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Review

PRO AND CONTRA ON ADJUVANTS TO NEUROAXIAL ANESTHESIA AND PERIPHERAL NERVE BLOCKS

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ABSTRACT – Modern approach in surgical treatment and in managing acute and chronic pain is nowadays more and more based on the implementation of all possible techniques of regional anesthesia (RA). Local anesthetics (LA) are needed to achieve standard regional anesthesia. Local anesthetics are primarily characterized by time constraints and duration of action, and depending on the amount applied, adverse effects on the cardiac and central nervous system may occur.

Adjuvants are drugs used together with LA due to their synergistic effect, i.e. they improve start latency and duration of sensory and motor blockade and enable reduction of cumulative dose of LA and reduction of adverse effects on cardiac and nervous system. Nowadays, there is a huge variety of drugs that can be administered in combination with LA, and they, in general, can be divided into opioid and non-opioid adjuvants. The administration of opioids in RA over an extended time period was accompanied by some negative characteristics as respiratory depression, nausea, vomiting. So, their usage is still under a special control. Due to the positive effects shown by drugs from non-opioid adjuvants group (e.g. adrenaline, alpha adrenergic agonists, steroids, magnesium, midazolam, ketamine etc.), indications for their administration broadened. However, there are still some restrains in clinical practice based on the fact that neurotoxicity and demonstration of neurological complications in regional anesthesia haven't been properly researched yet.

Key words: *adjuvants; local anesthetics; neuraxial block; peripheral neural block; opioids; non-opioids*

Introduction

The success of the techniques of the regional anesthesia depends on the knowledge of pharmacokinetics of local anesthetic (LA) as well as pathophysiology of the phenomena of pain because it enables the adequate choice of the type, concentration and a dose of drugs to use. It also enables the adequate choice of types of drugs used for the purpose of prolonging the analgesia. At the same time, this gives insight into the choice of RA techniques by which centrally and peripherally caused adverse effects of local anesthetics (LA) can be diminished. Generally speaking, the local anesthetics (LA) function in a way to infiltrate into a nerve and stop the transfer of pain signals into the brain. (1)

Anesthetic effect of LA on the nerve blockade lasts only for few hours. The main problem with RA is that patient, soon after the operation, may experience medium to strong postoperative pain. The duration of the LA can be prolonged by increasing

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the dose or by applying continuous infusion of LA, which may lead to the cumulation of drug and to adverse effects on cardiac and/or central neural system, depending on the dose applied. In the last couple of years, through the development of ultrasound-guided regional techniques the popularity of peripheral nerves blocks and its continuous infusion modalities has risen, especially within the framework of postoperative analgesia. (2)

The main complications of peripheral blocks refer to the appearance of systemic toxicity (LAST), hematoma, allergies, infections and, rarely, injuries of the peripheral nerve. Several drugs have been clinically tested, to improve the efficiency of peripheral and central nerve blocks, i.e. to reduce the total quantity of LA and thus reduce their potential toxicity. Most of them demonstrated positive effects to various degrees in terms of shortening the start latency of the block, lengthening the duration of the sensory block, strengthening motoric blockade, i.e. through their application, the desired diminishing of the total dose of LA was achieved. These types of drugs are called additional analgesics / adjuvants and can be used in neuraxial, peripheral and regional - fascial blocks. Adjuvants are injected perineurally in combination with LA to potentiate desired positive effects of both types of drugs, without the appearance of known or any new risks of adverse effects. Even the adjuvant itself can demonstrate side effect, which should be taken into consideration prior to administering it.

Although the usage of certain types of drugs together with LA is an accepted and verified approach, and even though there are numerous clinical observations and so-called off-label clinical researches, many adjuvants still have not been approved by American Food and Drugs Administration (FDA), so one should be very precautious when using all additional drugs. (3)

This article will focus on explanation, strategies, pros and restrictions in application of different categories of additional analgesics, and it is based on current evidence with the aim of optimizing regional anesthesia and postoperative pain.

What is the aim of combining local anesthetics with adjuvants?

