRA and regional anaesthetic techniques (3, 4). However, most of published articles refer to specific populations, such as obstetric patients with chorioamnionitis suspicion or patients with prosthetic infections (3, 5). Recent publications show a low incidence (0.007% to 0.6%) of infection of the central nervous system (CNS) after neuraxial puncture in patients at risk of or with ongoing bacteraemia (3, 5). Similarly, in patients with preexisting infection or immunosuppression, a low incidence of infections following regional anaesthetic techniques has been reported. Therefore, it is generally concluded that it is hard to find strict contraindications for these procedures and that the risk-benefit ratio should prevail. Conceptually, additional potential risks of immunosuppression or infection should be considered, such as the hemodynamic status, the nature of the infection and dissemination possibilities from the main source, the planned technique and approach of regional anaesthesia (peripheral nerve blocks, single-dose or continuous NRA techniques), and the distance from the puncture site in case of localised infections. Moreover, none of the guidelines and recommendations on diagnosis and treatment of septic patients refers to regional anaesthesia and/or its level of recommendation.

In this article, we review the published literature on the use and possible indications of NRA in patients with established infection and sepsis.

Literature Search Criteria

The PubMed database was reviewed. The search criteria were the following: [sepsis] OR [septic] AND [epidural anaesthesia OR spinal anaesthesia]; [Infection] AND [regional anaesthesia OR local anaesthesia OR epidural anaesthesia OR spinal anaesthesia]; [local anaesthetics] AND [infection OR sepsis OR septic]; all in Title/Abstract; date of publication 2005-July 2016, including articles published in English, Spanish, French, German, Portuguese and Italian. References of retrieved articles were manually reviewed. Clinical practice guidelines and/or recommendations of anaesthesia and critical care societies related to sepsis, as well as infectious complications or infection prevention in relation to regional anaesthetic procedures, were also scrutinised (Annex 1).

The studies on single-dose or continuous peripheral nerve blocks and paediatric neuraxial blocks were excluded. Infections related to neuraxial puncture were also not included.

NRA in Immunosuppressed Patients

The immunosuppression status may be due to immunosuppressive therapy that induces a reduction in leukocyte populations, with phagocytic dysfunction and an impaired production of cytokines; acquired viral immunodeficiencies, with a significant prevalence of opportunistic infections despite concomitant antiretroviral therapy (high-activity antiretroviral therapy, HAART); or other conditions frequently found in clinical practice, such as diabetes mellitus, alcohol or drug abuse, antibiotic therapy, cancer and trauma (6).

After neuraxial techniques, several case reports of epidural abscesses following administration of epidural steroids for radicular pain treatment have been published. This topic will not be addressed here.

On the other hand, the organ transplantation patients are not considered to be at an increased risk of infectious complications during regional anaesthetic procedures (6).

Regional Anaesthesia in Patients with Active Infection

Infections Due to Bacteria

The infection can be localised (with local signs of inflammation or infection) or disseminated (systemic infection). A prerequisite for the development of infectious complications of regional anaesthesia is the existence of bacterial colonies growing with or without specific signs of inflammation at the puncture site (6). The prevalence of colonisation in this setting varies between 16.7% and 57% (7) of the procedures.

In the case of systemic infection, the patient can show fever, leukocytosis, elevated acute phase reactants or elevated sepsis risk markers, but bacteraemia may occur without clinical symptoms. From reports assessing the incidence of CNS infections following neuraxial techniques in patients with bacteraemia, three etiopathogenic possibilities could be suggested: unsuspected bacteraemia, ongoing bacteraemia, or risk of bacteraemia.

A study reviewing more than 23,000 obstetric neuraxial procedures to examine the incidence of accidental dural puncture and post-dural-puncture headache reported only 1 case of meningitis following spinal anaesthesia for caesarean section. Streptococcus viridans was isolated in cerebrospinal fluid CSF, a microorganism whose source was probably the nasopharynx (8). Regardless of aseptic measures, other possible causes of bacteraemia should be taken into account, such as toothbrushing, which produces 10.8% of bacteraemia episodes. If unsuspected bacteraemia occurs, minimal trauma or bleeding in the subarachnoid space during a neuraxial puncture could facilitate its dissemination to the CSF (9).

Isolated cases of patients with known bacteraemia that developed a CNS infection despite the established antibiotic therapy have been published (10). However, underreporting is possible.

