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Intrathecal hyperbaric bupivacaine 0,5% versus intrathecal hyperbaric prilocaine 2% for scheduled cesarean section

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1. **INTRODUCTION**

In case of scheduled cesarean section, intrathecal anaesthesia, in the absence of contraindications, is the choice of anesthetic technique (1). This procedure is simple to perform and involves the administration of local anaesthetic with or without adjuvant, into the subarachnoidal space surrounding the spinal nerves and the spinal cord. It leads to a rapid onset of surgical anesthesia with a good quality motor and sensory nerve block to let the surgeons do their surgery in good conditions as well for the patient (2). So, it allows the parent, the mother in particular, to have a better experience of the delivery during the c-section.

Nevertheless, there are secondary effects due to this procedure and the local anaesthetics. Principally, haemodynamics effects such as major low blood pressure can decrease the utero-placental perfusion and cause nausea and vomiting (3,4). The outcome of the newborn is essentially related to the duration of maternal hypotension (5,6). Some prophylactics measures or treatements are taken, such as preloading perfusions, mother's position (left tilt) and the use of vasopressors drugs (ephedrine, phenylephrine) (3,4,7), but their efficacity remains questionable (8). Today, the studies' authors agree on the fact that the haemodynamics effects of the intrathecal injection are directly linked to the dose of the local anaethetic (9).

For over 30 years, hyperbaric bupivacaine 0,5%, an amide-type local anesthetic of long action time, is the most used drug for spinal injection in c-section, associated to opiods (sufentanyl or fentanyl and morphine) (10,11). However, its use is frequently followed by haemodynamical instability and by a motor nerve block of long duration, two factors that lead to an increased fœtal risk and maternal discomfort (12).

The arrival on the market of newer short and intermediate duration time local anaesthetics such as chloroprocaine and prilocaine, seems to offer a good alternative for hyperbaric bupivacaine (13). This coincides with practice trends in anaesthesia for more ambulatory perioperative pathways and to a fast track rehabilitation in every speciality, obstetrics included.

Prilocaine, in particular, since its recent marketing into its stable hyperbaric form, has already been used for spinal injection in many studies in orthopedic surgery, gynaecologic surgery, and urologic surgery where it permitted a good quality nerve blockade with less secondary effects (14, 15). Its use, indeed, has shown a rapid onset anaesthesia (from 8 to 18 minutes maximum), a shorter action during time compared to the bupivacaine and a faster motor block offset in postoperative time, determined at 118 minutes (16).

In obstetrics, the former prilocaine isobaric form has been used only for epidural analgesia for the labour and vaginal delivery. Nevertheless, newborn high methemoglobinemia has been observed, due to long time epidural perfusion, at elevated doses in a range of 5,4-6,7 mg/kg (higher doses than 600mg) (17). Recently, hyperbaric prilocaine, without opiods adjuvants, has been used for c-section surgery in intrathecal injection in a pilot study realised to determine the efficacity dose 95 (ED95) (18). The results seem to be promising.

Until now, no study has ever compared prilocaine versus bupivacaine in spinal injection for c-section.

Our primary goal is to analyse the place of hyperbaric prilocaine 2% in a context of scheduled cesarean section by a power comparison study versus hyperbaric bupivacaine 0,5%, to find the most efficient one with a shorter action time and less secondary effects between this two local anaethetics.

2. MATERIAL AND METHOD

It is a prospective, randomised (double blinded), multicentric study, with parturients undergoing scheduled cesarean section performed with intrathecal anaesthesia.

2.1. Population

Patients will be included in the study, after reading, understanding and accepting the document explaining the goals and the procedure of the study protocol and signing their consent. The study will proceed in the department of Anesthesiology-Reanimation of the CHU Saint-Pierre and in the department of Anesthesiology of the Hospital Sainte-Anne Saint-Rémi in collaboration with their respective department of obstertrics. The number of patients to be included in this study has been determined by a power study based on previous results. The trial will be end when a sample of 100 parturients will undergo a scheduled cesarean section performed with intrathécal anaesthesia.
The primary goal is to compare prilocaine with bupivacaine usually used in spinal injection; parturients will be assigned after randomisation into 2 groups:

G1 : Hyperbaric Bupivacaine 10 mg (Marcaine®)
G2 : Hyperbaric Prilocaine 50 mg (Tachipri ®)

To each dose will be added 2.5 µg of sufentanyl and 100 µg of morphine and the total injected volume will be identical for every group.

