Pudendal nerve block in patient treated for hemorrhoidectomy under spinal anaesthesia: prospective randomized single blind controlled trial

Clinical Study Protocol

Pudendal nerve block in patient treated for hemorrhoidectomy under spinal anaesthesia: prospective randomized single blind controlled trial

Pudendal nerve block for hemorrhoidectomy

Study Type:	Prospective randomized single blind controlled trial
Study Categorisation:	altre sperimentazioni cliniche secondo OSRUm cap. 4
Study Registration:	2017-00769
Study Identifier:	CE TI 3222
Sponsor, Sponsor-Investigator or Principal Investigator:	**Dr. Med Davide La Regina, viceprimario Chirurgia** ORBV, Bellinzona (GPC statement levels I and II done)
Investigational Product:	**None**
Protocol Version and Date:	**Version 1.2, 8.10.2018**

Signature Page(s)

Study number	2017-00769
Study Title	Pudendal nerve block in patient treated for hemorrhoidectomy under spinal anaesthesia: prospective randomized single blind controlled trial

The Sponsor-Investigator and trial statistician have approved the protocol version **1.2, 8.10.2018**, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Dr. Med Davide La Regina, Viceprimario chirurgia ORBV, Bellinzona

Bellinzona 8.10.2018

Place/Date

Signature

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Dr. Med Davide La Regina, Viceprimario chirurgia ORBV, Bellinzona
Study Title:	Pudendal nerve block in patient treated for hemorrhoidectomy under spinal anaesthesia: prospective randomized single blind controlled trial
Short Title / Study ID:	Pudendal nerve block for hemorrhoidectomy
Protocol Version and Date:	Version 1.2, 8.10.2018
Trial registration:	CE TI 3222, BASEC 2017-00769
Study category and Rationale	Prospective randomized single blind controlled trial
Clinical Phase:	Study Phase 3
Background and Rationale:	Haemorrhoids are common disease in the population and the surgical treatment is among the most frequently performed surgical procedures in the world[1]. The post-operative pain is an important issue. A.Medina-Gallardo and coll[2] published a study showing that the Milligan-Morgan hemorrhoidectomy is a procedure in which severe pain and demand for opiates are comparable to major surgery. The evidence-based recommendations of 2016 (PROSPECT Working Group)[3] for the management of pain after hemorrhoidectomy include: topical application of lidocaine 2% and nitro-glycerine 0.2% (Grade A), administration of metronidazole (Grade A) and laxatives (Grade A), NSAID (Grade B), acetaminophen (Grade B), strong and weak opioids (Grade B). It is preferable the perianal infiltration of local anaesthetics rather than the peripheral nerve blocks (perineal, pudendal or ischiorectal), due to the simplicity of the procedure[3]. Although the recommendations do not suggest the peripheral nerve block, the level of evidence is weak and there are no recommendations regarding a type of anaesthesia rather than another. Imbelloni LE and coll[4] have published a randomized study for the pudendal nerve block evaluation, reporting a high rate of efficacy and a lower use of opioids compared to the control group. Tepetes K and al[5] demonstrated in a randomized prospective trial that anaesthesia with the pudendal nerve block is more effective than the perianal infiltration of local anaesthetic during the hemorrhoidectomy procedures. Z. Naja and coll[6] published a study that compares the pudendal nerve block driven by neurostimulation and sedation with general anaesthesia in patients undergoing hemorrhoidectomy. They have demonstrated a benefit in terms of prolonged postoperative analgesia, a reduced use of opioids, NSAIDs and a reduced length of hospital stay. Similarly, C.Rubod and coll[7] in a prospective single-centre randomized trial have shown that the pudendal nerve block driven by neurostimulation is a simple and a useful technique that reduce the postoperative drugs intake.

