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At the attention of the EMA

Brussels, 14 July 2021

To whom it may concern,

EudraCT clinical trials results – clinical trial with partial results

Sponsor	Centre Hospitalier Universitaire Brugmann		
Title	Comparative study between conventional epidural versus ambulatory epidural: effect during labor in pregnant women.		
EUDRACT	2014-000470-19	**Sponsor reference**	CHUB-PDB001

I hereby notify you that the study identified above was closed on 22 December 2017, without meeting its recruitment goal. The standard of care protocols of obstetrical analgesia had changed since the beginning of the study, causing it to lose its pertinence. The decision was thus taken to terminate the study.

The clinical trial summary report is annexed to this letter.

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

Kind regards,

Pr Van der Linden

Clinical Trial Summary Report

Title	Comparative study between conventional epidural versus ambulatory epidural: effect during labor in pregnant women.
Phase	IV
Registered names(s) of the IMP(s) under investigation	Sufentanil Mylan Levobupivacaïne Fresenius Kabi
Sponsor	Centre Hospitalier Universitaire Brugmann 4 Place A Van Gehuchten 1020 Brussels
Principal investigator	Pr Van der Linden
Protocol identification	CHUB - PDB001
EudraCT	2014-000470-19
CTA identification	AFMPS/R&D/CED/mm 675620
Centers	Monocentric study CHU Brugmann 4 Place A Van Gehuchten 1020 Brussels
Trial duration	28 April 2014 - 22 December 2017
Report date	14 February 2018
Publications	Graduation work Dr Gamela (annex)

Pr Van der Linden
Signature:
Date: 2/2/2018

1. Context

Continuous Lumbar Epidural Anesthesia is the most effective, most "governable" and safest technique for obstetric analgesia. Apart from the potential complications associated with the medical act itself, the technique can be responsible for certain disadvantages such as an increased labor duration, a motor block, and urinary retention. To a lesser extent, it also increases the risk of instrumentation at delivery, of caesarean sections, of increased doses of oxytocin and high blood pressure.

Knowing that restricting the use of epidural analgesia does not seem an option in itself, several authors have proposed alternative techniques to try to reduce the side effects associated with epidural analgesia, mainly by reducing the concentration of the local anesthetic. This proportionally reduces the motor block. The risk of possible maternal discomfort can be overcome by an increase in the morphinics concentration. Walking can, in addition, improve patient satisfaction. Indeed, a meta-analysis suggested that the vertical posture has advantages on labor progress. Reducing the concentration of local anesthetic could also reduce dyskinesia and the risk of instrumentation.

2. Objectives

Main objective

The main objective of the study is to determine whether, compared to the dosage routinely used in the CHU Brugmann hospital, the utilization of a low concentration of local anesthetics for the epidural analgesia during labor reduces the incidence of instrumentations and caesarian sections linked to dyskinesia.

Primary end point: incidence of instrumentation or caesarian sections

Secondary objective

The secondary objective of the study are

- to test if, for this type of analgesia, ambulation is proportionally more important.
- compare the two groups in terms of side effects

Secondary end points: - ambulation %
- incidence of side effects

3. Inclusion criteria

Parturient aged 18-40 years

Nulliparous

ASA I or ASA II

Singleton pregnancy with a foetus in cephalic position

Pregnancy over 36 weeks and under 42 weeks

Cervical dilatation between 3-6 cm

VAS > 30 mm

No counter-indications for epidural

4. Exclusion criteria

Multiparous
Twin pregnancy
Pregnancy under 36 weeks and over 42 weeks
Fœtus in breach position
Previous history of caesarian/instrumentation
Analgesia or sedation within 6h
Counter-indications for epidural

5. Methods

Patients were randomized into two distinct groups: ambulatory group (levobupivacaïne 0.07% and Sufentanil 0.3 µg/ml) and control (levobupivacaïne 0.1 % and sufentanil 0.2 µg/ml) according to a randomization list created by the Pharmacy. Products were mixed in NaCl 0.9%.

Two pouches of 100 ml were prepared per patient and kept at 4°C, with an expiry date of 1 month.

The study had a double blind masking (patient and anesthesiologist).

Epidural was performed according to the standard of care. After the administration of a test dose of 3ml of xylocaine 2% and adrenaline 1/200000 in the epidural catheter, the patient received a loading dose of 15 ml of the study solution, followed by a continuous flow dose of 10ml/h of the study solution.

In case of insufficient analgesia and after a physical examination by the midwife, the anesthesiologist would perform an assessment of the patient sensory level. A first bolus of 10 ml of the study solution could be administrated. In case of persistent pain, a second bolus of 5ml xylocaine 2% could be considered whatever the group was, for an insufficient sensitive level (inferior to Th10). If pain was still present, the anesthesiologist would violate the protocol and use its own experience to ensure sufficient analgesia.

One hour after the loading dose and after each bolus, the anesthesiologist evaluated the walking capacity of the patient. Three criteria had to be met: modified Bromage score superior to 5, with the possibility of standing on one leg, negative Romberg test during 20 to 30 seconds, and absence of orthostatic hypotension (diminution of more than 20% of the patient arterial pressure).

Ambulation was defined as a mobilization of min 5 minutes of walking per hour. Fetal monitoring was possible by means of telemetry with a Avalon CTS Philips system.

Midwives monitored the fetal heart rate continuously after the epidural placement.

Within the first hour of the epidural placement and after each bolus, the patient's vital parameters (non-invasive blood pressure, heart rate, oxygen saturation) were recorded as well as the pain score (visual analogue scale).