The mechanism of transmitting pain in the central and peripheral nerve system is very complex and includes a whole series of different neurotransmitters and several interconnected signaling pathways. One method or only one means may not be enough to qualitatively block transmitting pain within so complex neurological system. Therefore, it is rational to add to LA some other drug/drugs which will enable good anesthesia, quicker reaction of sensory block (shorten latency) while at the same time prolonging the analgesic effect, lessening the total dose of LA and thus diminishing potential appearance of various undesired phenomena. This application of additional drugs in combination with LA is clinically called "multimodal regional anesthesia". This synergy enables satisfactory level of anesthesia/analgesia in terms of potentiating positive effects and at the same time diminishing potential neurotoxicity and tissue damage caused by using high doses of LA.

Adjuvants are various drugs from different pharmacological groups as opioids, steroids, and alpha 2- agonists etc., which, in combination with LA, demonstrate synergic effect during the blockade of nerves. What is more, these drugs when in clinically relevant doses do not demonstrate neurotoxicity. However, they also have some effect that can be added together with effects of LA as hypotension, sedation, bradycardia, etc.

The administration of adjuvants in hospital environment in clinical approach has an important role because by using them the need for continuous catheters and the application of perfusion pumps can be eliminated, therefore, the risk of infection becomes lower. (4)

In the modality of day-stay surgery, adjuvants are important because they make it possible that

without strengthening the motoric blockade a good anesthesia can be achieved. It ensures quicker mobilization of a patient and at the same time enables longer postoperative analgesia.

However, even though all adjuvants are continuously used in clinical practice, none of them has been approved by FDA. The use of such drugs is still off-label, and their application depends only on anesthesiology evaluation of risk and benefit ratio. Fentanyl, dexmedetomidine and dexamethasone are just some of the adjuvants, which, as based on the evidence, have strong positive impact in combination with LA, especially in peripheral and fascial blocks. As for these drugs, numerous studies have proved that this risk-benefit ratio definitely turns out to be a benefit.

Classification of Adjuvants

Adjuvants are classified according to their mode of action, mode of administration and other parameters.

There are two major groups: non-opioid and opioid, non-opioid being various alpha2-agonists, vasoconstrictors, anti-inflammatory agents, acetylcholinesterase inhibitors (neostigmine), midazolam, NMDA antagonists, magnesium and sodium bicarbonate.

Opioid adjuvants

Opioids were the first and still are the most frequently used LA adjuvants. Over the last 50 years, or since the discovery of opioid receptors, their usage in neuraxial and peripheral nerve blocks has developed a lot. The recommendation is to use specific opioids (hydrophilic or hydrophobic) in adequate doses within the chosen application technique because the aim is that their effect is achieved on spinal level and not through the system activation. Afferent harmful impulses from peripheral tissues converge into the dorsal horn of spinal cord, where nociceptive primary neurons synapse with interneurons and second-order nociceptive neurons in spinothalamic tract. The blockade of these opioid receptors by agonists helps to eliminate afferent nociceptive gate from the region of pain by regulating the release of peptides, which are active in pain transmission pathways. Opioids produce analgesia by imitating the action on specific receptors of endogenous opioid peptides. Three major types of opioid receptors are mu (μ), delta (δ) and kappa (κ). The most important target for opioids is μ-receptor (endorphin) and it seems that intrathecal opioids selectively modulate C- and A- fibers with minimum impact on axons of dorsal root. Enkephalins are primary endogenous ligands of delta receptors and are involved in analgesia on the spinal level. Dynorphin is a ligand for a kappa receptor. By activating kappa receptors, segmental analgesia on the spinal level and sedation can be realized. Most of the mixed agonist-antagonist opioids like butorphanol bond themselves to kappa receptor. (5)

Every drug administered intrathecally is quickly redistributed within CFS; the existence of opioids in cisterna magna can be proved within 30 minutes from lumbar intrathecal administration. This is valid for lipophilic drugs as sufentanil, too. Lipophilic opioids go very quickly through dura mater where they stay trapped in epidural fat and this way get into system circulation. The same way they very quickly penetrate spinal marrow where they bond to non-specific sites within the white matter and to receptors dorsal horns and, finally, they also enter system circulation after being flushed out from the spinal cord. This quick transmission of opioids from CSF towards the spinal cord and epidural fat explains a quick action as well as a quick drop of lipophilic opioids in CSF, with minimal rostral expansion, with the absence of later respiratory depression and with relatively small area of covered dermatomes during the chronical administration. Numerous studies show that fentanyl administered as an epidural bolus acts mainly on spinal level by realizing segmental anesthesia, while, if administered as epidural infusion, it act mostly on supraspinal sites resulting in systemic analgesia. Certain studies show that this "dual action" is due to the high level of doses being used.