	The pudendal nerve block with local anaesthetic is effective to reduce the postoperative pain for up to 24 hours[8]. Currently no randomized study compares the effectiveness of perianal nerve blocks as adjuvant to spinal anaesthesia in the management of postoperative pain in patients undergoing hemorrhoidectomy. On the other hand, the pudendal nerve block procedure is safe, economic and simple. Complications related to the procedure such as intravenous injection of the anaesthetic, the formation of a retroperitoneal hematoma or abscess of the psoas muscle are described, although extremely rare[9]. The aim of this prospective randomized double-blind study is to compare the postoperative pain in patients undergoing Milligan Morgan hemorrhoidectomy under spinal anaesthesia with or without the pudendal nerve block.
Objective(s):	The objective is to assess the efficacy of the pudendal nerve block in patients treated by hemorrhoidectomy under spinal anaesthesia
Outcome(s):	Primary outcome: • Postoperative pain measured on VAS scale at 6, 12, 24, 48 hours Secondary outcomes: • Antalgic drugs as needed (opioids needed) • Length of hospital stay • Safety of the pudendal nerve block
Study design:	Randomized control single-blind trial
Inclusion / Exclusion criteria:	Inclusion criteria: • Patients affected by haemorrhoids (grade III and IV) and treated with Milligan-Morgan hemorrhoidectomy under spinal anaesthesia • Signed informed consent Exclusion criteria: • Age < 18 year-old • Pregnancy • Allergy to local anaesthetics
Measurements and procedures:	Patients' clinical data and operative time will be collected Patients selected will be randomized in two groups. • Group A will undergo Milligan-Morgan hemorrhoidectomy under pudendal nerve block plus spinal anaesthesia • Group B will undergo Milligan-Morgan hemorrhoidectomy under spinal anaesthesia The randomization list will be created by the CTU-EOC and the randomization will be performed by the authorized personnel (physician responsible for the study, the anaesthetist and the surgeons) of the participating centre via RedCap®. Only the physician responsible for the study, the anaesthetist and the surgeons will be informed about the treatment arm.

	After the operation all the patient will receive Metronidazole 500 mg x3 + Paracetamol 1 gr x4 + NSAID + opioids as needed for at least 48 hours. The postoperative pain will be evaluated at 6, 12, 24, 48 hours with VAS scale both as in-patients or out-patients on specific formularies. In-patients will be then controlled after 1 months, while out-patients after 1 and 4 weeks. Results will be collected on specific printed Case report form. The Principal Investigator will preserve the sensitive data in his office in a closed cabinet key. Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians responsible for the study) will have the access rights and all changes on the database are trackable.
Study Product / Intervention:	The pudendal nerve block will be done after the spinal anaesthesia: Ultrasonography allows the visualization of important landmarks: the ischial spine, pudendal artery, sacrospinous ligament, sacro-tuberous ligament and pudendal nerve. It also allows real-time needle advancement and confirmation of injectate spread within the interligamentous plane. A low frequency 2-5 MHz curved array ultrasound probe is used. After skin preparation with Povidoneiodine and sterile probe preparation within a transparent plastic sheath, scanning is performed in transverse planes to visualize the ischium forming the lateral border of the sciatic notch. By moving the ultrasound probe in a cephalad-caudal direction, the ischium appears as a progressively lengthening hyperechoic line that is widest at the ischial spine level. The ischium is initially seen as a curved line as it forms the posterior aspect of the acetabulum. When the probe is at the ischial spine level, the ischium will appear as a straight line. At this level, a colour Doppler is used to localize the internal pudendal artery pulsations in close proximity to the ischial spine. Another arterial pulsation is often seen lateral to the tip of the ischial spine and is accompanied by the sciatic nerve. This is the inferior gluteal artery. Mistaking this artery for the pudendal artery will result in sciatic nerve block. The sacrospinous ligament appears as a hyperechoic line in continuity with the ischial spine, with lower echogenicity than bone. Similarly, the sacrotuberous ligament is seen as a light hyperechoic line deep within gluteus maximus muscle and appears parallel and superior to the sacrospinous ligament in ultrasound images. Localization of the pudendal nerve is targeted in the plane between these 2 ligaments. Under ultrasound guidance, a peripheral nerve stimulating needle is inserted from the medial aspect of the probe. It is advanced in line with the ultrasound probe to the medial aspect of the internal pudendal artery. Once the needle passes through the sacrotuberous ligament, a “click” is usually felt and a small volume (1 – 2 mL) of local anaesthetic is injected. The solution appears as a hypoechoic collection, in order to identify the plane between the sacrotuberous and the sacro-spinous ligaments and to accentuate the pudendal nerve appearance (pudendal nerve however is not always visible). The needle is inserted medially toward the pudendal artery as the pudendal nerve is principally located medial to this artery. 10 mls of ropivacaine 0.75% are injected within this fascial plane, after negative aspiration. The procedure is than repeated identically on the contralateral side[10].