At the end of labor, the anesthesiologist would notify:

- the time interval between the epidural placement and childbirth
- the duration of effective analgesia (interval between the loading dose and the first bolus, or the loading dose and childbirth)

- the delivery mode (natural, instrumented, surgical)
- the state of the perineum (with or without lesions of the genital sphere associated with childbirth)
- the use of colloids or vaso-constrictors in case of hypertension during labor, emergency caesarian excluded
- biometric data
- APGAR score of the newborn
- maternal satisfaction

Statistical analysis

Primary endpoint was the instrumentation and caesarian sections rate.

The power calculations were based on childbirth data from the Brugmann University Hospital between January and April 2012 (instrumentation rate and caesarean sections rate related to a dyskinesia of 21% in primiparous women).

To reduce this rate by 50% with a power of 80% (1-β) and a significance level (two-sided α) of 0,05, a sample of 170 patients per group was needed. An intermediate analysis was performed. With a non-Gaussian distribution, data was analyzed using the Mann-Withney tet or the Chi carré test. Results are expressed as medians with an interquartile interval, or as percentages with $p<0.05$ considered as significant.

6. Results

These are the results of the intermediate analysis performed in August 2015 on 118 patients.

The study did not meet its recruitment goal. The standard of care protocols of obstetrical analgesia have changed since the beginning of the study, causing it to lose its pertinence. Decision was thus taken to terminate the study on December 22 2017.

Eligible patients: 1074

Patients enrolled: 118

Ambulatory group: 47 in accordance to protocol
12 in violation (extra pain management - more than 2 boluses)

Control group: 45 in accordance to protocol
14 in violation (extra pain management - more than 2 boluses)

Demographic data

	Ambulatory group (N=59)	Control group (N=59)	P value
Maternal age (years)	27 [23-31]	27 [23-31]	0.979
Weight (kg)	77 [69-87]	73 [68-85]	0.634
BMI (kg/m2)	29 [25-32]	28 [26-31]	0.887
Gestational age (weeks)	40 [39-41]	40 [39-40]	0.073
Ethnic group			
- African n (%)	4 (7)	3 (5)	
- Maghreb n (%)	20 (34)	23 (39)	

- Caucasian n (%)	30 (51)	28 (47)	
- Middle east n (%)	5 (8)	5 (9)	
Cervical dilatation (cm)	4 [4-4]	4 [3-5]	0.111
Water pouch intact n (%)	22 (37)	23 (39)	0.850
Spontaneous release n (%)	30 (51,7)	32 (55,2)	0.710

Labor and childbirth data

	Ambulatory group (N=59)	Control group (N=59)	P value
Epidural duration (min)	368 [245-435]	321 [225-423]	0.645
Effective analgesia (min)	155 [90-260]	159 [105-267]	0.844
Number of bolus	1 [0-2]	1 [1-2]	0.809
Violation: More than 2 bolus n (%)	12 (20,3)	14 (23,7)	0.657
Ambulation			0.004
- none n (%)	22 (38,6)	41 (69,5)	
- possible n (%)	10 (17,5)	6 (10,2)	
- executed n (%)	25 (43,9)	12 (20,3)	
Expulsion time	66 [35-118]	57 [45-109]	0.926
Delivery mode			0.074
- spontaneous n (%)	45 (76)	36 (61)	
- instrumentation or caesarian n (%)	14 (24)	23 (39)	
Perineal lesions			0.803
- none n (%)	22 (37,3)	20 (34,5)	
- episiotomy n (%)	25 (42,4)	28 (48,3)	
- V tear n (%)	12 (20,3)	10 (17,2)	
Arterial hypotension n (%)	0 (0)	3 (5,1)	0.079
Vasoconstrictor use n (%)	0 (0)	1 (1,7)	1
Colloïds use n (%)	2 (3,4)	0 (0)	1
Maternal satisfaction	8.5 [6.6 -10,0]	8,0 [7,0-9,0]	0.713

APGAR score

	Ambulatory group (N=59)	Control group (N=59)	P value
Apgar 1 min	9 [9-10]	9 [9-10]	0.567
Apgar 5 min	10 [10-10]	10 [9,75-10]	0.693
Apgar 10 min	10 [10-10]	10 [10-10]	0.846
Arterial pH	7,26 [7,22-7,32]	7,29 [7,26-7,33]	0.293
Weigth	3,28 [3,06-3,70]	3,33 [3,10-3,56]	0.669

- The demographic data is not significantly different between the two groups.
- The instrumentation and caesarian rate was 24% in the ambulatory group versus 39% in the control group (p=0,074).
- Ambulation was possible but not performed in 17,5% in the ambulatory group versus 10,2% in the control group. Ambulation was performed in 44% of the ambulatory group versus 20 % in the control group (p=0,004).
- Maternal satisfaction was 8,5 versus 8,0 (p=0,713).
- There were no differences in the other parameters of the two groups.
- The biometric data of the newborns and their wellbeing was not significantly different between the two groups.

Preliminary results from this study show that, in the group with a low dose of local anesthetic in the mixture injected in the epidural space, there appears to be a trend toward a decrease of the instrumentation and caesarean section rates. Although walking is significantly greater, there are no differences in terms of maternal satisfaction or side effects compared to the dosage conventionally used.

We suppose that, with a lesser motor block, the muscle tone of the perineum is preserved. The expulsive efforts of the patient are thus more effective. Therefore, it is possible to imagine that the progression of the newborn in the birth canal and the head rotation are better. However, we did not observe any significant difference in the duration of expulsion. It could be explained by the inexperience of the patient at delivery.

7. Annexes

Graduation work Dr Gamela