

# Ropivacaine 75mg versus placebo in perineal infiltration for analgesic efficacy at mid- and long-term for episiotomy repair - The ROPISIO study: a two-center, randomized, double-blind, placebo-controlled trial

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## Study protocol

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# Abstract

**Background** Perineal pain due to episiotomy is commonly reported and can be severe enough to disturb the mother-infant dyad during the postpartum period. Its incidence at day 7 postpartum varies from 63% to 74%. Recent studies have already showed the analgesic efficacy of perineal infiltration of ropivacaine after episiotomy, but have only focused on the immediate postpartum period (at 24 and 48 hours after birth). Large, adequately powered, multicenter, randomized controlled trials are required to evaluate the impact of ropivacaine infiltration on perineal pain and quality of life at mid- and long-term before the widespread use of ropivacaine to prevent perineal pain after episiotomy can be recommended.

**Methods** The ROPISIO study is a two-center, randomized, double-blind, placebo-controlled trial in La Roche sur Yon and Nantes, France. It will involve 272 women with vaginal singleton delivery and mediolateral episiotomy at term ( $\geq 37$  weeks). Perineal infiltration (ropivacaine 75mg or placebo) will be administrated just after vaginal birth and before episiotomy repair. The primary outcome will be the analgesic efficacy at day 7 postpartum (mid-term), defined by the numerical scale of pain (ENS) strictly superior to 3/10 on the perineal repair area. Secondary outcomes will be the analgesic efficacy (ENS), the impact of pain on daily behavior, on the quality of life (36-Item Short Form Health Survey), on the occurrence of symptoms of postpartum depression (Edinburgh Postnatal Depression Scale) and on sexuality (Female Sexual Function Index) at 3 and 6 months (long-term) using validated online questionnaires. This study will have 90% power to show a 30% reduction in the incidence of perineal pain at day 7, from 70.0% to 50.0%.

**Discussion** This study will investigate if perineal ropivacaine infiltration just after birth can reduce mid- and long-term postpartum pain and increase quality of life in women with mediolateral episiotomy. Ropivacaine was a promising candidate drug, inexpensive, easy to administer, and easy to add on the routine management of deliveries in labor ward.

## Background

Episiotomy is a surgical enlargement of the vaginal orifice done with scissors and requires sutures to be repaired [1]. The midwife or the obstetrician can perform an episiotomy to facilitate the childbirth in case of severe fetal heart rate anomaly, and it is occasionally achieved to prevent obstetric anal sphincter injury in vaginal delivery [2]. Considering all maternal consequences of episiotomy, its routine use has been questioned, and restrictive episiotomy policies are recommended by clinical practice guidelines [3, 4]. Despite this restrictive policy, the episiotomy is still a common surgical procedure in pregnant women [5].

Perineal pain is a common consequence of episiotomy and affects up to 97% of women on day 1 postpartum [6, 7], up to 70% of women at day 7 to 10 postpartum [8–10] and may persist until 5 months postpartum and after [11, 12]. Pain after perineal wound (apart from episiotomy) are also reported but less studied because of the high variability of the localization and the depth of the tear. Postpartum perineal pain may have a negative maternal impact and altered the quality of life of the mother and may be severe enough to disturb the postpartum period and the mother-infant dyad [6, 7]. Symptoms of postpartum depression affect variously 10-15% of women [13, 14]. The association between persistent

perineal pain and symptoms of postpartum depression was found in several studies [15, 16]. An increased risk for depression was showed at 4-6 weeks and 6 months compared women who had perineal pain to those without perineal pain after adjusting for covariates [17]. In this prospective study, pain at 3-5 days postpartum was a predictor for symptoms of postpartum depression at 3 months [17]. Moreover, dyspareunia rate around 25% was observed in women who had an episiotomy [18, 19]. Sexual dysfunction in women with postpartum perineal pain was already and specifically reported [11, 20, 21]. In addition, clinical study showed that 12.8% of the women who underwent episiotomy presented chronic perineal pain at 5 months, related to obstetric and postpartum factors ( i.e. perineal pain in the first 48 hours) [12].

