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The right drug and dose for neuraxial labour analgesia

P. Y. DEWANDRE

INTRODUCTION

Neuraxial analgesia has been demonstrated for many years to be the only safe and effective way to provide labour analgesia (1). However, labour epidural analgesia relying on high doses of local anaesthetics (LA) produced motor block interfering with labour and the mode of delivery.

To reduce these side effects, adjuvants are routinely combined with local anaesthetics since more than 20 years.

New LA has become available during the last 10 years and new modes of administration of analgesics have also gained in popularity during the last decade i.e. patient-controlled epidural analgesia (PCEA) and combined spinal-epidural (CSE).

Therefore, an adequate understanding of those improvements is required to provide the optimal neuraxial analgesia during labour and delivery.

DRUGS

Local anaesthetics

The last ten years have been marked by the arrival of two new local anaesthetics (LA), ropivacaine (Naropin®) and levobupivacaine (Chirocaine®). Their advantages would be a reduced systemic toxicity and a better preservation of motor function. For those reasons, they have been challenging bupivacaine (Marcaine®) as the most widely used LA in obstetric analgesia so far (2, 3). The majority of authors agree that toxicity is not an issue when low doses and concentrations of local anaesthetics are used as it is the case for modern neuraxial obstetrical analgesia. The benefits of reduced motor impairment with ropivacaine remain controversial. A first meta-analysis reported obstetrical and neonatal benefits with ropivacaine compared with bupivacaine when used at "historical" high concentrations (0.25%) (4). These results were not confirmed by a subsequent meta-analysis or randomised trials that failed to identify any difference between both drugs in terms of obstetrical outcome when "modern" dilute concentrations are used (5-7).

Ropivacaine and levobupivacaine have been reported to be less potent than bupivacaine when compared using the MLAC model (8-9). However, this difference in potencies has not been confirmed is when these drugs are used at clinically useful concentrations.

A study reported less motor block with ropivacaine 0.08% plus fentanyl 2 µg/ml than with same concentration of bupivacaine plus fentanyl when this block is evaluated on a 6 points modified Bromage's scale or by the ability to ambulate (10).

However, another study that took into account a reduced potency of ropivacaine and compared "equipotent" dilute solutions i.e. bupivacaine 0.0625% *vs* ropivacaine 0.1% failed to demonstrate any difference on the ability to ambulate (11).

These minor and controversial differences in clinical outcome and the differences of cost of these new agents have led several authors to divergent conclusions regarding the place of the most recently marketed LA for labour analgesia (12-14).

Therefore, it seems evident that the adequate dilution of local anaesthetics and the strategies aiming to reduce their consumption are more important than the choice of the local anaesthetic by itself when the goal is to provide optimal neuraxial obstetrical analgesia.

Several strategies have been proposed to reduce the LA concentration and consumption i.e. the admixture of adjuvants such as lipophilic opioids, clonidine, adrenaline and neostigmine to epidural local anaesthetics.

P. Y. DEWANDRE, M.D., University Department of Anaesthesia & ICM, CHR de la Citadelle, University Hospital, 4000 Liege, Belgium.

Correspondence address : Dr. Pierre-Yves Dewandre, University Dpt of Anaesthesia and ICM, CHR de la Citadelle, B-4000 Liege. Tel. : 32-4 225 6470. Fax : 32-4 225 7308. E-mail : pydewandre@chu.ulg.ac.be.

Opioids

Fentanyl and sufentanil used in combination with LA allow effective analgesia using concentration of LA that would otherwise be sub-therapeutic. Their use has become routine from the mid 80's.

This approach reduces motor blockade and the incidence of instrumental delivery compared with LA-only solutions (15). Pruritus is the most common side effect of opioids and is dose dependent. Potential maternal and neonatal respiratory depression must also be considered. Epidural sufentanil doses ranging from 7.5 µg to 30 µg have been reported to improved quality of analgesia as well as reduce motor block and instrumental deliveries (16-17). Sufentanil 0.75 µg/ml has been described by some authors as the optimal concentration when combined with bupivacaine 0.125% administered in intermittent top up (18). However, others reported that reducing sufentanil concentration to 0.156 µg/ml reduced pruritus without altering the quality of patient-controlled epidural analgesia with bupivacaine 0.125% (19).

Dose-dependent reduction of the MLAC of bupivacaine has been reported for sufentanil concentrations between 0.5 µg/ml and 1.5 µg/ml and for fentanyl concentrations between 1 µg/ml and 4 µg/ml when administered in a 20 ml volume (20-21).