It is believed that, as opposed to the continuous infusion, bolus administration results in higher concentration gradient between epidural and intrathecal space, which enables bigger gateway of fentanyl into intrathecal space and reaching dorsal horns, which results in spinal analgesia. Such difference in gradient is not possible by continuous infusion, so lipophilic opiate is redistributed into systemic circulation and this way supraspinal analgesia is achieved. Due to the fact that during the postoperative epidural analgesia, low concentration solutions (e.g. for fentanyl suggested limit for effective concentration is 10mg/ml) are most frequent in postoperative epidural analgesia. So, it is evident why supraspinal and not spinally mediated analgesia is realized.

Morphine, a prototype of hydrophilic opioid, realizes a similar transmission through the spinal

cord and in the epidural space; however, it partially bonds with the fat within the epidural space and with non-specific receptors within the white matter of the spinal cord. The transmission into systemic circulation is also slower than for the lipophilic drugs. This advantage of combining LA and opioids is explained by their synergistic analgetic characteristics, i.e. their capacity to block pain on two different levels. Opioid drugs produce analgesia by specific bonding and activation of receptors in substantia gelatinosa, whilst LA produces analgesia by blocking the transmission of impulses in the nerve roots and in dorsal roots ganglia. Subsequently, LA are responsible for segmental-spinal analgesia and opiates are used to realize supraspinal analgesia. (6)

The acting of opioids in peripheral blocks still does not have a defined mechanism. There is evidence of the existence of peripheral opioid receptors. The prolongation of analgesic effect in peripheral block , when LA is used together with opioids, is explained by axonal diffusion (e.g. through neural sheath of brachial plexus) into extradural or subarachnoid space and by direct bonding onto opioid receptors in dorsal root or

it can be explained as a consequence of central action achieved after peripheral systemic resorption. (7)

Morphines

Due to the fact that morphine is relatively less hydrophobic in comparison to other opioids, it retains a bit longer in liquor and, thus, occupies rostral receptor sites longer than other opioids. During the intrathecal administration (100-200μg), morphine provides longer analgesia of higher quality. However, this huge advantage is accompanied by greater possibility of side effects, especially postoperative respiratory depression, urinary retention, vomiting, nausea, sedation, which is still a great concern among anesthesiologists. The recommended dose for intrathecal administration is 50-300 μg, while 2-5 mg of epidural bolus dose is considered adequate. The risk of side effects exponentially grows with the quantity of the dose. Clinical studies on the administration of morphines in peripheral blocks present contradictory results. Some show prolongation of analgesia, whilst the others claim that there is no benefit. However, most studies never proved any significant benefit in administration of morphine in peripheral blocks in comparison to its intravenous or intramuscular administration. (8) (9)

Fentanyl

It acts on receptors of spinal cord and on peripheral receptors, and as LA adjuvant significantly prolongs analgesia. The recommended intrathecal dose is 10-25μg and the optimal epidural bolus dose is considered to be 50-100μg. When combined with LA, it can postpone the start of sensory and motoric blockade, due to the fact that there is a change in pH mixture and it causes slower penetration of LA into the nerve tissue. Analgetic effect is 2-4 hours, it does not prolong the motoric block LA, it does not disturb the recovery of the motoric function and at the same time, the risk of respiratory depression is very low and short-termed. In modalities of continuous epidural analgesia, there are contradictory studies about its combination with LA. (10)

As for peripheral blocks, various studies are not in favor of administration of fentanyl with LA, e.g. with ropivacaine or lidocaine, because of minimum effect achieved. (11) However, some newer studies demonstrate that in cervical and paravertebral blocks the combination of fentanyl with 0.25% of bupivacaine and epinephrine prolongs the anesthesia for 18 hours. (12)