<u>Inclusion criteria</u>

- ASA < III
- Age 18-40 year
- Weight <110 kg
- Height between 160 and 175 cm
- Gestational age>37 SA
- Scheduled cesarean section
- Single fetus
- Non complicated pregnancy

<u>Exclusion criteria</u>

- Twin pregnancy
- History of 2 cesarean section or more
- Diabetes and gestational diabetes
- Placenta praevia

- Congenital foetale abnormality
- Patient in labour
- Membrane rupture
- Allergy to local anaesthetics
- Disagreement of the patient
- Gestational low blood pressure
- Pre eclampsia and eclampsia

2.2. Anaesthesia plan

Preoperative :
Patients will undergo a combined spinal and epidural anaesthesia, to allow for supplementation of the anesthesia in case incomplete or insufficient blockade.

2.2.1. Preoperative

- Premedication : PO ranitidine 300mg the day before, in the morning PO ranitidine 150mg and PO metoclopramide 10mg 30 minutes before the combined anaesthesia, PO citrate of sodium 30ml before the operating room.
- Coagulation test, full blood count, blood group, cross match and irregular antibodies check, and renal tests
- Miction before the operating room, evaluation of the bladder volume (Bladderscan) before the intrathecal anaesthesia in the operating room.

2.2.2. Peroperative

- Monitoring :

ECG, NIBP, pulse oximetry (SpO2), peripheral venous access 18G or 16G, urinary catheter, Bair hugger.

- Realisation of the combined anaesthesia :

Vascular co-loading with 1000ml of Hartmann solution.
The patient is in a sitting position, L3-L4 level is localised. With a Vygon combined anesthesia set, the epidural space is reached with a Tuohy 8 cm needle, 17G with a low resistance syringe filled with saline. Then, a 29G needle is used through the Tuohy needle to access to the spinal space ; once the cephalo-spinal liquid reflux is positive, the test solution with 100 µg of morphine is injected into the spinal space in approximatively 20 seconds. Then an epidural multiperforated catheter is introduced until 3-4 cm in the epidural space, an aspiration test is done but no test dose is injected. The patient is placed, after 5 minutes minimum of the intrathecal injection, in supine position with a left tilt and 3l/min of nasal O2.
Every patient receive, after randomisation, a predetermined local anaesthetic dose (bupivacaine or prilocaine).

- Nerve blocade evaluation :

The evaluation of the sensitive level will be realised by a *pressure test, a cold test and a pin-prick test.*

The block will be considered as a :

- **SUCCESS** : bilateral T4 level reached in 15 minutes after intrathecal injection without additional epidural injection needed within 45 minutes peroperative ; no pain at the skin incision, no pain during 45 minutes after the skin incision.
- **FAILURE** : level < T4 at 15 minutes after the intrathecal injection or the additional epidural injection needed during the cesarean section (*lidocaine 2% with epinephrine*) by 5ml/5minutes for a VAS< 3.

- Low blood pressure evaluation :

As low blood pressure, we define a blood pressure lower than 20% or more than the basal blood pressure (Systolic BP before spinal anesthesia).
Treatment : *Ephedrine 5mg/ml, phenylephrine 100 µg/ml* by titration (ml by ml); blood pressure goal : Systolic BP before spinal injection -10%.

2.2.3. Postoperative

- Postoperative analgesia : Paracetamol + NSAID at the end of the surgery.
- Removal of the urinary catheter : after complete offset of the motor block and a stand up trial (after a forced extention of the legs against resistance, about 3 hours after the intrathecal injection) ; and/or S2 level restored.
- Monitoring of the bladder volume 1x/hour, by Bladderscan examination until first miction.

In case of bladder retention, defined such as a bladder volume higher than 600ml, associated at a spontaneous miction, a bladder catherisation will be realised.

- Walking : it will be asked to the patient to do a walking test (6 minutes walking test) with a minimum of 25 m to walk, 1h, 2h, 3h and 4h after a complete released of the motor block and a sensitive block lower than L5-S1.

2.3. Statistical analysis method

The primary outcome that will be analysed in this study is the time to motor block resolution after intrathecal injection of the two local anaesthetics.
Every patient will receive, after randomisation, a dose of local anaesthetic (bupivacaine or prilocaine); the study will be powered to highlight a difference of 20% for the principal variable between the groups.