	This procedure is usually a quite painful technique; thus, it is important to perform it after the spinal anaesthesia. It would be necessary to do it before the spinal anaesthesia just in case the pain would be associated to a nerve lesion. In this study the infiltration is not done on the nerve but in a muscular plane, thus is not needed the patient's sensibility[11]. The procedure will be performed at our institution by one of the three expert anaesthesiologists in the peripheral nerves' blockage. Those anaesthesiologists are: • Dr. Med. Luciano Anselmi, Primario di Anestesia ORBV • Dr. Med. Andrea Saporito, Caposervizio Anestesia ORBV, board member of the Swiss Society of Loco-regional Anaesthesia • Dr. Med. Fabrizio Beretta, Caposervizio Anestesia e responsabile terapia del dolore ORBV
Control Intervention (if applicable):	None
Number of Participants with Rationale:	Based on previous studies we will expect a 33% reduction in VAS scale. To detect a clinically relevant difference between groups with a type I error of 0.05 and a power of 0.80 we determined a sample size of 18 subjects per group. Taken into account a possible drop out for different reasons of 10% we calculated the definitive sample size in 20 patients per group.
Study Duration:	According to the volume of the Milligan-Morgan hemorrhoidectomy performed every year in our centre, the estimated duration of the study is 2 years.
Study Schedule:	First-Participant-In planned: 01.01.2018 Last-Participant-Out planned: 31.12.2019
Investigator(s):	Dr. Med Davide La Regina, Viceprimario Chirurgia ORBV, Bellinzona, davide.laregina@eoc.ch Dr. Med Andrea Saporito, Caposervizio di Anestesia ORBV, Bellinzona, andrea.saporito@eoc.ch Dr. Med Di Giuseppe Matteo, Capoclinica Chirurgia ORBV, Bellinzona, matteo.digiuseppe@eoc.ch Dr. Med Francesco Mongelli, Medico Assistente Chirurgia ORBV, Bellinzona, francesco.mongelli@eoc.ch
Study Centre(s):	Single-centre