Sufentanil

This potent agonistic opioid, a piperidine derivative, is 6-10 times stronger than fentanyl, depending on the mode of administration. It is considered to be better soluble in lipids, it is better ligand of mu(μ) receptors and thus extremely potent opioid with faster start of action. The recommended intrathecal dose is 2.5-10μg, while epidural bolus dose is 10-50μg. It has short-time action and the incidence of adverse effects depends on the administered dose. (13)

Its benefit is not shown in peripheral blocks. (14)

Tramadol

Tramadol hydrochloride (HCL) is a weak opioid with central acting composed of 2 enantiomers. Central and peripheral analgetic effects of tramadol aren't fully explained, but it is a selective agonist of μ-receptor. Tramadol also prevents reuptake of noradrenaline and intensifies the release of serotonin and noradrenaline. Monoaminergic activity of tramadol intensifies inhibitory activity of descending pain pathways, which results in nociceptive transmission on the level of spine. In addition, tramadol does not cause clinically important respiratory depression, does not cause the release of histamine or skin redness nor idiosyncratic hypotension. There are numerous clinical studies on intrathecal administration in doses of 10-50μg, i.e. in epidural administration in doses 1-2μg / kg in various operations with diverse level of success. Due to the fact that it enables satisfactory postoperative analgesia, without a significant sedation, skin rush and respiratory depression, tramadol represents a good alternative to morphine.(15) In peripheral blocks, its combination with LA demonstrates unsatisfactory safety profile (nausea and vomiting with 200mg dose), so, it can only be recommended in post-operative epidural infusion.

Non-opioid adjuvants

Vasoactive drugs

Vasoactive drugs are the oldest adjuvants used to prolong anesthetic and analgetic action of LA. The first vasopressor in clinical use was epinephrine.

Epinephrine

The typical epinephrine concentration dose of 5-10μg/mL has proven efficient in achieving vasoconstriction, in decreasing the blood flow at injection

sites, in decreasing systemreabsorption as well as in decreasing of system toxicity of LA. It has antinociceptive effect because it acts directly on alpha-2 adrenoceptors from substantia gelatinosa of the dorsal-horn of the spinal cord, which results in presynaptic inhibition of releasing neurotransmitters from Aδ and C fibers. It is assumed that during the epidural anesthesia, the primary mechanism of the epinephrine action is the decrease of the resorption of LA from the epidural space by local vasoconstriction. Since the effect of epinephrine on blood flow depends on concentration, it is expected that the flow will decrease in those tissues where epinephrine is in high concentration (vasoconstriction), whilst the flow will increase if its concentration in tissue is low (vasodilatation). It is important to be reminded that in epidural space LA, in comparison to opioids, can increase the local blood flow and thus increase its own excretion. This characteristic can explain why the effects of epinephrine on pharmacokinetics of opioids are more evident than on pharmacokinetics of LA.

The outcome on the effective duration of LA is variable, depending on the type of LA. The LA with shorter action (lidocaine, procaine) when diluted by epinephrine 1:200000 demonstrates longer degree of the prolongation of the action in comparison to epinephrine being added to LA of the longer duration (ropivacaine).

In axillary block, for example, lidocaine with high epinephrine dose (200mcg/mL) proved itself to be efficient in prolonging of the motor and sensory block for 25 to 40 minutes, but with stronger presence of tachycardia and hypertension. Lower dose of 25 mcg/mL had minimum effect on potentiating its strength. It prolonged the motor block for 10 minutes and sensory block for 30 minutes, but with safer hemodynamic profile. (16)

Despite numerous advantages of epinephrine as LA adjuvant, studies have shown that it has impact on decrease of the blood flow in neural tissue. It was proved that epinephrine causes higher neurotoxicity in patients with diabetes, i.e. that there is a minimum effect on peripheral

nerve blocks. There is also a concern that epinephrine is a strong vasoconstrictive agent that can endanger the blood supply to the spinal cord and cause its ischemia which will result in permanent damage.(17)

Numerous researches have proved that epinephrine in combination with LA rarely demonstrates negative hemodynamic effects and that is safe foro use in patients where there is a possibility for hypertension or tachycardia.

