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NEURAXIAL TECHNIQUE FOR LABOR ANALGESIA: CURRENT TRENDS

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Intense pain during labor can cause some adverse effects in parturient, like uncoordinated uterine contractions, prolonged duration, or stalled labor, as one of the most important reasons leading to caesarean section (C-S) worldwide. Unrelieved labor pain, which can lead to post-traumatic stress disorder or postpartum depression, in addition to discomfort, causes physiological stress that has an adverse effect on the mother and the newborn. Unrelieved pain stimulates catecholamine release, it causes hyperventilation and hypocapnia, which further constricts uterine blood vessels, reduces ventilation stimulus between contractions, causing a leftward shift of the oxygen dissociation curve; and all these phenomena compromise oxygen supply to the fetus, leading to fetal hypoxemia. Premature "movement down" of the fetus can lead to a canal trauma and injury during childbirth; parenteral opioids may exacerbate maternal respiratory depression, while regional (neuraxial) analgesia may reduce adverse effects of labor pain and sympathetic system responsiveness. Therefore, good labor analgesia aims not only to reduce the pain and suffering of the parturient, but also decreases the risk of fetal acidemia and, in general, makes the labor process safer, both for the mother and neonate.

Although the origin of labor pain is created by two different mechanisms, the process of pain relief should include several stages of pain relief, each of them with different intensity and character, starting from the initial stage and finishing with the final act of childbirth. During the initial - first stage of labor, the pain is the result of uterine contractions and the dilation of the uterine cervix, which radiates to the lower back and the sacrum; painful impulses are transmitted through the efferent nerve fibers that start from the uterus, and together with the sympathetic nerve endings enter the spinal cord at the segmental level from T10 - L1, whereby analgesia covers that segment of pain. During the second stage of labor, there is a strong perineal distension by the fetal leading part, leading to appearance of strong and precisely localized pain that radiates to the vagina, rectum and perineum. It signals the end of the first and the beginning of the second stage of labor, and occurs as a result of the movement of the fetus towards the exit segment. In this phase, somatic pain predominates, which, unlike visceral, is sharp and specific, and is the result of the stretching of the structures from the distal birth canal caused by the delivery of the fetus. In this final phase, additional sacral analgesia is needed at the sensory S2-S4 level.

Traditionally, methods of pain relief have been classified as non-pharmacological, pharmacological and regional (neuraxial) techniques. Hereby, the latest findings and evidence on

the efficacy and safety of the most commonly used methods of neuraxial type of labor analgesia are presented.

Epidural technique and regimens -Epidural analgesia (EDA) remains the standard neuraxial procedure for labor analgesia and, as a catheter technique, provides effective and long-lasting analgesia. Its popularity and widespread exploitation are evident, and the concern about an increased rate of C-Ss seems to remain unfounded, because the research excludes such a risk, even when it comes with early initiation of neuraxial blocks (1,2).

After the epidural space is identified by the "loss of resistance" technique (fluid or air), the epidural catheter (EDC) is placed no more than 5cm into the space; the initial loading dose of diluted local anesthetic with opioid is administered in doses of 5ml, with careful observation and mandatory monitoring of parturient blood pressure and heart rate between the dose bolusing. The epidural technique may require a different dosage of mixture, depending on many factors, but for adequate labor analgesia at the initial period it needs to top-upto 15ml (max. 20ml) of bupivacaine 0.0625 - 0.125 % (ropivacaine 0.08-0.1%) + fentanyl up to 4mcg/ml (or sufentanil). Historically, 3ml of 1.5% lidocaine with 1:200,000 epinephrine was used as a "test dose"; lidocaine makes a rapid proof of spinal anesthesia (motor blockade) and IVepinephrine will cause a transient tachycardia, but the sign is uncertain due to confusion with the tachycardia caused by labor painful contractions. The current trend is to use low dose of local anesthetic without epinephrine as a "test dose", which helps to reduce the motor blockade and to improve the ambulation of the parturient; there is a wide variation with test doses today (from 3-20mg bupivacaine and 15-90mg lidocaine), but any dosing via ED catheter, whether for the initial block or for the treatment of breakthrough pain, should be treated as a "test dose", because ED catheter can migrate intrathecally or IV, despite the initial correct placement in the epidural space (46). Further on, identification of the epidural space in pregnant women could be technically challenging, and even when the ED catheter is inserted without difficulty, unilateral block and missed segments with inadequate analgesia can occur (in 1of 8 parturients).