Prospective and retrospective clinical studies including patients with possible bacteraemia have been reported, showing very low rates of CNS infectious complications. Gritsenko et al. (3), in a retrospective study of 474 surgical prosthetic replacements due to knee and hip prosthesis infections operated under neuraxial anaesthesia, found CNS infectious complications in 0.6%, bacteraemia being found in 4.2% of cases. Rasouli et al. (5) conducted a prospective study in 539 patients scheduled for lower-limb prosthesis replacement due to infection. There was a threefold increase of systemic infectious complications in patients undergoing general anaesthesia compared with those under neuraxial anaesthesia (12% vs. 4%, $p<0.001$), with 1 epidural abscess (0.007%) and no cases of meningitis. The authors urge anaesthesiologists to reassess the 'risk of sepsis' as a relative contraindication to neuraxial techniques.

As a general rule, controlled animal studies and retrospective human studies suggest a low incidence of meningitis or abscesses after the spinal puncture during bacteraemia, provided that antibiotic therapy has been previously administered (11).

Infections Due to Viruses

Controversy regarding the safety of NRA in patients with HIV infection of causing neurological sequelae through the needle trauma has been underlined (12), but a definite contraindication has never been established (13).

HIV is a neurotropic virus and affects the CNS since the early stages of the infection; in fact, virions and antibodies can be isolated in CSF (13). It is responsible for 30%-40% of neurological dysfunction in HIV patients at the time of diagnosis. Most of the published studies were conducted in pregnant women, and they concluded that NRA is the anaesthetic method of choice when compared with general anaesthesia (6, 13, 14). This is because it does not accelerate the neurological disease progression (13) and because the inherent risks of general anaesthesia in these patients (that can suffer from dementia, oesophageal and oropharyngeal disorders predisposing to regurgitation and aspiration, and opportunistic lung infections that may prolong postoperative mechanical ventilation). Moreover, drug interactions and the impact of general anaesthesia on organs (14), liver or renal dysfunction, and the history of drug abuse should be taken into account.

The indication of a blood patch (with autologous blood) after dural tap is considered to be safe, and it does not predispose to neurological disease progression (15).

Treatment with protease-inhibitor drugs (due to the relative risk of overdosing with opioids, non-steroidal anti-inflammatory drugs and benzodiazepines), the existence of previous neuropathy, thrombocytopenia (which usually does not reach figures that contraindicate a regional technique) and infection at the puncture site (14) should be carefully considered.

Viremia due to any virus from the herpesvirus family (herpes simplex virus 1 and 2, and herpes virus varicella-zoster) usually occurs during primary infection, and then there is a neuronal persistence with ulterior viruses reactivation (4). Again, studies in pregnant women with active herpetic lesions have shown no infectious complications following neuraxial anaesthetic techniques (16, 17).

However, large studies and reviews showed different results. Chen et al. (18), in a retrospective study of 160,000 caesarean sections, showed a low incidence of herpetic reactivations after the neuraxial anaesthesia. In a review, Bauchat (19) reports a higher rate of oral herpetic reactivations after epidural morphine when compared to intravenous administration in obstetric patients, but the author emphasises again that the benefit of labour analgesia surpasses the risk of foetal herpesvirus transmission (19).

Although all studies had the same conclusion about the safety of the NRA techniques, the authors agreed that a safe distance between the puncture site and active lesions needs to be considered.

Technical and Clinical Issues

Puncture Site: Single Puncture Versus Continuous Techniques

The only absolute contraindication for any type of puncture in regional anaesthesia is infection at the puncture site (6), or a known epidural abscess (20). However, there are no recommendations regarding the minimum distance between the puncture site and the site of infection.

Single-dose techniques minimise the risk when compared to catheter insertion. The use of catheters in patients with active infection is only recommended after antibiotic therapy has been started, with clinical and biological adequate responses, and the risk-benefit ratio should be documented (6, 11).

Neuraxial Regional Anaesthesia

The New York Society of Regional Anesthesia (21) sets the same absolute contraindication for the puncture site infection, and it defines sepsis of different origin at the puncture site as a relative contraindication (including chorioamnionitis and lower-limb infection). In these cases, if antibiotic therapy has been instituted, and there is hemodynamic stability, spinal anaesthesia might be performed.

Goodman et al. (22) and Bader et al. (23) analysed patients with chorioamnionitis without bacteraemia or sepsis signs, and they found no infectious complications related to the regional anaesthesia. However, recently, Elton and Chaudari (24) in a review article, while recognising the same evidence, cited that neuraxial block approaches are generally contraindicated in obstetric sepsis due to poor hemodynamic tolerance, the probability of coagulopathy or thrombocytopenia, and the risk of meningitis or epidural abscesses, despite the few cases described.