Obstetrical analgesia after a vaginal delivery received less attention than pain during labor or after a cesarean delivery. Epidural analgesia allows episiotomy to be performed without additional anesthesia. Therefore, local anesthetic injection at the time of the episiotomy may be necessary, even in women with epidural analgesia. The anesthetic perineal infiltration corresponds to subcutaneous, muscular-aponeurotic space or serosa injection of analgesic drug, next to the surgical site. Their effectiveness is based on the widest possible diffusion of the product and on the blocking of the most distal nerve endings [22]. The main property of local anesthetic drugs is to temporarily block pain message transmission from nociceptive terminations. Locally injected into an operative scar, their action exceeds this framework. Local anesthetic drugs have an anti-inflammatory effect which limits self-maintenance of pain in peripheral lesion. This peripheral hypersensitization is responsible for a prolongation of the parietal genesis of the pain messages. Then, prolonged bombardment of the medullary structures by repeated and intense influxes from operated territories leads to sensitization of the central structures (central hypersensitization). This implies a pain area extension; a pain threshold decreases and a risk of postoperative chronic pain. By blocking parietal component over a sufficiently long time, it would be possible to reduce peripheral and central hypersensitization phenomena [23, 24]. Furthermore, clinical studies confirm that local anesthetic infiltration, even in a single post-operative injection, is beneficial over a period that exceeds the product persistence at the site of administration. At the end of laparoscopy, local anesthetic instillation of ropivacaine prevents postoperative pain and decreases the need for morphine during the first 24 hours [25]. Another prospective randomized study concerning groin hernia surgery showed that local anesthesia was superior to regional or general anesthesia in decreasing postoperative complications, duration of surgery and anesthesia, length of postoperative hospital stay, and time to normal activity [26]. For the same surgery, preoperative inguinal infiltration of ropivacaine provides benefits for patients in terms of faster recovery, less pain, better mobilization and higher satisfaction throughout the until 7 days postoperative [27]. For tonsillectomy under general anesthesia, a preoperative infiltration of tonsils with bupivacaine showed almost no constant pain occurred in the bupivacaine group at 5 days postoperative compared to normal saline serum, and the difference in pain intensity was present even on the 10<sup>th</sup> postoperative day [28]. Ropivacaine is a drug already used in clinical practice for the treatment of acute pain in adults. For example, during childbirth (continuous or bolus epidural infusion), parietal infiltration or peripheral nerve blocks have been reported with high rate of decreased pain [29]. Ropivacaine is an anesthetic with longer duration when compared to lidocaine

[30]. A complication of infiltration techniques is the systemic toxicity of local anesthetics. It's result from large doses anesthetic administration or from an injection into a space with important systemic resorption. In both cases, knowledge of the products and injection sites, and usual precautions when injecting a local anesthetic, make possible to guard against this.

Three studies have already studied the analgesic efficacy of ropivacaine in perineal infiltration after episiotomy [31–33]. Significant results on pain levels with the use of ropivacaine have been found in two studies [31, 33]. However, these studies are focused on 24 and 48 hours after childbirth and no analysis of the mid and long-term pain levels, dyspareunia or depression occurrence have been realized. If the mother present less pain at mid-term (7-10 days after post-partum), it could increase mother-infant interaction and bonding.

Mediolateral episiotomies are associated in early and mid-term postpartum with perineal pain. Both theoretical arguments and results from precedents study indicate that ropivacaine as promise in prevention of perineal pain. Nevertheless, there are not enough well conducted studies to reach any definitive conclusion. We therefore designed the present randomized, controlled trial (ROPISIO). This study is a superiority study of ropivacaine 75 mg versus placebo in perineal infiltration for women who had received an episiotomy. The primary end point is analgesic efficacy at day 7 postpartum (mid-term) measured with the numerical scale of pain (ENS). The patient will be recruited at 2 centers.

## Methods / Design

### Aim, design and setting

The aim of this study is to compare the analgesic effect of a perineal infiltration of ropivacaine after vaginal delivery with mediolateral episiotomy, versus placebo in a two-center, randomized, double-blind, placebo-controlled trial.