In the recent period, various EDA regimens have been investigated: continuous epidural infusion (CEI) with low concentrations of anesthetic (bupivacaine 0.1% with fentanyl 2mcg/ml) leads to a significantly higher number of spontaneous (unassisted) deliveries compared to the higher concentrations of the traditional method (0.25% bupivacaine), so it is concluded that "in terms of the method of delivery, the use of traditional epidurals is no longer justified" (3). Manual but more programmed intermittent bolus (PIEB) delivery is a good alternative to CEI for maintaining epidural analgesia, with the note that PIEB may improve the quality and duration of labor analgesia (4).

The patient-controlled epidural analgesia (PCEA) regimen allows the pregnant woman to self-delivering intermittent bolus doses, thus providing flexibility in relation to analgesia requirements as labor progresses. Labor pain is highly variable in intensity, and the character of the pain often changes as the labor process progresses, prompting a sense that parturient could be

the best managerof their own pain relief. There is recent evidence that genetic polymorphisms may influence the labor progress and the response to labor analgesia; namely, a μ-opioid receptor gene (OPRM1, A118G), which is believed to be present in 30% of pregnant women during labor, may influence the response to neuraxial-applied opioids (37).

During PCEA, the anesthesiologist takes care of adjusting the delivery program, he namely determines: the bolus and maximum dose delivered, the lock-out interval and the base (background) infusion rate, if there is any. This method of self-titration by the parturient allows improving the dose-requirement ratio in view of the labor progress. From that point of view, PCEA is related both to reduced demand and consumed dosage, especially in the first stage of labor. PCEA can be administered as a single dose-demand regimen (dosing as needed by the parturient) or as a background continuous epidural infusion (CEI), plus dose-demand regimen. Demand dose involves the delivery of a fixed high dose administered by the parturient with pressing the PCEA button without concomitant use of a background CEI. The role of the background CEI in the PCEA regime seems to be still insufficiently explained in the literature: while some studies suggest that CEI with PCEA increases anesthetic consumption without analgesic benefits, other studies show a reduced need for analgesia in the presence of background CEI. Thus, further studies are needed to analyze against background CEI (5).There are observations that the administration of a part (33%) of the maximum hourly demand dose as a background infusion (CEI) in accordance with PCEA, could be the optimal choice for labor analgesia in most of the parturient. However, it can be considered that high-level delivery pumps as the background infusion mode (CEI) improve labor analgesia in the setting of PCEA and as such, it is the best analgesic approach, also recommended by the American Society of Anesthesiologists (ASA) in Obstetric Anesthesia Guidelines (39).

Today, in part of the "smart" pumps, it is possible to analyze the condition of the woman in labor and her analgesia needs in the previous hour (based on the needs of PCEA), whereby the basal (background) infusion is automatically adjusted accordingly. Hence, the basal infusion rate will automatically increase for pregnant women who make more demands, and such a mode of computer analysis and delivery is part of the so-called mode of computer integrated (CI) analgesia, which can also run as CI-PCEA. In some comparative studies between CEI and CI-PCEA, it is shown that CI-PCEA can reduce the incidence of labor breakthrough pain, thereby achieving higher satisfaction in parturient (6).

Effects of EDA on the progress and mode of delivery-The topic has been controversial for many years and there are different opinions on this issue, nevertheless several studies are unanimous in the view that (7,8):

1. The epidural infusion with a low concentration of local anesthetic (0.0625% - 0.125% bupivacaine with 2mcg/ml fentanyl) does not increase the risk of C-Ss nor instrumentally assisted deliveries, although for the latter there are also opposite conclusions especially seen with higher concentrations of local anesthetic;

2. Neuraxial analgesia in early labor (<4cm dilation) does not increase the C-S delivery rate; whereas compared to systemic analgesia, it provides better analgesia and shortened labor duration (9).

The impact of exposure to neuraxial anesthetics on neonate neurodevelopment has not been fully studied and there are not definitive results regarding this item. EDA increases the risk of intrapartum fever in the mother, which may be adverse to neonatal outcome. According to some studies, EDA usage may also cause more frequent neonatal injuries during instrumental deliveries, although long-term adverse events are rarely described. On the other hand, EDA may reduce postpartum depression and, thus, may produce beneficial effects on neurocognitive development in childhood, but definitive evidence for this is still lacking (10).