It has been recommended by experts (level of evidence C) not to perform neuraxial procedures in patients with untreated systemic infection, and although antibiotic therapy provides safety in dural puncture (level of evidence A), catheter insertion (epidural or spinal) remained controversial (11), while single shot spinal anaesthesia can be performed if there is no serious risk of transient bacteraemia (level of evidence B) (4).

Role of Thoracic Epidural Anaesthesia in Sepsis

The role of thoracic epidural anaesthesia as part of the treatment of peritonitis and sepsis has been investigated since the 1970s (see classical references in Annex 2). It is considered that splanchnic hypoperfusion and hypoxia are key factors for the development and evolution of the SIRS and multiple organ failure in sepsis (25). The role of epidural anaesthesia in sepsis has its foundation in the improvement of these pathophysiological aspects (besides other beneficial effects, such as analgesia, bowel function, etc.).

Although recent publications support the positive role of thoracic epidural anaesthesia both in experimental and in a few clinical studies, it has never been considered, nor included, in the septic patient management clinical guidelines (see reviewed guidelines in Annex 1).

Mutz and Vagts (25) highlighted the role of increased sympathetic activity as a facilitating mechanism of SIRS splanchnic hypoperfusion and hypoxia, and the harmful or protective effect of thoracic epidural anaesthesia depending on the sepsis phase, the degree of extension of the epidural blockade, and the co-administration of supportive therapies. In this regard, the authors noted the need for comparable future studies in terms of normovolaemia at the time of the study, sympathetic block level (including or excluding cardioaccelerator nerves), defining the developmental stage of sepsis (early or hyperdynamic, late or hypodynamic) and demonstration of a maintained sympathetic block (again the level including or excluding adrenal glands).

Subsequent studies reported positive effects of thoracic epidural anaesthesia on pulmonary endothelial capillary integrity in septic rats in the hyperdynamic phase, modulating the production of nitric oxide (effects not found in rats with sepsis in the hypodynamic phase) (26). Authors also reported positive effects on the hepatic microcirculation and inflammatory response in these animals, concluding that in the late phase, cardiac output was not affected, while liver hypoperfusion was reversed (restoring the arterial buffer system mechanisms), and the intrahepatic leukocyte adhesion improved (27). The improvement of intestinal microvascular blood flow was also observed, with no alteration in the blood flow to the brain, heart, liver and kidney, in a model of endotoxemia (28), perhaps by improving the total flow to organs. Intestinal perfusion was increased due to sympathetic blockade, this being already found in previous studies at the muscularis and the mucosal layers (29, 30), and in other experimental models in multiple organs (see Annex 3 for additional references).

This improvement has also been shown in bleeding animal models involving risk for infection (see above). The effect of epidural anaesthesia is usually neutral or decreases the splanchnic perfusion in normal subjects (31, 32), but improves tissue oxygenation in patients undergoing abdominal surgery (33, 34).

Clinical studies demonstrated a reduction in non-infectious systemic inflammatory response with neuraxial anaesthesia (35), but studies of patients with infectious systemic inflammation are less frequently found.

In patients with non-infectious SIRS, thoracic epidural anaesthesia attenuates stress-induced immunosuppression during abdominal surgery (36-38). In SIRS due to infection, Spackman et al. (39) published the first prospective clinical study that supports clinical improvement in non-surgical peritonitic patients using thoracic epidural anaesthesia.

In 2011, Tyagi et al. (40) published the first prospective clinical study showing benefits on intestinal function in surgical peritonitic septic patients, using thoracic epidural anaesthesia for several hours before the intervention with the aim of blocking the thoracic sympathetic response and maintaining it 48 hours later. They found that 0.125% bupivacaine concentration was sufficient, without causing hemodynamic deterioration, and concluded that this type of anaesthesia increased intestinal perfusion, prevented leukocyte adhesion to endothelium in cases of visceral hypoperfusion, and protected against bacterial translocation in cases of ischaemia. There was no evidence of meningitis or epidural abscesses.

An experimental study showed the immunomodulatory mechanism of the epidural infusions of lidocaine and its role in SIRS control through the detection of an increased expression of the bacteriostatic protein lipocalin-2 by leukocytes, and it found an attenuation of bacterial growth (Escherichia coli) at the site of infection (41).