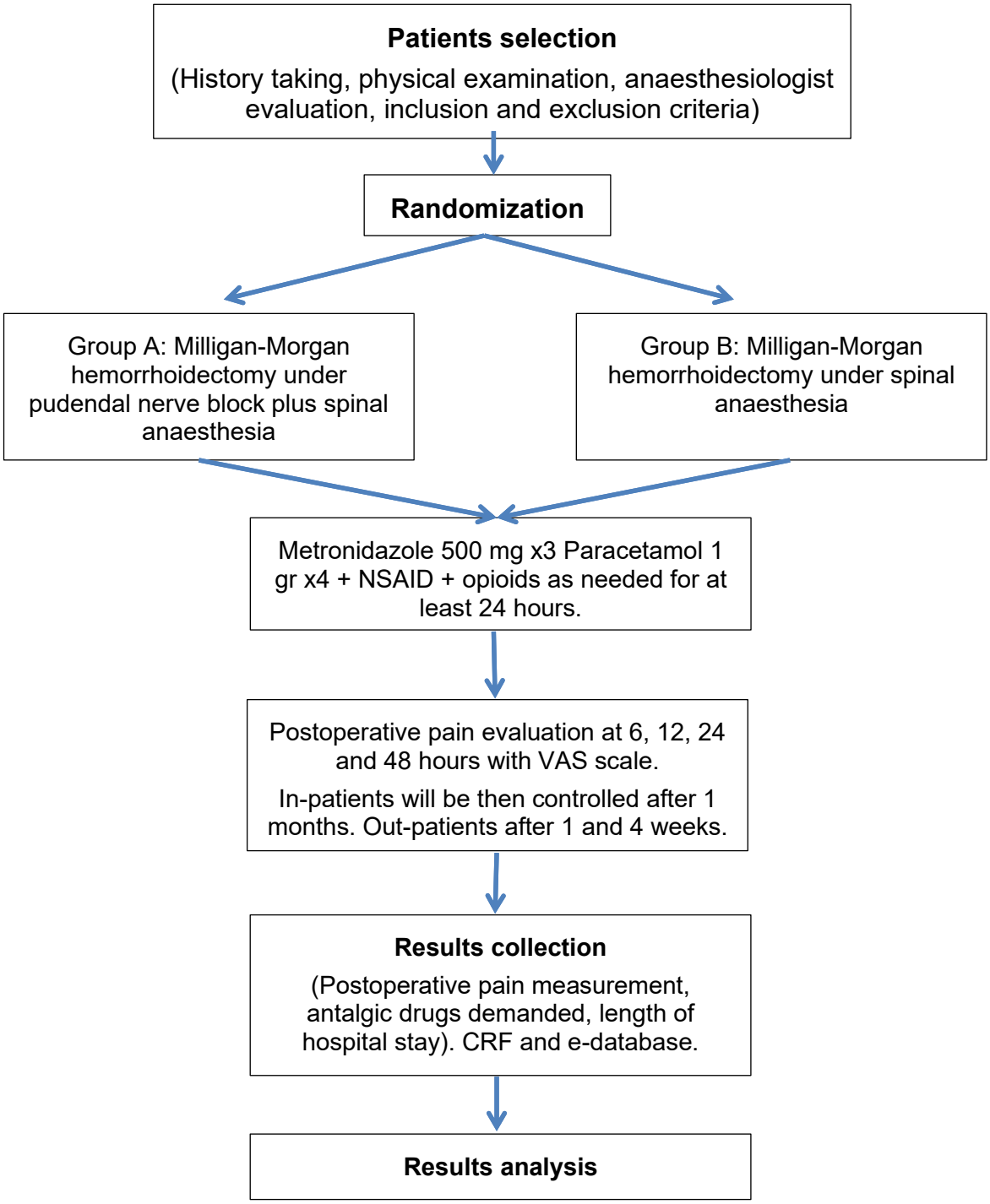
Statistical Considerations:	Descriptive statistics will be presented as mean with standard deviation (SD) or as median with interquartile range (IQR) for quantitative data. Qualitative data will be presented as absolute numbers with percentages. Comparisons of postoperative pain measured on VAS scale at 6, 12 and 24 h after surgery between group A and group B will be performed with the non-parametric repeated measures analysis of variance (Friedman test). By statistically significant p-value, post-hoc tests will be performed taken into account the multiple comparisons. Qualitative data between groups of patients will be compared with the Chi-Square test, or the Fisher exact test as appropriate. By statistically significant result post-hoc comparisons were made with the appropriate critical level adjustment. Comparisons of quantitative data between groups will performed with the Student's t-test or with the Mann-Whitney test as appropriate. All tests will be conducted two-sided, and p-values < 0.05 will be considered statistically significant. Stata version 12.1 (StatCorp. LP, College Station, TX, USA) will be used for all statistical analysis.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements. The Principal Investigator Dr. med Davide La Regina has obtained the GPC statement I and II level in June 2017

ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
GCP	Good Clinical Practice
ISO	International Organisation for Standardisation
IQR	Interquartile Range
NSAID	Nonsteroidal anti-inflammatory drug
PI	Principal Investigator
SD	Standard Deviation

STUDY SCHEDULE



1. STUDY ADMINISTRATIVE STRUCTURE

Sponsor/PI: Dr. Med Davide La Regina, Viceprimario Chirurgia ORBV, Bellinzona, davide.laregina@eoc.ch. 091 811 9106

Coordinator: Dr. Med Andrea Saporito, Caposervizio di Anestesia ORBV, Bellinzona, andrea.saporito@eoc.ch