When should EDA be discontinued? There is insufficient evidence that epidural analgesia should be discontinued in late labor as a means of reducing adverse effects of delivery. In such a way, the rate of inappropriate pain in the second labor stage increases, but a meta-analytic survey of high-quality studies showed no significant differences in the mode of delivery (outcome) with these different approaches to analgesia during the second stage of labor (42,43).

Combined spinal-epidural (CSE) analgesia-The technique is a suitable option for labor analgesia for severe pain, usually associated with more advanced labor. It enables rapid and profound analgesic action (2-5 minutes vs. 15-20 minutes), caused by the spinal dosage. If necessary, the block is potentiated or continued with the additional epidural dosage applied through the epidural catheter.

It is stated that the CSE technique may have certain advantages over EDA: 1. Rapid start of the analgesic block including sacral analgesia, which leads to greater satisfaction of parturient, 2. Confirmation of correct placement of the epidural needle. The appearance of cerebrospinal fluid in the spinal needle during CSE is a confirmation of the correct placement of the epidural needle. This is especially important in those with difficult anatomy or the obese, which results with a higher rate of success. When compared with conventional EDA, the overall failure rate (accidental intravascular placement of the epidural catheter, inadequate epidural analgesia—unilateral or “patchy” block, reduced need for additional bolus doses, reduced total anesthetic dose, repeated catheter replacements) is significantly lower in patients receiving CSE analgesia compared to EDA (12), 3. It allows greater mobility of parturient, 4. Block caused by spinal dose (especially in primiparous women in the early stage of labor) may lead to faster progress of cervical dilatation compared to EDA (11,12), 5. An unsatisfactory spinal block can at any time be corrected, continued or switched in anesthesia for emergency C-S.

The same regime of intrathecal component from the spinal (single-shot) analgesia can be used in the CSE method (1-2.5mg 0.5% Bupivacaine + Fentanyl 15-25mcg), with the possibility of an additional epidural dose. This synergistic action allows analgesia lasting 90–120 minutes, with the presence of minimal motor block, while intrathecal opioid (ITN) can provide satisfactory

analgesia in the early latent phase, but almost always requires the additional analgesia (bupivacaine) in the mixture for satisfactory analgesia in advanced labor. Some studies suggest using lower opioid and local anesthetic doses (max. 15µg fentanyl, 5µg sufentanil), but despite the increasingly widespread use of this technique, as well as numerous published studies, the optimal intrathecal regimen of the mixture has not yet been defined. An intrathecal (spinal) dose provides satisfactory analgesia until the onset of therapeutic analgesia levels caused from the epidural dose or infusion, which can sometimes begin soon after the spinal injection, thus creating a "perfect" transition from spinal to epidural analgesia. The regime of epidural infusion of bupivacaine (0.0625-0.08- 0.125 + Fentanyl 2mcg/ml, at a rate of 8-15ml/h, which can be activated later (i.e. 30-40 minutes after spinal injection or before the end of its analgesic effect), is the most often used. Serious maternal side effects from the recommended doses of this regimen are rare.

The most common side effects of CSE in practice still remain the following: 1. Fetal bradycardia (FB), which is not accompanied by a higher risk of C-Section, and 2. Pruritus. It is hypothesized that FB is caused by uterine hypertonus induced by decreased circulating catecholamines and could be avoided by a reduced dose of intrathecal opioid. Unsettled FB can usually be treated with the usual procedures that include repositioning (left lateral tilt), IV bolus fluids, IV terbutaline, ephedrine or phenylephrine. Itching after CSE usually subsides after 45–60 minutes and can be minimized with reduced fentanyl doses (10-15mcg); small IV dose (5mg) of nalbuphine (mixed agonist-antagonist) which successfully relieves the effect without reducing analgesia. Concerns about an increased risk of infection or PDPG associated with spinal needle dural puncture are unfounded.

Although the functionality of epidural catheters placed during CSE at the beginning of the block cannot be accurately determined (due to the nonfunctional test dosage), evidence suggests that ED catheters placed via CSE are more reliable than ED catheters placed during a standard ED procedure.

Better satisfaction among parturients, faster onset of action and general impression, may account for the wider use of CSE, but whether there are definitive reasons for favoring CSE over EDA remains undefined. An extensive Cochrane study (e.g. 19 studies, 2,658 pregnant women) suggests that there is little basis for offering CSE over epidurals, despite the reported positive effects and overall impression of it (13). In practice, the choice between conventional epidural and CSE is usually dictated by the clinical situation, institutional protocols, equipment availability and anesthesiologist's experience, i.e., depending on the preferred method.