The objectives are to assess the impact of perineal infiltration of ropivacaine 75mg on perineal pain after vaginal birth and mediolateral episiotomy for medical indication on different symptoms at short-, mid- and long-term. The specific objectives are as follows:

- Primary outcome: analgesic efficacy at day 7 postpartum (mid-term) measured with the numerical scale of pain (ENS) strictly superior to 3/10 on the perineal repair area.
- Secondary outcomes:
  - Evaluate the short-term postpartum perineal pain (at 12, 24 and 48 hours) and the long-term perineal pain (at 3 and 6 months) using the numerical scale of pain (ENS).
  - Evaluate the use of analgesic for perineal pain between H2 and H12, H12 and H24, H24 and H48, H48 and J7, M3 and M6 postpartum.
  - Assess the impact of pain on daily behavior with a scale of pain repercussions on daily behavior at D7, M3 and M6 postpartum.

- Characterize the type of persistent pain at J7, M3 and M6 postpartum with the simplified DN4 questionnaire at J7, M3 and M6.
- To assess the impact of perineal pain on the quality of life using the 36-Item Short Form Health Survey questionnaire (SF36) on D7, M3 and M6 postpartum.
- To assess the impact of perineal pain on the occurrence of symptoms of postpartum depression using the Edinburgh Postnatal Depression Scale (EPDS) at D7, M3 and M6 postpartum.
- To assess the impact of perineal pain on female sexuality using the Female Sexual Function Index questionnaire (FSFI) at D7, M3 and M6 postpartum.

The ROPISIO study is a two-center randomized, double-blind, placebo-controlled trial in two tertiary centers (one general hospital and one university hospital) to test the hypothesis that ropivacaine perineal infiltration after mediolateral episiotomy will reduce postpartum pain at mid- and long-term and increase quality of life. Figure 1 shows an adapted version of the SPIRIT Figure for the ROPISIO trial.

## Study population

Information on the trial will be provided to patient without planned cesarean by obstetricians and midwives during the 8<sup>th</sup> month in La Roche sur Yon and Nantes maternity hospital. At the latest, this information will be given when the women arrive in delivery room. Each woman will then confirm her participation and provided informed written consent before delivery. All randomized patients will be included in the full set of analysis (intent to treat basis).

To be randomized patients should fulfill all the following inclusion criteria (1) age 18 years, (2) gestational age at birth 37 weeks of gestation, (3) spontaneous vaginal delivery or operative vaginal delivery, (4) singleton pregnancy, (5) mediolateral episiotomy, (6) delivery under epidural anesthesia, (7) patient can be followed on the 6month study, (8) patient can understand the protocol, (9) informed consent form signed.

Exclusion criteria were: (1) known allergy to local anesthetics, (2) absence of epidural anesthesia during labor, (3) opioid dependence, (4) chronic pelvic pain before pregnancy, (5) deprived of liberty women (trusteeship, guardianship), (6) liver or kidney diseases, (7) acute porphyria, (8) elective cesarean section, (9) third and fourth degree perineal tears, (10) multiple pregnancy, (11) poor understanding of French language.

## Randomization

The randomization will be centralized and stratified by center and parity and performed according to a ratio 1:1. Once a woman has been included, through the filing of an electronic case report directly

by internet (Clinsight software), she will retain her randomization number (if it has been assigned to her) even if she withdraws from the study or refuses randomization afterwards.

Women will be randomized after episiotomy and before the beginning of the suture, to receive either 75mg of ropivacaine (Fresenius Kabi, Sèvres, France; Marketing authorization number: 3400957740832 [2009, RCP rév 08/09/2016]) in a 20-mL syringe (10-mL of ropivacaine 7.5mg/mL and 10-mL of normal saline) or 20-mL of placebo (normal saline, Fresenius Kabi, Sèvres, France; Marketing authorization number: 34009415 73941). The randomization list will be created by La Roche sur Yon Clinical Research Unit and transmitted to the pharmacy department of University Hospital of Nantes, which will prepare the blinded products. Numbered and identically labelled boxes with the study number will be produced. Each box will contain a 20-mL vial of the study drug (ropivacaine or placebo according to the randomization number). This will ensure the woman's safety and the double-blinding procedure (participants and obstetric staff).