Dr. Med Di Giuseppe Matteo, Capoclinica Chirurgia ORBV, Bellinzona, matteo.digiuseppe@eoc.ch

Data collector: Dr. Med Francesco Mongelli, Medico Assistente Chirurgia ORBV, Bellinzona, francesco.mongelli@meoc.ch. 091 811 9465

1.1 Sponsor, Sponsor-Investigator

Sponsor/PI: Dr. Med Davide La Regina, Viceprimario Chirurgia ORBV, via Ospedale, Bellinzona, davide.laregina@eoc.ch. 091 811 9106

The role in the study is to provide the rationale of the study, the study design and has the overall responsibility for it.

1.2 Principal Investigator(s)

For this study the sponsor and the PI are the same person, as mention above

1.3 Statistician ("Biostatistician")

Dr. Med Pagnamenta Alberto, OBV

1.4 Monitoring institution

The Monitor of the study will be:

- Dr. Med. Stephan Engelberger, Caposervizio Chirurgia Vascolare OCL Lugano. GCP statement I and II level

1.5 Data Safety Monitoring Committee

The monitor will perform 2 inspections / year and will send to the Local Ethical Committee 1 report / year about safety data.

1.6 Any other relevant Committee, Person, Organisation, Institution

None

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) and/or competent authorities

2.1 Study registration

2017-00769

2.2 Categorisation of study

The risk categorization for this study is A.

The treatment option proposed for group A and B are both widely used in the current clinical practice. Risks related to the pudendal nerve block are extremely rare[9].

2.3 Competent Ethics Committee (CEC)

The competent ethics committee is the Comitato etico cantonale, c/o Ufficio di sanità, Via Orico 5, 6501 Bellinzona

No changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from the competent authority before the start of the clinical trial.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

We declare no conflicts of interest

2.7 Patient Information and Informed Consent

All patient will receive an informed consent to participate to the study.

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the CEC and to the competent authority to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), the monitor, a competent authority or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Haemorrhoids are common disease in the population and the surgical treatment is among the most frequently performed surgical procedures in the world[1]. The post-operative pain is an important issue. A.Medina-Gallardo and coll[2] published a study showing that the Milligan-Morgan hemorrhoidectomy is a procedure in which severe pain and demand for opiates are comparable to major surgery.

The evidence-based recommendations of 2016 (PROSPECT Working Group)[3] for the management of pain after hemorrhoidectomy include: topical application of lidocaine 2% and nitro-glycerine 0.2% (Grade A), administration of metronidazole (Grade A) and laxatives (Grade A), NSAID (Grade B), acetaminophen (Grade B), strong and weak opioids (Grade B). It is preferable the perianal infiltration of local anaesthetics rather than the peripheral nerve blocks (perineal, pudendal or ischiorectal), due to the simplicity of the procedure[3]. Although the recommendations do not suggest the peripheral nerve block, the level of evidence is weak and there are no recommendations regarding a type of anaesthesia rather than another.

Imbelloni LE and coll[4] have published a randomized study for the pudendal nerve block evaluation, reporting a high rate of efficacy and a lower use of opioids compared to the control group. Tepetes K and al[5] demonstrated in a randomized prospective trial that anaesthesia with the pudendal nerve block is more effective than the perianal infiltration of local anaesthetic during the hemorrhoidectomy procedures. Z.Naja and coll[6] published a study that compares the pudendal nerve block driven by neurostimulation and sedation with general anaesthesia in patients undergoing hemorrhoidectomy. They have demonstrated a benefit in terms of prolonged postoperative analgesia, a reduced use of opioids, NSAIDs and a reduced length of hospital stay. Similarly, C.Rubod and coll[7] in a prospective single-centre randomized trial have shown that the pudendal nerve block driven by neurostimulation is a simple and a useful technique that reduce the postoperative drugs intake.

The aim of this prospective randomized single-blind study is to compare the postoperative pain in patients undergoing Milligan Morgan hemorrhoidectomy under spinal anaesthesia with or without the pudendal nerve block.