Dural puncture via epidural (DPE) is gaining more popularity in the last decade. The procedure is similar to the CSE technique, but the intrathecal administration of anesthetic is omitted. Intentional dural perforation is thought to allow some passage of the epidural dose intrathecally, thereby improving the epidural function. Studies regarding the superiority of DPE over traditional EDA are equivocal. A recent systematic review concludes that there is a lack of

clear benefit over EDA (14), the next one notes that although "overall results remain equivocal," epidural puncture with 25-G spinal needles (not 26- or 27-G) provide higher success rates compared to standard EDA without dural puncture (15).The remaining two studies are also unanimous that DPE puncture results in fewer unilateral blocks and better sacral coverage compared to traditional epidural analgesia. When compared to CSE, DPE results in comparable analgesia (onset 11 min. vs. 2 min.) although with fewer maternal and fetal side effects (pruritus, hypotension, fetal bradycardia) (16).

Both techniques are useful to localize the epidural space, when the possibility of identification is limited, unclear or difficult to recognize. The flow of CSL through the spinal needle provides reliable evidence that the tip of the epidural needle is close to the dura, confirming the correct identification of the epidural space.

Spinal (singleshot) analgesia is an alternative method to the epidural which is usually applied where the epidural is not possible for various reasons, and that in the advanced stage of birth, preferably in multiparous mothers. The limited duration, as well as the impossibility of additional analgesia in the second stage of labor, represent limiting factors for more frequent application. The advantages come from the simple and practical performance, the low dose, as well as the rapid onset of action with immediate sacral analgesia. Side effects occur as a result of dural puncture (nowadays, very rare due to small atraumatic needles) and limited analgesic duration and possible impact on fetal ejection. Changes in the fetal heart rhythm are mostly of the FB type. The spinal cocktail of local anesthetic and opioid has a mutual synergistic effect, which deepens and prolongs the analgesic effect, reduces the total amount of local anesthetic and the risk of possible complications (2.5mg 0.5% bupivacaine plus fentanyl 25μgr has a synergistic effect with a duration of 90-120 minutes).The addition of a low-dose hydrophilic opioid (morphine ≤ 200μg) provides prolonged analgesia for up to 4 hours (17,18). Studies suggest that the addition of epinephrine to the combination of a standard intraspinal dose of bupivacaine and fentanyl (in CSE), provides a significant prolongation of single spinal analgesia.Out of the 4 doses tested (12.5-25-50-100μgr), it appears that 12.5μgr of epinephrine may be the optimal dose for this clinical purpose (45).

Continuous spinal analgesia -This technique can provide rapid analgesia or anesthesia with less amount of local anesthetic, but in expense with more difficulties and failure during spinal catheter insertion, compared to epidural analgesia. It is theoretically advantageous in the management of morbidly obese parturients, those with significant comorbidities who cannot tolerate hemodynamic instability, and those with a potentially difficult airway undergoing C-S. It allows for gradual dose titration and a slower onset of subarachnoid block. However, this technique is still less frequently used, due to the risk of more frequent occurrence of PDPH, as well as neuraxial infection (40).

Intrathecal opioid application (intrathecal analgesia, ITN) has its advantages, but also side effects. The application of spinal opioids in the recommended doses, does not cause sympathetic

blockade or mobility affection, nor does it affect the expulsion of the fetus in the second stage. From that aspect, it is useful in high-risk parturients, where functional spinal sympathectomy represents a risk (hypovolemia, aortic stenosis, tetralogy of Fallot, pulmonary hypertension, etc.).It causes fewer emetic complaints and less fetal affection when compared with IV analgesia.

ITN is usually insufficient to relieve labor pain in the second stage of labor, thus remaining a potential problem in most of the cases, so the addition of a local anesthetic is of great benefit. Nausea and vomiting, itching, respiratory depression and fetal bradycardia may occur. Repeated opioid doses result in poor results due to the development of tachyphylaxis. Liposoluble fentanyl is the most widely used intrathecal opioid for labor analgesia, primarily because of its rapid onset of action and deep analgesia without motor blockade. It is the most often used liposoluble opioids: fentanyl 10-25µg, sufentanil 5-10µg or 10-12mg meperidine (pethidine) possibly in combination with low-dose water-soluble morphine (max. 200µg), providing longer-lasting analgesia in the first birth stage (17,19).