2.4. Collect of the data

2.4.1. Patients

- Name, number of file, age, weight, height, BMI, parity/gestity, ethnicity, number of previous c-section, term.
- Blood pressure, cardiac frequency, pre operatory SpO2 and before anesthesia.
- Bladder volume before Spinal injection.

2.4.2. Central block (spinal injection)

- *Sensitive block* : level (pressure test, cold and pin-prick) every 2 minutes after spinal injection for 15 minutes, then every 5 minutes until the end of the surgery, then every 30 minutes until the complete release of the sensitive block (T12-S1) ;
- Time between spinal injection and reached of T4 level ;
- Obtained level 5 minutes after spinal injection ;
- Maximum sensitive level ;
- Complete lifetime of the sensitive block (as the period between maximun level and the regression to the level T12-S2) ;
- Lifetime of an adequate anesthesia for surgery (as the period between spinal injection and a VAS≥3 or a sensitive level superior regressed below T4 ;
- Lifetime of the complete anesthesia (as the period between spinal injection and a VAS≥0.
- *Motor block* : Modified Bromage score (from 1 to 6), before spinal injection, 10, 15, 20 minutes after injection, then every 15 minutes until the end of the surgery, then every 30 minutes until the complete released of the motor block (Bromage 6) ;
- Time of installation of the motor block (time between spinal injection and maximum motor block or Modified Bromage score of 1) ;
- Total lifetime of the motor block (time between maximal blockade/ Modified Bromage score 1 and a Modified Bromage score 6).

2.4.3. Surgical variables

- Time between spinal injection and skin incision ;
- Time between spinal injection and placental delivery ;
- Time between skin incision and placental delivery ;
- Time between uterine incision and placental delivery ;
- Lifetime of the surgery.

2.4.4. Haemodynamic variables

- BP (BP/ 1' for 15 minutes, then BP/2,5' until the end of the surgery, BP/20' in the awaking room), CF ;
- Needs of vasopressors drugs, total dose of administrated vasopressor drugs (phenylephrine, ephedrine).

2.4.5. Ventilation, state of conciousness

- SpO2, respiratory frequency, situation of respiratory depression (RF< 10c/minutes or SpO2< 95%) ;
- State of conciousness every 10 minutes after the spinal injection for one hour.

2.4.6. Secondary effects

- Pain :VAS at incision time, placental delivery time, peritoneal closing time, skin closing time and every 5' during the c-section, then every 4 hours for 24h ;
- Nausea/ Vomiting, Headache, Prurit from 15 minutes after spinal injection, then every 4 hours for 24h ; marked as : 0= no symptoms ; 1= symptoms with no treatment necessary ; 2= Symptoms present and treated ;
- Total blood loss (ml) ;
- Transcient neurologic symptoms at D0, D1, D3 and D15, Defined as pain or dysesthesia or both, showed after complete released of the block in the lower limbs (19).

2.4.7. Post-operatory analgesia

- Lifetime between the first administration of antalgic drugs after the spinal injection, doses of the administrated drugs by day et total of injections for 72h.

2.4.8. New born

- Fetal cardiac frequency at the admission, weight, Apgar score, pH of the ombilical cord, SpO2, methemoglobinemia ;
- Time between skin incision and birth, time between birth and the end of the surgery.

2.4.9. Quality of the technic

- Time of the bladder catheterisation, time of the first miction, residual bladder volume between the end of the bladder catheterisation and the first miction, urinary retention ;
- Walking time, possibility of doing the 6MWT and the number of meters achieved, 1h, 2h, 3H and 4h after a complete recuperation of the motor block and a sensitive block below L5-S1 (after cold test and pin-prick test) ;
- Maternal satisfaction about the anesthetic technic during the surgery. It will be evaluated at the arrival in the awaking room by two methods : a) with a visual analogic scale where 0 cm = very unsatisfied and 10 cm = very satisfied ; and b) patients who have beneficiated of a previous c-section, will be asked to answer the question if they prefere the actual technic, the previous technic or have no preference (20) ;
- Maternal rehabilitation : it will be evaluated at D1, D2 and D3 in the hospitalization unit by two methods : a) with a visual analogic scale where 0 cm = very poor and 1à cm = excellent ; and b) with the QoR score (Quality of Recovery score) (20) ;
- Obstetrician and midwife satisfaction with a four points scale (0= unsatisfied/ poor quality ; 1= low satisfaction ; 2= satisfied/ good quality ; 3= very satisfied/ very good quality ; 4= excellent).
- Global cost of the technic

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