Phenylephrine

Phenylephrine is a vasoconstrictor whose mechanism of acting is similar to that of epinephrine. It enables the decrease of total LA dose and prolongs total duration of their action. Phenylephrine in 2-5mg dose, in a similar way as epinephrine, prolongs the spinal anesthesia administered by lidocaine, as well as by tetracaine. The use of phenylephrine has significantly dropped in popularity due to its connection with temporary neurological symptoms (TNS). So, it is not to be recommended for peripheral blocks.

Alpha Adrenergic Agonists

Alpha Adrenergic Agonists (clonidine, dexmedetomidine) are drugs that are used as adjuvant to local anesthetics because they give adequate result both in centro-axial and regional/ peripheral block anesthesia.

Clonidine

It is an imidazole derivative, which has lately been in focus due to its sedative, analgesic, perioperative sympatholytic, anesthetic and hemodynamical stabilizing characteristics. Central α-2-AR agonist which inhibits nociceptive impulses by activating postjunctional α-2- adrenoceptors in dorsal horn of the spinal cord. These receptors are located at primary afferent

terminals (both on peripheral and spinal endings), on neurons at the superficial laminae of the spinal cord and inside few cores of the brainstem responsible for analgesia. They block transmission of C and A-delta fibers and they enlarge the conductivity of potassium in neurons, thus intensifying transmission blockade. Clonidine potentiates and prologs sensory blockade as well as motoric blockade of local anesthetics with all types of regional anesthesia. It causes local vasoconstriction, too, which decreases vascular resorption of LA around neural structures and thus directly prolongs the action of LA. (18)

Alpha-2 adrenergic agonists intensify intrathecal opioid analgesia by interacting with pre- and

post synaptic receptors inside the spinal cord. Neuraxial application of clonidine effects locally sympathetic nerves in the spinal cord. Intrathecal application of clonidine is accompanied by the appearance of sedation, bradycardia and hypotension, whilst a dose of 150 μg in peripheral blocks potentiates motoric block and prolongs the analgesia time (for 2-2.5 h) without increasing the side effects. (19)

Dexmedetomidine

Dexmedetomidine is seven times more selective agonist of alpha-2 receptors than clonidine (seven times more specific for alpha-2 than alpha -1), but it has a similar mechanism of blocking action channels activated by hyperpolarization. Researches have demonstrated that in regional anesthesia it has analgetic and hypnotic effect with simultaneous appearance of hypotension and bradycardia. When used as LA adjuvant with neuraxial block (intrathecal 5-10 μg, epidural 1 μg/kg, dexmedetomidine leads to decrease of shortening of start latency of the sensory and motoric blocks, prolonged duration of sensory block and significantly delayed recovery of motoric blockade. This leads to the prolongation of postoperative analgesia, lesser need for additional analgesics, postponed first "rescue" analgesic and diminished postoperative tremor, also to postponing motoric recovery. That is the main reason why it is not recommended in one-day surgery modality. The standard dose added to LA in spinal anesthesia varies from 3 to 15 μg. (20)

It has been shown that in peroral, intramuscular and/or intravenous application both clonidine and dexmedetomidine prolong anesthetic effect of intrathecal LA. Significant prolongation of motor blockade, caused by dexmedetomidine, regardless of the type of LA, is the main contraindication for its use in spinal anesthesia as part of one-day surgical modalities. Clinical studies demonstrate that dexmedetomidine can prolong the blockade of peripheral nerve for 200 min in a dose of 1 μg/ kg. In meta-analyses it is presented within brachial plexus blocks system in combination with the following doses: 0.75 μg/ kg, 1.0 μg/ kg, 30 μg and 100 μg/ kg, and it is confirmed that it significantly prolongs motoric block and analgesia, i.e. there has been registered lesser need for "rescue" analgesics. However, at the same time, the studies have confirmed a higher frequency of hypotension as side effect, i.e. bradycardia is present in less than 10% of patients. The sensory block has not shown statistically significant change. (21) It has been proven in other blocks as supraclavicular, interscalene and cervical plexus that dexmedetomidine increases the quality of motoric block and the length of analgesia when combined with standard local anesthetics as ropivacaine and bupivacaine. (22) There are other studies that give advantage to dexmedetomidine in 1 μg/ kg dose, in comparison to clonidine, in different plexus blocks, which highlight the importance of good assessment due to its emphasized bradycardia. (23) To date, studies have not proved neurotoxicity of dexmedetomidine in perineural space, i.e. its toxicity in intrathecal space has not been proved on animal models. The most frequent registered side effects are hypotension and bradycardia, which react very well to conventional therapy. Due to dexmedetomidine, bradycardia may be resistant to atropine and higher doses may be required, and although this occurs very rarely, cardiac arrest may occur. (24)