Anti-Inflammatory, Antimicrobial and Immunomodulatory Effects of Local Anaesthetics

Anti-inflammatory, antimicrobial and immunomodulatory effects of local anaesthetics have been widely evaluated (Annex 4, references 1 and 2). Since 1978, several experimental studies have been published, showing the immunomodulatory role of lidocaine, as well as the anti-inflammatory and antimicrobial effects of local anaesthetics (LA) (see Annex 4 for additional references). Moreover, studies have provided the basis of an excessive inflammatory response that would help to explain the LA effects mediated by mechanisms other than the effect on sodium channels.

Classical references cite procaine, alone or in combination with antibiotics, as treatment for acute inflammatory and

suppurative pathology of peripheral, intrathoracic or intra-abdominal foci. In these studies, LA were administered by multiple routes (intraosseous, intra-arterial, intraperitoneal and multiple regional block approaches).

Reviews (42-45) summarised that anti-inflammatory effects of LA occur at all levels of the inflammatory cascade (endothelial cell adhesion, transendothelial migration, phagocytosis and inflammatory mediators release such as histamine and leukotrienes, that have significant involvement in inflammation-mediated tissue damage). However, other studies found a slowing of the acute inflammatory response resolution mediated by upregulation of pro-inflammatory proteins (S100A8/9 and CRAMP/LL-37), and downregulation of peptides and anti-inflammatory and pro-resolutive proteins (IL-4, IL-13, TGF-alpha and Galectin-1) (46). The anti-inflammatory effects are believed to be due to the LA action at different sites than the voltage-dependent sodium channel, as well as to modulation of signals mediated by G protein-linked receptors (45).

LA do not interfere with the normal activation process of polymorphonuclear leukocytes, but rather selectively inhibit their 'priming', a process whereby the response of polymorphonuclears to a stimulus is potentiated, releasing oxygen metabolites in a particularly increased way (the so-called overactive inflammatory response). This process has proven to be key in the development of polymorphonuclear mediated tissue damage (43). These effects can be achieved at plasma concentrations usually reached with epidural or intravenous LA infusions (1-5 micromol L^{-1}).

The antibacterial, antifungal and antiviral properties of the LA are proportional to their concentration, to the point of conferring bactericidal/bacteriostatic and fungicidal/fungostatic properties, both in vitro and in experimental animal models (44, 47). The LA indirect effect of increased tissue perfusion due to vasodilatation and the ability to damage the microbial cell membrane permeability to the point of cell lysis seem to play an important role (47).

As lipophilic amines, LA can inactivate lysosomal functions. In a viral infection, LA could prevent the first RNA transcription inside the lisosome and therefore the intracellular replication and transportation of the viruses. Miller (48) found that all lipophilic amines tested in his study inhibited viral infection at the time of infection (prior to the first transcription of RNA), being effective if given on time (1 hour after infection induction, when lysosomal internalisation was complete).

Multiple LA at concentrations usually employed were studied. Bupivacaine (0.125%-0.75%) and lidocaine (1%-3%) showed a greater inhibitory ability on fungal and bacterial growth than ropivacaine and levobupivacaine (44, 47). However, this might depend on the investigational model used (49). The inhibitory ability is proportional to the concentration, temperature and the exposure time to the LA (43, 47).

False negative and suboptimal microbiological culture results in microbiological sampling have been described when previous infiltration with LA was performed, as well as a 70% decrease in the number of colonies of bacteria, suggesting a role of LA in the prophylaxis of infection of infiltrated surgical wounds (50).

The role of peritoneal lavage with bupivacaine and lidocaine has also been studied on the survival of rats with faecal peritonitis. In the study groups, mortality was lower than in controls (drainage alone, not washed or washed with saline) (51, 52).

Conclusion

Performing or not regional anaesthesia or NRA in the patient with an active infection is not supported by strong evidence. Only the presence of infection at the puncture site or catheter insertion may be contraindicated. Single-puncture techniques can be safe. The available information so far indicates that the insertion of catheters requires an antibiotic pretreatment of the infection followed by a clinically appropriate response.

Regarding thoracic epidural anaesthesia use in SIRS or in surgical or non-surgical sepsis, numerous experimental studies and a few clinical studies provide some evidence that its effects can be beneficial depending on the time of its establishment.

Although it may be ethically conflicting, randomised studies are necessary in selected patients or groups of patients to assess the aforementioned advantages and indications. The future use of regional anaesthesia in patients with sepsis is open, both through clinical and experimental investigations.

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Annexes

Annex 1. Revised sepsis guidelines and web based resources (accesed 20-11-2016).

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