## Study interventions

The intervention will be the perineal infiltration of a 20-mL blinded vial of the study drug (either 75mg of ropivacaine or placebo, according to the randomization group) in the margins of the episiotomy. Careful aspiration before and during injection of the product should be performed to prevent intravascular injection. The entire 20-mL syringe will then be injected slowly at several points of infiltration. All sutured plans will be infiltrated (vagina, muscle and skin). Infiltration will be performed by the midwife or the obstetrician, who performed the episiotomy and who is accustomed in his / her current practice to perform episiotomy sutures.

Except for the content of the study drug vial, all aspects of management of the third stage of labor and early postpartum period will be identical in the both arm:

- All drugs usually used in labor ward are allowed in this study, as prophylactic intravenous injection of 5 IU oxytocin at delivery to prevent postpartum hemorrhage.
- Installation of a catheter for epidural anesthesia with continuous epidural infusion of sufentanil 5micrograms/mL, ropivacaine 0.75% and physiological saline serum.
- A protocol for administration of analgesics will be carried out on the participating centers, namely:
  - Level 1 of analgesia proposed to the painful patient to H2 of the postpartum: paracetamol 1g,
  - If the patient is still painful at the end of 6 hours, proposal of level 2 analgesia: paracetamol 1g + ibuprofen 200 mg,
  - If the patient is still painful after 6 hours, proposal of level 3 analgesia: paracetamol 1g + ibuprofen 200 mg + tramadol 50 mg.

A meeting will be organized in each maternity unit before the beginning of the study to verify the attendants' agreement to and understanding of the protocol and their ease in practicing the study procedures.

## **Study assessments**

A summary of the study timeline and investigations is presented in Figure 1. Included women are provided with a study calendar to assist them to prospectively record data relevant to the study questionnaires. Research staff members are trained in standardized administration of all study questionnaires and data collection procedures.

## **Outcomes measures**

### **Primary outcome measure**

The primary outcome is the analgesic efficacy of ropivacaine at day 7 postpartum (mid-term) measured with the numerical scale of pain (ENS), strictly superior to 3/10 on the perineal repair area. The systematic use of a numerical scale of pain (ENS) will allow an objective measurement of the perineal pain in the postpartum period.

### **Secondary outcomes**

#### **Short- and long- term analgesic effect**

Perineal pain will be measured by a numerical scale of the pain (ENS) in the immediate postpartum period at H12, H24, and H48 by a midwife in the maternity ward. Perineal pain will also be measured by ENS at 3 months and 6 months using an online questionnaire.

#### **Quality of life**

The impact of perineal pain on quality of life will be assessed by the French version of the SF-36 using an online questionnaire at D7, M3 and M6 [34]. SF-36 is a validated and easily self-report quality-of-life measure for routine monitoring and assessment of care outcomes in adult patients. The SF-36 consists of 36 questions related to eight areas about the last four weeks: physical activity, life and relationships, pain, perceived health, vitality, mental limitations, physical condition and mental health. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower score is associated with the more disability [35].

#### **Pain characteristics**

The pain characteristics will be assessed by the French version of the DN4 questionnaire using an online questionnaire at D7, M3 and M6 [36]. The simplified DN4 is a self-report questionnaire that can be useful in helping to diagnose neuropathic pain, and consists of 4 questions and 10 items. If the patient's score is superior or equal to 4/7, the pain may be considered as neuropathic [36, 37].

## **Sexual function**

The impact of perineal pain on female sexuality will be assessed by the French validated version of the FSFI [38, 39] using an online questionnaire at D7, M3 and M6. This 19-items questionnaire is adapted for both sexually active and non-active women, and allows the assessment of the different parts of sexual function (desire, arousal, lubrication, orgasm, satisfaction and pain) over the past four weeks. The total score ranges between 2 and 36; higher scores are associated with a lower degree of female sexual dysfunction (FSD). A consensus seems to be found in the literature for values of less than 23 to define FSD [38, 40].

## **Postpartum symptoms of depression**

The impact of perineal pain on mood will be assessed by the French version of the EPDS [41, 42] using an online questionnaire at D7, M3 and M6. The EPDS is a 10-item self-report scale, and the total score ranges between 0 and 30; higher scores are associated with more symptoms. EPDS has good sensitivity and specificity for identifying probable clinical postpartum depression in community samples [43], and a score of  $\geq 12$  on the EPDS was used as a measure of symptoms of maternal postpartum depression [44, 45].