Steroids

Dexamethasone

Acute inflammation caused by tissue damage has an important role in surgical pain, and glucocorticoids can be useful because of their anti-inflammatory effect. For the last decade, dexamethasone has become extremely popular LA adjuvant in all regional techniques. Even though it does not speed up the start of sensory or motoric block, it is believed that it enables the realization of more qualitative anesthesia and longer analgesia. The researches have not so far strictly defined its exact mechanism of action on LA. However, there are numerous studies which are in favor of it because it does not only decrease the release of anti-inflammatory mediators, or it decreases ectopic neuron release, but it can also act on K+ channels on nociceptive C fibers through glucocorticoid receptor, by which it directly effects fiber activity.

Dexamethasone, when in doses ranging from 1,2,4 to 8 mg, has proven to be a very efficient LA adjuvant in various regional techniques: intrathecal, epidural, in supraclavicular, interscalene and brachial blocks, in paravertebral and TAP blocks. It, for example, prolongs the blockade of brachial plexus from 168 to 343 minutes if combined with medium-acting LA (e.g. ropivacaine), and in combination with long-acting LA (e.g. bupivacaine) it prolongs the effect from 730 to 1306 minutes, too. Shared positive effect is that it prolongs the length of sensitive block and analgetic action without showing side effects. Various studies suggest that low doses of perineural dexamethasone (1-2 mg) are by efficiency equal to higher intravenous doses (4mg), which is important because it enables decrease of side effects of adjuvant itself. (25)

Even though numerous studies have confirmed the efficiency of perineural application of dexamethasone, it should be mentioned that there are studies which haven't demonstrated such beneficial outcomes, so, there is still an ongoing discussion if analgesia ensured by dexamethasone is linked to its systemic administration. (26) (27)

NMDA antagonists

Ketamine

Ketamine is a non-competitive antagonist of NMDA receptors which also has local anesthetic characteristics through the blockade of natrium channels. It demonstrates central antinociceptive effect because it, at the same time, affects monoaminergic receptors, opioid receptors, voltage-gated calcium channels and muscarinic receptors. Systemic ketamine causes central summation in pain neurons of second order and decreases strong pain. Clinical studies have demonstrated that epidural administration of ketamine in 0.5-1mg/kg dose decreases intraoperative and post-operative needs for analgesic, without the increase in side effects. For intrathecal application S(+)-ketamine without preservative is strictly recommended. Its intrathecal and epidural application is most frequently studied as part of a Caesarean section, prostate operations and orthopedic procedures. It has been confirmed that it potentiates LA effect by shortening the start of sensory and motor block, and at the same time it shortens the duration and extent of motor block. This is the main reason why it has become so popular in day-case surgery where there is a desired quick start of the block and early motor strength recovery as well as prolongation of analgesic effect. (28) Despite numerous studies which confirm that intrathecally ketamine achieves good results, there are a few studies on ketamine administration as adjuvant in peripheral blocks. In the study by Lee and associates the application of 30mg ketamine in combination with ropivacaine had no impact on sensory or motor blockade of peripheral nerves. As opposed to that, this study confirms unacceptably high rate of adverse effects as hallucinations, nausea, and sleepiness in the group which along with LA was administered ketamine. Thus, ketamine is not to be recommended as addition in peripheral nerve blockade. (29)