Local anesthetics and adjuvants for labor analgesia -Local anesthetics such as ropivacaine and levobupivacaine, although having less potential for cardiotoxicity and motor blockade, are significantly more expensive than racemic bupivacaine. With the widespread use of dilute anesthetic concentrations, as well as with the CSE method, the likelihood of systemic toxicity caused by higher concentrations of bupivacaine remains very low. Clinical studies have also failed to show that ropivacaine or levobupivacaine offer any advantage over bupivacaine in terms of placental transfer and neonatal outcome, and therefore it appears to have little justification for their use in daily practice, so the popularity of bupivacaine as one of the most widely used local anesthetics remains largely unchanged (20,21).

An important progress in the quality of labor analgesia is the addition of the "adjuvant drugs" in the anesthetic mixture, with the intention of maintaining or improving the quality of analgesia at the expense of reduced doses and concentration of local anesthetic administered, which would result in less motor block and fewer instrumental interventions. Many adjuvants have been tested, such as midazolam, magnesium, ketamine, meperidine (Dolantin) and dexamethasone, but concerns about side effects and minimal efficacy have prevented wider testing and use, particularly in the obstetric population. However, some adjuvants have already gained popularity and wider application, such as the alpha agonists clonidine and dexmedetomidine, as well as neostigmine and epinephrine. Since opioids, alpha-agonists and neostigmine produce analgesia through different mechanisms of action, combining all these adjuvants may have the effect of further improving the quality and duration of analgesia, in terms of reduced local anesthetic dosing. For example, the addition of dexmedetomidine (an alpha2-adrenoceptor agonist, 0.5µg/mL) to epidural solutions has been shown to provide superior labor analgesia with fewer side effects (pruritus, nausea and vomiting) compared to opioid adjuvants (sufentanil) (22).Studies evaluating the safety, efficacy, optimal dose and method of drug delivery (PIEB, PCEA) with clonidine (α2-agonist) and (or) neostigmine (as adjuvants to a local anesthetic), with or without an opioid, consider that an epidural clonidine 75µg with neostigmine 750µg are

effective in initiating labor analgesia without inducing motor or sympathetic block (23,24). However, further research is needed to definitively evaluate their effectiveness and side effects before they are put into official use in obstetric anesthesia.

Complications from neuraxial anesthesia - Technical problems during needle insertion, unintended dural perforation and blood vessel injury (dural, bloody tap), hypotension and unsatisfactory block remain the most common adverse complications in obstetric neuraxial analgesia. The excessive motor block can have a prolonged effect on the course of the second labor stadium and increases the risk of instrumental delivery. PDPG develops in about 52-60% of parturients in whom inadvertent dural puncture is caused by an epidural needle, while it is, usually, much less common after dural perforation caused by spinal needles (from 0.5-2% with atraumatic needles). Recent studies show that PDPG in obstetric cases is mostly rare, but its association with a serious type of neurological complications (such as, for example, cerebral venous thrombosis, subdural hematoma, bacterial meningitis and other complications, persistent lower back pain, chronic headache) cannot be ruled out, emphasizing the need for early diagnosis and prompt treatment (25).

The occurrence of high neuraxial block is identified as one of the most common serious complications of neuraxial anesthesia in the obstetric population (1 in 4,336 procedures)(26). This serious complication usually occurs as a result of incorrect placement or migration of the ED catheter from the epidural space during labor, but it can also occur after spinal anesthesia for C-S, administered after a non-functional epidural labor analgesia (14%). Therefore, it is justified to warn the parturient that the placement of the ED catheter cannot be fully guaranteed, so the catheter may be placed again if the relief of labor pain is partial or unsuccessful. More recent knowledge about factors that contribute to failed epidural conversion, early replacement of dysfunctional catheters and their management during labor etc., can significantly help in reducing this type of complications (27,28).

Conversion of epidural labor analgesia to surgical anesthesia for C-S - The recommendation "early epidural analgesia for labor should be considered whenever possible, in order to reduce the risks associated with general anesthesia, especially in the setting of emergency C-S" implies the active involvement of the anesthesiologist from the very beginning of the laborprocess, familiarization with the health condition and possible comorbidities of the pregnant woman, as well as early and timely placement of ED catheter especially in those who have less chances to deliver spontaneously. The importance of this recommendation was emphasized during the COVID-19 pandemic, and soon afterwards it was affirmed by the Societies of Maternal-Fetal Medicine (SMFM) and Obstetric Anesthesiologists and Perinatologists (SOAP) (26).