3.2 Clinical Evidence to Date

The pudendal nerve block with local anaesthetic is effective to reduce the postoperative pain for up to 24 hours[8]. Currently no randomized study compares the effectiveness of perianal nerve blocks as adjuvant to spinal anaesthesia in the management of postoperative pain in patients undergoing hemorrhoidectomy. On the other hand, the pudendal nerve block procedure is safe, economic and simple. Complications related to the procedure such as intravenous injection of the anaesthetic, the formation of a retroperitoneal hematoma or abscess of the psoas muscle are described, although extremely rare[9].

3.3 Rationale for the intended purpose in study

The pudendal nerve block will be done as follow before the spinal anaesthesia:

Ultrasonography allows the visualization of important landmarks: the ischial spine, pudendal artery, sacrospinous ligament, sacrotuberous ligament and pudendal nerve. It also allows real-time needle advancement and confirmation of injectate spread within the interligamentous plane. A low frequency 2-5 MHz curved array ultrasound probe is used. After skin preparation with Povidoneiodine and sterile probe preparation within a transparent plastic sheath, scanning is performed in transverse planes to visualize the ischium forming the lateral border of the sciatic notch. By moving the ultrasound probe in a cephalad-caudal direction, the ischium appears as a progressively lengthening hyperechoic line that is widest at the ischial spine level. The ischium is initially seen as a curved line as it forms the posterior aspect of the acetabulum.

When the probe is at the ischial spine level, the ischium will appear as a straight line. At this level, a colour Doppler is used to localize the internal pudendal artery pulsations in close proximity to the ischial spine. Another arterial pulsation is often seen lateral to the tip of the ischial spine and is accompanied by the sciatic nerve. This is the inferior gluteal artery. Mistaking this artery for the pudendal artery will result in sciatic nerve block. The sacrospinous ligament appears as a hyperechoic line in continuity with the ischial spine, with lower echogenicity than bone. Similarly, the sacrotuberous ligament is seen as a light hyperechoic line deep within gluteus maximus muscle and appears parallel and superior to the sacrospinous ligament in ultrasound images. Localization of the pudendal nerve is targeted in the plane between these 2 ligaments. Under ultrasound guidance, a peripheral nerve stimulating needle is inserted from the medial aspect of the probe. It is advanced in line with the ultrasound probe to the medial aspect of the internal pudendal artery. Once the needle passes through the sacrotuberous ligament, a “click” is usually felt and a small volume (1 – 2 mL) of local anaesthetic is injected. The solution appears as a hypoechoic collection, in order to identify the plane between the sacrotuberous and the sacrospinous ligaments and to accentuate the pudendal nerve appearance (pudendal nerve however is not always visible). The needle is inserted medially toward the pudendal artery as the pudendal nerve is principally located medial to this artery. 10 mls of ropivacaine 0.75% are injected within this fascial plane, after negative aspiration. The procedure is than repeated identically on the contralateral side[10].

This procedure is usually a quite painful technique; thus, it is important to perform it after the spinal anaesthesia. It would be necessary to do it before the spinal anaesthesia just in case the pain would be associated to a nerve lesion. In this study the infiltration is not done on the nerve but in a muscular plane, thus is not needed the patient’s sensibility[11].

The procedure will be performed at our institution by one of the three expert anaesthesiologists in the peripheral nerves’ blockage. Those anaesthesiologists are:

- Dr. Med. Luciano Anselmi, Primario di Anestesia ORBV
- Dr. Med. Andrea Saporito, Caposervizio Anestesia ORBV, board member of the Swiss Society of Loco-regional Anaesthesia
- Dr. Med. Fabrizio Beretta, Caposervizio Anestesia e responsabile terapia del dolore ORBV

3.4 Explanation for choice of comparator (or placebo)

Since the efficacy of the pudendal nerve block in patient operated for hemorrhoidectomy under spinal anaesthesia is not well established, the purpose is to evaluate differences in the postoperative pain if the nerve block is performed or not.

3.5 Risks / Benefits

The risks related to the pudendal nerve block are extremely rare[9]. Complications include the intravenous injection of the anaesthetic, the formation of a retroperitoneal hematoma or abscess of the psoas muscle. In case such complications occur, a multidisciplinary team composed by anaesthesiologist, surgeons and interventional radiologist will be promptly available.