Magnesium

Magnesium sulphate is antagonist N-methyl-D-aspartate receptor which has an important role in modulation of calcium ions entry into neurons. Researches have proved that magnesium decreases excitability of peripheral nerves and increases the ability of lidocaine to raise stimulus threshold in A-beta fibers. (30) Studies have demonstrated that in neuropathic pain intrathecal application of magnesium sulfate inhibits nociceptive impulses and increases antinociception. Intrathecal and epidural application of magnesium in anesthesia shows different shortening of sensory and motor block onset times, different prolongation of senso-motoric recovery times, but certainly leads to a significant improvement in quality of analgesia while delaying the first postoperative analgesic requirement. The same positive effects are expressed when applied as adjuvants to LA in different peripheral blocks (interscalene, axillar, femoral). In neuraxial administration of magnesium there have been rare advert effect as bradycardia, hypotension, sedation, headache, disorientation or paraumbilical burning or pain. (31)

Most studies on magnesium in peripheral blocks show no serious adverse effects (only transient pain on injection site), except for Lee and associates study which indicates the appearance of nausea within the first 12 hours after interscalene block (in this study the dose applied was 200 μg, while in most other it was 150 μg).

The lack of well-defined studies on neurotoxicity of magnesium sulphate limits the recommendation of it as adjuvants in LA regional anesthesia. (16)

Other adjuvants

Midazolam

Midazolam is benzodiazepine that is soluble in water and is applied as adjuvant in neuraxialanesthesia due to its suppressive effect on spinal cord sensory function and antinociceptive effect mediated by gabaergic and opioid mechanisms (direct agonist at kappa and delta opioid receptors). (32)

A dose of 1-2.5mg in intrathecal application proved to be efficient in realization of prolonged postoperative analgesia in lower abdomen, orthopedic and urologic operations and in obstetrics. In upper abdominal surgery, an epidural dose of midazolam of 50μg/kg potentiates the effect of bupivacaine and reduces overall analgesic requirements. (33) FDA has not approved its use in regional anesthesia, so it is not routinely used as LA adjuvant in peripheral perineural blocks.

Neostigmine

Neostigmine is acetylcholinesterase inhibitor that can intensify analgesia by acting on muscarine receptors and by enlarging endogenous acetylcholine at the nerve ending. Due to the fact that it has a modest effect on onset times or on prolongation of senso-motoric recovery time from anesthesia inside the intrathecal application, i.e. due to frequent nauseas and vomiting, dizziness, bradycardia and subsequently lon-

ger recovery from spinal anesthesia, it is considered not to be efficient as LA adjuvant. The dose of intrathecal neostigmine is from 10 to 50 mg, and the reverse effect is enlarged by the dose used.

There is certain restraint regarding the use of neostigmine in perineural application, especially because various studies in animal models have shown some level of neurotoxicity which is also possible in humans and depends on the dose administered. For this reason, at this moment, the application of this adjuvant in peripheral nerves blocks is not recommended. (34)

Sodium bicarbonate

To this day, the effects of bicarbonate on LA in peripheral block still remain undefined. The explanation for their actions is based on the fact that the majority of LA solutions have a pKa between 7.5 and 9, less than 3% of total LA solution are „non-ionized free-based". The addition of sodium bicarbonate to the LA solution serves to raise the pH as close as possible to the pKa value and thus increases the proportion of non-ionized form and improve the solubility of LA solution in fat. This emphasizes conduction through the axonal membranes, and as a result would achieve the desired acceleration of the performance and prolong the regression time of the motor block. (35)

To compare the effects, most researches used epidural block as a standard template. Clinical studies confirm that the addition of bicarbonate to pure 2% lidocaine without epinephrine shortens the onset time and potentiates the depth of the epidural block. On the other hand, when combined with 2% lidocaine with epinephrine, there is no change either at the time of onset or at the depth of the epidural block.

Although the theory tells us that sodium bicarbonate could be a good adjuvant in peripheral nerves blocks, conflicting results from numerous studies do not explicitly confirm this. The most significant effect achieved by its application is the shortening of the onset time of the peripheral block, but the clinical significance of this is not clear. (36) Ririe et al.observed that the addition of bicarbonate produce more rapid onset of motor block for median nerve by four minutes, and Tetlaff et al.observed that bicarbonate shortened the mean onset of action from 2.7minutes to 1.0 minute. (37) (38)