Epinephrine

Epinephrine is another widely accepted adjuvant for neuraxial analgesia. It decreases dural blood flow which is responsible for clearance of epidural drugs and makes more drug to be able to diffuse to the CNS. Moreover, it has a direct analgesic and produces segmental analgesia. One possible mechanism is an effect on the α_2-adrenergic receptors in the dorsal horn. Epinephrine enhances central antinociception, reduces vascular uptake of analgesics, increases the neuronal block induced with LA and decreases their risk of systemic toxicity. It has also been widely used to detect intravenous injection of LA. Side effects related to epinephrine administration are a reduced uterine blood flow and a reduce uterine contractility. Epinephrine is also responsible of an increased incidence of motor block, maternal hypotension, pruritus,nausea and vomiting. These controversial side effects seem to be dose-related and apparent in concentrations up to 1/300.000.

Therefore the addition of epinephrine to LA and/or opioids remains questionable and even more with the new LA that possess intrinsic vasoconstrictor properties (22).

Clonidine

Epidural administration of clonidine**,** an a_2-agonist, has also been largely investigated (23).

Its analgesic properties have been well demonstrated by its sparing effect on the MLAC as well as on the LA consumption.

However clonidine has a very narrow therapeutic range, as it is ineffective with bolus below 60 µg and is responsible for increased incidence of maternal hypotension and sedation as well as fetal heart rate alterations with bolus higher than 75 µg or repeated administrations (24-29). Moreover clonidine has not been approved by the FDA for use in obstetric analgesia. Recently, analgesic efficacy and side effects of sufentanil and clonidine has been compared.

75 µg clonidine or 5 µg sufentanil produces similar reduction of the MLAC of ropivacaine (30). Administered at these equianalgesic doses, clonidine induces more frequent and severe maternal hypotension while sufentanil is responsible for more frequent pruritus (31). For those reasons, clonidine is not a first choice adjuvant for epidural administration (32).

Concerning intrathecal administration of clonidine, doses as low as 15 to 30 µg have been reported to increase incidence of maternal hypotension, ephedrine requirements and incidence of fetal heart rate abnormalities (33-34). Therefore administration of intrathecal clonidine during labour is not recommended.

Neostigmine

The opioid, noradrenergic and adenosine analgesic systems involve cholinergic stimulation of nicotinic and muscarinic receptors in spinal cord interneurons. Neostigmine, a cholinesterase inhibitor, has demonstrated interesting neuraxial analgesic properties.

Epidural administration of neostigmine at doses ranging from 500 to 750 µg combined with 10 µg sufentanil provides reasonable early labour analgesia without any significant maternal or fetal side effect. Nevertheless, the side effects associated with repeated doses or continuous infusion remain to be determined (35-37).

Intrathecal administration of neostigmine alone at the dose of 10 µg is ineffective and provides inconstant enhancement of analgesia with

sufentanil and bupivacaine. Moreover this intrathecal administration is associated with an unacceptable high incidence of nausea unresponsive to antiemetics. These side effects preclude its intrathecal use (37).

Mode of administration

If the choice of drugs, concentrations and combinations is of the highest importance, their mode of administration is also very important. Patient-controlled epidural analgesia sometimes following a spinal administration of an opioid with or without LA (combined spinal-epidural : CSE) has replaced the historical intermittent "top-ups" or continuous infusions in order to improve analgesia while reducing LA consumption and motor impairment.

Combined spinal epidural

Combined spinal epidural (CSE) for labour analgesia is slowly gaining popularity. Analgesia is initiated with a spinal administration of an opioid sometimes combined with a LA. Thereafter, analgesia is maintained via an epidural catheter. This technique allows a faster initiation of analgesia with spinal opioid alone in early labour and a reduction of anaesthetic requirements as compared to epidural analgesia.

The preservation of mobility and consequently the ability to ambulate was supposed to offer benefits on labour evolution and mode of delivery. Unfortunately, no randomised trial has been able to confirm that theory (38-41).

It must be kept in mind that CSE has been reported to be responsible of a higher incidence of fetal heart rate abnormalities and uterine hyperactivity especially with sufentanil doses higher than 5 µg. The spinal administration of LA may be associated with an increased incidence of motor block (42-44). Here again, the adequate combination of LA and opioids makes possible to provide adequate analgesia while reducing the side effects of each drug.

PCEA

Patient controlled epidural analgesia has become the gold standard to provide labour epidural analgesia. This mode of administration is superior to intermittent top-ups in terms of maternal satisfaction (45) and to continuous infusion in terms of local anaesthetics consumption and incidence of motor block (46). Controversy still remains about the usefulness of a background infusion. Initial studies addressing this issue favoured PCEA without basal rate with bupivacaine 0.125% plus sufentanil and with ropivacaine 0.1% plus sufentanil while more recent publications evaluating lower concentrations of LA favoured PCEA with basal rate (47-53).

Conclusions

All those considerations on the pharmacodynamic properties of the different analgesics that can be used for neuraxial analgesia demonstrate clearly that it does not exist one single "magic bullet" able to provide ideal analgesia and that an optimal combination of drugs is needed to obtain the adequate analgesia without interfering with labour evolution or the mode of delivery and without inducing maternal or neonatal side effects.

Optimal method of administration is at least as important as it plays a major role on the quality of analgesia, maternal satisfaction and incidence of side-effects.

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