## **Statistical analysis**

Data analysis will be done in an intention-to-treat analysis, follow the CONSORT guidelines for randomized controlled trials and will be conducted with the statistician and researchers blinded to group status. The two groups will be compared for demographic characteristics and risk factors for perineal pain after episiotomy. The existence of a “Ropivacaine effect”, that is, a difference between the two groups for the primary outcome measure and the secondary outcome measures will be analyzed. In case of missing data for the primary end-point, the result would be impute as the worst case: ENS strictly superior to 3/10 on the perineal repair area. The comparisons will use nonparametric statistical tests when required by the constraints of population size or distributions. Comparisons of the categorical variables will use chi2 and Fisher exact tests, as appropriate, and analysis of variance and Kruskal and Wallis’s nonparametric test for the continuous variables will be used. Effects will be measured as relative risks, with their 95% confidence intervals.

## **Feasibility**

The participating centers have previously worked together in previous trials. Incidences of episiotomies are around 10 % of deliveries at La Roche sur Yon and Nantes hospitals. Recruitment will therefore be quick and easy. Moreover, the participating centers belong to the GROG (*Groupe de Recherche en Obstétrique et Gynécologie*) national network.

## Sample size

According to previous study [6, 9, 10], approximately 70% of the patients suffered from perineal pain due to an episiotomy at D7 postpartum. To show a relative reduction of at the least 30% in this incidence in the ropivacaine arm, with 90% power at the 5% level of significance, and a bilateral test, the study requires 136 women with episiotomy in each group.

## Data management

The clinical research technician will complete data throughout the trial with Clinsight software, under the responsibility of each investigator. The electronic case report file (eCRF) for each woman will contain:

- 1 file completed by the clinical research technician concerning the maternal and obstetrical characteristics: woman's characteristics, course of the pregnancy, labor, and delivery,
- 1 file completed by the clinical research technician about the postpartum events after leaving the delivery room, and the results of the numerical scale of the pain (ENS) in the immediate postpartum period at H12, H24, H48.
- Questionnaires on D7, and on M3 and M6 postpartum, about perineal pain (ENS), pain characteristic (DN4), quality of life (SF-36), sexual function (FSFI), and psychological status (EPDS), sent by the technician to the women by email and completed by them in the electronic file.

The data management and statistical aspects will be handled centrally by the La Roche sur Yon Hospital (Clinical Research Centre). Quality control will be conducted according to the standard operating procedures of the sponsor concerning trials in the investigational centers which comply with the Declaration of Helsinki and Good Clinical Practices. An independent data monitoring committee will control the quality and the safety of the trial procedures and the data collected, with regular visits and reports in each center by clinical research assistants. The standard operating procedures of the sponsor concerning trials (compliance with the defined research protocol, verification of all informed consents for included women, accuracy and the examination of the source documents and their comparison with the data reported in the eCRF, consistency of the data and the missing data) will be reviewed at each inspection in each center.

# Safety consideration

As recommended for trials using drugs in France, an independent Safety Monitoring Committee (SMC) will meet at minimum yearly to examine recruitment figures, baseline data, retention and adverse events. The trial coordinator will report to the ANSM within 72h all suspected unexpected serious adverse reactions (SUSARs), including maternal death, myocardial infarction, seizure, or suspected drug reactions. In particular in cases of strong suspicion of SUSARS related to the Investigational Medicinal Products, the blinding will be broken by the SMC if considered appropriate. The SMC will also inform the ANSM, the trial sponsor and the Chair of the Ethics Committee, and is authorized to recommend to the Scientific Committee that the trial be stopped.

## Discussion

The ROPISIO study will assess the efficacy of ropivacaine infiltration to reduce perineal pain in the postpartum period at mid- and long-term and increase the quality of life. This antalgic management can improve the women's quality of life in postpartum (earlier mobilization, better interaction with the baby, decrease analgesics used). At long term, we expect a decrease in dyspareunia and a better overall quality of life for the women.