It is difficult to determine the utility of the observed differences in onset of action, as peripheral nerve blocks are often performed some time before the patient enters the operating room. Although accepted in clinical practice, the addition of sodium bicarbonate to local anesthetics in central and peripheral nerves blocks has not been approved for clinical use, therefore its use should be exercised with caution. (39)

Conclusion

A high level of efficiency and security have made regional anesthesia very acceptable not only for modern surgery but also for patients. LA are basic drugs in regional anesthesia, but they have a limited duration, that is they can demonstrate certain adverse effects on cardiovascular and nerve system, these effects being directly dependent on the applied dose. With the purpose of keeping positive characteristics of regional anesthesia, which means the decrease of potentially negative characteristics of LA, more and more frequently a so-called multi-modal approach in adjuvants application is advocated in clinical practice. Adjuvants are drugs which act synergically with LA and enable quicker start, longer duration and better quality of anesthesia/analgesia, while reducing opioid analgesics and their side effects.

Opioids still remain the most frequently used adjuvants, while more and more popular are becoming alpha-2 receptor antagonists (dexmedetomidine) due to their analgesic, sedative and hemodynamic stabilizing characteristics. The demonstrated adjuvants are very different in their action mechanisms and all have the capability of additive and synergic action when added to LA. The choice of the specific one should be led by good clinical experience, security profile of the drug (appropriate dose), their correct administration and good knowledge of adverse effect that is how to solve them correctly. Anesthesiologists should be aware that there are still certain unknown facts about their neurotoxicity during perineural application, and consequently adapt the choice and combination of adjuvants to the desired goal. It is good to take into consideration that some clinical researches on LA adjuvants discussed her might contain a certain amount of enthusiasm towards good results or a specific drug, which we know to be present in other clinical fields. The lack of golden standards in clinical studies, the lack of comparison with placebo or the drug considered to be "the best in the class" still makes unbiased definition of security profile of a certain adjuvant hard.

With this study our wish is not to give advantage of one drug over the other, but to encourage the rational application of adjuvants in regional anesthesia either

as mono-adjuvant or as a combination of adjuvants with the goal of additionally optimizing regional anesthesia and the application of LA.

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Sažetak

PRO I CONTRA ZA ADJUVANSE U NEURAKSIJALNOJ ANESTEZIJI I PERIFERNIM BLOKOVIMA ŽIVACA

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Suvremeni pristup u kirurškom liječenju te u liječenju akutne i kronične boli danas se sve više temelji na primjeni raznovrsnih tehnika regionalne anestezije (RA). Lokalni anestetici (LA) su zlatni standard u ostvarivanju regionalne anestezije.

Lokalne anestetike prvenstveno karakterizira vremenski definirano trajanje učinka, a ovisno o primijenjenoj količini uvijek postoji mogućnost pojave štetnih učinaka na srčani i središnji živčani sustav.

Adjuvansi su lijekovi koji se kombiniraju sa LA zbog njihovog sinergističkog učinka, odnosno poboljšavaju početnu latenciju i trajanje senzoričke i motoričke blokade te omogućuju smanjenje kumulativne doze LA i smanjenje štetnih učinaka na srčani i živčani sustav.Danas postoji veliki izbor lijekova koji se mogu davati u kombinaciji s LA, a općenito se mogu podijeliti na opioidne i neopioidne pomoćne tvari. Primjena opioida u RA tijekom duljeg vremenskog razdoblja bila je popraćena nekim negativnim karakteristikama kao što su respiratorna depresija, mučnina, povraćanje, pa je njihova primjena i dalje pod posebnim nadzorom. Indikacije za primjenu lijekova iz skupine neopioidnih pomoćnih tvari (npr. adrenalin,

alfa adrenergički agonisti, steroidi, magnezij, midazolam, ketamin itd.) su se zbog njihovih pozitivnih učinaka sve više proširile. Međutim, u kliničkoj praksi još uvijek postoji određena suzdržanost o njihovoj primjeni a na temelju činjenice da još uvijek nije dovoljno istražena njihova neurotoksičnost, odnosno nije definirana njihova uloga u pojavi neuroloških komplikacija u tijeku regionalne anestezije.

Ključne riječi: *Adjuvansi; lokalni anestetici; neuraksijalni blok; periferni blok živaca; opioidi; neopioidi*