Several precautions should be taken when converting a neuraxial labor block to anesthesia for C-S and the first step of the set of measures is 1. The verification of the functionality of the ED catheter and the eventual presence of reduced labor pain. The inability to obtain satisfactory analgesia, i.e. the presence of a unilateral or inadequate (patchy) block and the need for an

increased number of bolus doses to maintain satisfactory analgesia, indicates the non-functionality of the ED catheter and, in principle, it should not be used for further conversion; 2. The visual inspection of the site of the inserted catheter is also essential, as well as;3. Careful aspiration through it, in order to exclude possible migration outside the epidural space (subdural or spinal location).Unrecognized spinal migration is one of the most common and serious complications in obstetric anesthesia - almost 1/4 of high neuraxial blocks are the result of unrecognized spinally inserted catheters, and even 93% of them refer to obstetric cases (26); 4. during the conversion to C-S, the timing since the last epidural dose should be taken into account- if the interval is less than 30 minutes, the possibility of high spinal block may be increased if spinal anesthesia is used for C-S (36).

The location or the place to administer the initial epidural dose for C-S can be the delivery box or the operating room, which in themselves have their own risks or benefits. The administration of the epidural dose in a labor box facilitates the rapid onset of surgical anesthesia, but may delay the diagnosis and management of possible complications (high spinal block, hypotension, systemic toxicity), whereas the initiation of the epidural dose in the operating room can delay the onset of surgical anesthesia. The final decision is made depending on the urgency of the C-S, as well as the possibilities for adequate monitoring and resuscitation during transportation. From a practical point, it may be the best to administer the initial epidural dose in the labor box through a fractionated test dose of 3-5mL 2% lidocaine with epinephrine (or 3% 2-chloroprocaine) and then immediately to transport the parturient to the operating ward, accompanied by an anesthetist and monitoring; after positive confirmation of progressive spread of bilateral cephalic block, an additional epidural dose is administered to achieve the desired block height (Th4).

Adjuvants for rapid conversion to C-S -Commonly used adjuvants are epinephrine, sodium bicarbonate and opioids that increase the speed, duration and quality of anesthesia. Epinephrine intensifies the surgical block, as a result of α2-adrenergic receptor stimulation located on the superficial laminae of the spinal cord.It is more effective when combined with lidocaine than with bupivacaine, and the concentration is 5mcg/mL (1:200,000).The addition of epinephrine to 2-chloroprocaine, although prolonging the duration of epidural analgesia and motor block, is not routinely used (35). Addition of 1mL of 8.4% sodium bicarbonate (1mEq/mL) to 10mL of 2% lidocaine increases its rate of action - by raising the pH of the solution to its pKa value, more of the ionized molecules are available for passage across neuronal lipid membranes. The time is shortened to 5.2 minutes when bicarbonate is added, vs. 9.7 minutes With the mixture of lidocaine-epinephrine-fentanyl (29). The addition of bicarbonates to bupivacaine (ropivacaine or levobupivacaine) causes precipitation and should not be used. Alkalization with 2-chloroprocaine slightly increases the speed of onset of epidural analgesia (12 minutes with bicarbonate vs. 14 minutes), although there are no studies with definitive results (33). Common practice is to use epidural 2-chloroprocaine in a higher (3%) concentration and without any adjuvant. It ensures a faster onset of action and avoids the delay in preparing the mixture when time is of the critical essence.

Opioids and new adjuvants -Lipophilic opioids such as fentanyl (50-100μg) and sufentanil (10-20μg) are commonly combined with a local anesthetic for rapid conversion to epidural anesthesia. They increase the speed of action, improve the quality of anesthesia and provide synergistic analgesia for the treatment of intraoperative visceral pain (34). The neuraxial addition of clonidine, dexmedetomidine, neostigmine, ketamine and magnesium have been suggested to improve analgesia for C-S. Clonidine can cause hypotension, bradycardia and sedation at higher doses and is therefore not recommended in US obstetric patients. However, the neuraxial use of these agents is not yet officially indicated, as further studies of their neurotoxicity, analgesic superiority and side effect profile are needed before they can be officially recommended as neuraxial adjuvants for labor analgesia.

