C H U | U V C
B R U G M A N N

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**At the attention of the EMA**

*Brussels, 16 July 2021*

To whom it may concern,

EudraCT clinical trials results – clinical trial with no patients included

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| **Sponsor** | Centre Hospitalier Universitaire Brugmann (CHU Brugmann) | | |
| **Title** | Effect of levobupivacaine infiltration versus placebo on perineal postpartum pain in episiotomy of primiparous, after instrumental delivery : randomized double blind clinical trial | | |
| **EUDRACT** | 2015-005247-14 | **Sponsor reference** | CHUB-Equidol |

I hereby notify you that the study identified above was closed on 29 May 2018 with no patients included.

The reasons for not including patients in this clinical trial were:

- Principal investigator left the institution (clinical trial aborted)
- Lack of human resources to perform the trial

The study design is annexed to this letter.

I remain at your disposition for further information on this clinical trial.

Kind regards,
Dr Besse-Hammer

C.H.U. BRUGMANN BRUXELLES
UNITÉ DE RECHERCHE CLINIQUE
DR BESSE H. TATIANA
1-84145-53-001

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| Title | Randomized double blind clinical trial on the effect of levobupivacaine infiltration in episiotomy , versus placebo, on the post partum perineal pain in primiparous women after instrumental delivery. |
| EudraCT | 2015-005247-14 |
| Sponsor | CHU Brugmann |
| Justification | An episiotomy is an incision of the perineum to facilitate childbirth by natural means. This gesture is performed in 68% of primiparous women and 31% of multiparous women, according to Audipog data of 2003, with a downward trend since the 80's. The episiotomy reduces the risk of occurrence of anterior perineal tears, but has no preventive effect on 3rd and 4th grade perineal tears, according to the Anglo-Saxon classification. The CNGOF (French national college of obstetricians and gynecologists) recommends thus a restrictive use of episiotomy.<br>Perineal pain are more frequent and intense if the incision of the perineum is important. In particular, simple vaginal or perineal tears are less painful than episiotomies in the first seven days postpartum, whereas at six weeks postpartum, there is no significant difference anymore. The patients are the most symptomatic in the immediate postnatal period, but the pain may persist up to 2 weeks after delivery in 20 to 25% of cases. These pains are often undervalued and may interfere with the mother-child bond in the absence of an effective treatment. Perineal pain are usually treated with painkillers, in particular non-steroidal anti-inflammatory drugs given orally or rectally and paracetamol.<br><br>The scar infiltration is one of the components of a multimodal postoperative analgesia strategy. It consists in the simultaneous use of several drugs or analgesic techniques, acting on different pain components in order to improve the overall efficiency. This also reduces the consumption of analgesics having multiple side effects, such as opioids. Local anesthetics act at several levels. First, they block the transmission of pain messages at the nocireceptors level and have an analgesic effect on the nearby surgery site. The immediate post-operative pain is thus diminished. Furthermore, by blocking the pain message at the peripheral level, local anesthetics might have an effect on the formation of central hyperalgesia, responsible for longer-term pain. The local anesthetics also have local and systemic anti-inflammatory properties, that may have an effect on postoperative pain and on the establishment of hyperalgesia phenomena.<br><br>The most used local anesthetics at present are bupivacaine, ropivacaine and levobupivacaine. Ropivacaine has a lesser vasodilatory effect than bupivacaine, resulting in longer persistence at the injection point and a blood resorption that is more spread. The systemic toxicity threshold is also higher. Levobupivacaine is the enantiomer of bupivacaine. It has vascular effects, and an intermediate systemic toxicity threshold intermediate between bupivacaine and ropivacaine. Lidocaine has a limited duration of action. Its use is interesting in complement infiltrations when a rapid onset of action is desired.<br><br>Many scar infiltration indications are documented in the literature, such as inguinal hernias, hemorrhoids cures, thyroidectomy, orthopedic surgery, breast surgery, and cesarean section. Various studies evaluated the effectiveness of different local anesthetics in episiotomies and perineal tears.<br><br>So far, there were no data in the literature regarding the effect of levobupivacaine in episiotomies associated pain. The objective of this study is to evaluate the effect of local injections of levobupivacaine on episiotomies associated pain. |

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| Primary outcome | - The main objective of this clinical trial is to evaluate the effect of the infiltration of levobupivacaine, versus placebo, on perineal pain caused by episiotomy, after instrumental extraction in patients under epidural anesthesia.<br><br>- The primary endpoint is: Pain evaluation on a simple numeric scale (ENS) at 24 postpartum. |
| Secondary outcome | The secondary objective of this trial are:<br>- to estimate the amount of analgesics taken in the first 48 hours, then in the first 15 days postpartum<br>- to assess the impact on the daily activities of patients in the first 15 days postpartum<br>- to evaluate the postpartum pain on day 15, by using a simple numeric scale<br>Page 3 of 4 Equidol, version N°1 07/02/2016<br>- to evaluate the healing of episiotomy at day 15 postpartum<br><br>- The secondary endpoints are:<br>- the need and amount of analgesics taken in addition to paracetamol in the first 48 hours postpartum (ketoprofen, nefopam)<br>- the need and amount of analgesics taken at day 15 postpartum<br>-the impact of pain secondary to episiotomy on the activities of daily life at day 1, day 2 and day 15 after delivery (sitting, walking, urinating, sleeping, child care)<br>-pain level (ENS) at day 15 post-partum<br>-healing of the episiotomy at day 15 postpartum |
| Phase | II |
| Study design | International randomized double blind clinical trial, parallel groups, levobupivacaine versus placebo. |
| Inclusion criteria | - Primiparous<br>- Vaginal delivery with instrumentation (Suzor forceps, vacuum extraction, Thierry spatulas) with episiotomy<br>- Foetus In cephalic position<br>- Single pregnancy<br>- Patient at least 18 years old<br>-Term superior or equal to 37 weeks of amenorrhea<br>-Patient under epidural analgesia<br>-Patient affiliated to a social security scheme<br>- Good understanding of French |
| Exclusion criteria | - Ineffective epidural analgesia, defined by the need for additional local anesthesia for episiotomy repair<br>- Perineal tear of the 3rd or 4th grade, according to the Anglo-Saxon classification<br>- Contra indications to levobupivacaine, paracetamol, ketoprofen<br>- Participation refusal<br>-Postpartum hemorrhage requiring arterial embolization, reoperation (evacuation of a vaginal thrombus, vessel ligation, hysterectomy by laparotomy) or placement of a Bakri® balloon. |
| Planned number of patients | 330 |
| Actual number of | 0 |

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| patients recruited | |
| Study duration | Start date : 09 August 2016<br>End date : 29 May 2018 |
| Study location | - Belgium:<br>CHU Brugmann<br>4 Place A Van Gehuchten<br>1020 Brussels<br>Principal investigator: Dr André Nazac<br><br>- France :<br>CHU Montpellier<br>191 avenue du Doyen Gaston Giraud<br>34295 Montpellier<br>Principal investigator : Dr Florent Fuchs |
| Statistical Analysis | The statistical analysis was meant to be performed by the team of Montpellier University Hospital.<br>Statistical analysis was meant to be performed by Student's t tests or Mann-Whitney U test for continuous quantitative variables depending on the normality of the data and the nature of the compared variables. Regarding qualitative variables, chi-2 or Fisher exact tests were meant to be used. The significance level was set at $p < 0.05$. Statistical analysis was meant to be performed by STATA v.13 software (Stata Corporation, College Station, TX). |
| Expected Benefits | Better management of the pain caused by the episiotomy |