Most studies on analgesic management of pregnant patients focused on pain during labor or following a cesarean section. Perineal pain in association with an episiotomy has been much less studied and often underestimated. Ropivacaine is a promising candidate drug, inexpensive and easy to administer and the infiltration of all episiotomies could be worldwide added to the routine management of all women after vaginal birth. The evidence currently available is too limited to justify its widespread use for perineal pain prevention in postpartum period. This adequately powered, multicenter, randomized placebo-controlled trial aims to determine if the risk-benefit ratio favors the systematic use of Ropivacaine after episiotomy to prevent postpartum perineal pain. A final report will be prepared for the funding body, and article will be prepared for publication with national and international dissemination.

## Trial Status

Enrollment is ongoing having started on October 2017. On 10 June 2019, 177 patients were included in the ROPISIO trial. Two Data Safety and Monitoring have confirmed the continuation of the study in January 2018 and February 2019. The current protocol version used for ROPISIO study is 4.0 dated 6 October 2017. Enrollment is expected to be completed in March 2020 by considering 9 inclusions per month. The total duration of the trial will be 35 months, including 29 months of inclusion and 6 months of follow-up in postpartum period (assessment of quality of life, pain characteristics, sexual function, and postpartum symptoms of depression).

## List Of Abbreviations

ANSM: French Health Products Safety Agency (*Agence Nationale de Sécurité du Médicament*); CRFs: case report files; DN4: Douleur Neuropathique 4; eCRF: electronic case report file; ENS: numerical scale of pain; EPDS: Edinburgh Postnatal Depression Scale; FSD: female sexual dysfunction; FSFI: Female Sexual Function Index questionnaire; SF36: 36-Item Short Form Health Survey questionnaire; SMC: Safety Monitoring Committee; SUSARs: Suspected unexpected serious adverse reactions.

## Declarations

Ethics approval and consent to participate

All participants were told about the study and were given written information by the attending physician or midwife during the 8<sup>th</sup> month. Written consent was obtained by the medical team in charge of the study before inclusion (attending physician or midwife). The study protocol and this consent procedure were approved by the Angers Committee Ouest II for the Protection of Research Subjects (Ethics Committee) on January 17, 2017 (2016-002786-62), and by the French Health Products Safety Agency (ANSM) on April 14, 2017 (2017-0057A-32). All participants underwent the informed consent process using institutional review board-approved consent documents. This trial is registered with [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03084549 on April 14, 2017).

Consent for publication

Not applicable.

Availability of data and material

This manuscript reports study protocols only, therefore no data are reported or available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GD conceived the study, led study design and coordination, and commented on the manuscript. CC assisted with study design and drafted the manuscript. NW, VD, and SP were involved in conception and design of the study during several meetings and are local investigators in the participating centers. All authors mentioned in the manuscript are members of the ROPISIO-study group or collaborators. ALT

assisted with study design and in particular the development of study databases. CC and GD edited the manuscript. All authors read and approved the final manuscript.

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## Figures

TIMEPOINTS (days)	STUDY PERIOD									
	Enrolment		Allocation	Post-allocation						Close out
	M-2	D0 (Birth)	D0 (Before episiotomy repair)	H12	H24	H48	D7 Online	M3 Online	M6 Online	
<b>ENROLMENT:</b>										
Eligibility screen	X									
Medical history	X									
Informed consent	X	X								
Randomization		X								
<b>INTERVENTIONS</b>										
Ropivacaine / Placebo perineal infiltration			X							
<b>ASSESSMENTS</b>										
ENS				X	X	X	X	X	X	
Analgesic drugs				X	X	X	X	X	X	
Quality of life questionnaire (SF-36)							X	X	X	
Symptoms of postpartum depression (EDPS)							X	X	X	
Sexual function (FSFI)							X	X	X	
Pain characteristic (DN4)							X	X	X	
Adverse events			X	X	X	X	X			
Analysis of study outcomes										x

**Figure 1**

SPIRIT figure. The figure shows the phases of the trial and data collection time points. SF-36 Short Form Health Survey, EPDS Edinburgh Postnatal Depression Scale, FSFI Female Sexual Function Index, DN4 Douleur Neuropathique 4.

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