Conversion failure for C-S -There are 3 main failure factors commonly reported in the literature, and these include: 1. The administration of the epidural by a non-obstetric anesthetist; non-obstetric anesthesiologists are more likely to induce GA and less likely to manipulate the ED catheter or option for another type of neuraxial technique when conversion fails (28,32); 2. The number of additional epidural boluses for labor pain relief. A non-functioning ED catheter may result in pain requiring additional bolus doses, and such a catheter is unlikely to be useful for surgical conversion (with parturient who receive 1 or more additional unplanned boluses, the failure rate is increased 3-fold)(32).It should be noted that breakthrough labor pain can also indicate a dysfunctional delivery, which necessitates an obstetrical evaluation of the progress of the delivery;3. Urgency of the C-S- is an important risk factor because there is less time to manipulate the epidural block, therefore conversion to GA is highest in most-urgent C-Ss (32).

Key recommendations to reduce the risk of failed conversion are: 1. Active communication with the obstetrician in order to identify women in labor at risk of C-S; 2. Removal of the inappropriate labor epidural blockade with timely optimization or replacement of the ED catheter that does not work with a new epidural or combined spinal-epidural anesthesia (CSE); 3. The confirmation of the location of the ED catheter by visual inspection and by the administration of a test dose before transport in the operating room; 4. Assessment of the block in the operating room - do not administer more than half of the full dose of local anesthetic if the block does not progress cephalically and bilaterally; 5. Application of an alternative anesthesia technique in case of failure, as said, one should always use the fastest-acting local anesthetic i.e. 2% lidocaine-epinephrine-bicarbonate with an opioid for C-S emergencies or 3% 2-chloroprocaine (35,36).

Management of failed epidural conversion - In most of the cases of C-S, the woman in labor should be trusted if she complains of pain and the anesthetic failure accepted. In general, epidurals have a higher failure rate compared to spinals. Not always the epidural block can provide 100% anesthesia even after the correctly performed procedure and its active management. The treatment of pain during C-S is extremely important because the inability to deal with it can lead to complications of psychological disorder (including post-traumatic stress disorder, 11%) and that can affect the long-term well-being of the patient (37). Moreover, according to a review of litigation on inadequate anesthesia during C-S, pain during neuraxial

anesthesia for C-S is one of the most common causes of these disputes in UK directed against obstetric anesthesiologists (35).

There are no complete practice guidelines for the optimal management of failed epidural anesthesia for C-S, but an option remains IV supplementation of fentanyl 25–50μg or alfentanil 250–500μg, and ketamine 10mg bolus doses, or conversion to GA. From that point of view, it is necessary to ensure an adequate neuraxial blockade before starting the surgical incision.

Intralipid infusion - Anesthesia safety becomes greater with the availability of intralipids as a countermeasure for local anesthetic toxicity. Intralipids bind with an amidoanesthetic molecules in the plasma, while reducing the free toxic fraction that depresses the heart muscle. It has become a widely accepted procedure and is part of resuscitation protocols for local systemic anesthesia-induced toxicity and should be readily available in all units practicing neuraxial analgesia (41).

Conclusion

There is no doubt that neuraxial analgesia is the most effective method for relieving labor pain and it remains the main analgesic approach in obstetric practice. In addition to eliminating labor pain, which is described as one of the strongest pains that a human being can experience, modern neuraxial analgesia allows minimal motor disability and enables ambulation during labor, minimal impact on the progress of labor, as well as safety and security of both mother and neonate. Decreasing the concentration of bupivacaine from 0.5% to 0.065%, and adding neuraxial opioids allowed achieving effective labor analgesia while minimizing potential adverse effects on labor progress, as well as less motor blockade. The techniques of epidural analgesia controlled by parturient itself are rapidly evolving to enable more flexible analgesia that is adaptable to the individual needs of women in labor (during the different stages of labor), while "smart" pumps and computer systems are being refined to a degree to provide maximum analgesia and comfort, starting from the initial block until the final act of laboring. Ultrasound (US) identification as part of the assessment of the depth of the epidural space, as well as for scanning the interfacial structures during truncal blocks, is also widely used in the obstetric population. Pre-procedural US reduces the risk of failed epidurals and traumatic insertion and is therefore approved by the US Institute of Health (NIH). New adjuvant drugs that improve the synergism and effectiveness of local anesthetics, while reducing the side effects of single high doses of local anesthetic, are already part of routine practice in obstetric anesthesia.

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