3.6 Justification of choice of study population

Patients affected by haemorrhoids (grade III and IV) and treated with Milligan-Morgan hemorrhoidectomy

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose is to evaluate differences in the postoperative pain if the pudendal nerve block is performed or not in patients treated for hemorrhoidectomy under spinal anaesthesia.

4.2 Primary Objective

Postoperative pain evaluation

4.3 Secondary Objectives

Antalgic drugs as needed (opioids needed)

Length of hospital stay

4.4 Safety Objectives

The safety of the pudendal nerve block will be assessed. The assessment will be evaluated recording complications (type and severity according to CTCAE Version 4.03 - June 14, 2010[12]) after the nerve block during the hospital stay. In-patients will be then controlled 1 months after the operation, out-patients after 1 and 4 weeks.

5. STUDY OUTCOMES

5.1 Primary Outcome

Postoperative pain measured on VAS scale at 6, 12, 24, 48 hours

5.2 Secondary Outcomes

Antalgic drugs as needed (type of drug and number of administrations)

Length of hospital stay (days)

5.3 Safety Outcomes

The type and the severity of AEs related to the pudendal nerve block will be recorded according to CTCAE Version 4.03 - June 14, 2010[12]. The evaluation will be done after the nerve block, during the hospital stay and 1 months after the operation for in-patients or after 1 and 4 weeks for out-patients.

6. STUDY DESIGN

6.1 General study design and justification of design

This study is a randomized control single blind trial.

Patient will be randomized: Group A will undergo the pudendal nerve block under ultrasonographic control with injection of 10 mls of ropivacaine 0.75% before the spinal anaesthesia.

The population include patients with haemorrhoids (grade III and IV)

The study is single blind: an expert from the anaesthesiology team will perform the nerve block, the surgeon will be informed about the group of randomization. The nursing personnel (blinded) or the patient itself on specific formularies will evaluate the VAS scale at 6, 12, 24, 48 hours.

The comparator is no treatment

The method of randomization will be created by the CTU-EOC and the randomization will be performed by the authorized personnel (physician responsible for the study, the anaesthetist and the surgeons) of the participating centre via RedCap®. Only the physician responsible for the study, the anaesthetist and the surgeons will be informed about the treatment arm.

The expected duration of the study is 2 years, 100 patients.

6.2 Methods of minimising bias

6.2.1 Randomisation

The randomization list will be created by the CTU-EOC and the randomization will be performed by the authorized personnel (physician responsible for the study, the anaesthetist and the surgeons) of the participating centre via RedCap®. Only the physician responsible for the study, the anaesthetist and the surgeons will be informed about the treatment arm.

6.2.2 Blinding procedures

The study is single blind: an expert from the anaesthesiology team will perform the nerve block, the surgeon will be informed about the group of randomization. The nursing personnel and patients that will fulfil the VAS scale formularies at 6, 12, 24, 48 hours are blinded, they will not know the arm of treatment.

6.3 Unblinding Procedures (Code break)

The Principal Investigator will be informed on the randomization and will be available 24/24 hours, 365 days/year in case of complications related to the pudendal nerve block occur. In case of serious complications also the authorized personnel (physician responsible for the study, the anaesthetist and the surgeons) will have the possibility to access to the randomization, the principal investigator will be always get informed.

7. STUDY POPULATION

7.1 Eligibility criteria

Inclusion criteria:

- Patients affected by haemorrhoids (grade III and IV) and treated with Milligan-Morgan hemorrhoidectomy under spinal anaesthesia
- Signed informed consent

Exclusion criteria:

- Age < 18 years old

- Pregnancy
- Allergy to local anaesthetics

7.2 Recruitment and screening

The population recruitment will be at the Proctology Consulting Room, ORBV Bellinzona.

7.3 Assignment to study groups

The randomization list will be created by the CTU-EOC and the randomization will be performed by the authorized personnel (physician responsible for the study, the anaesthetist and the surgeons) of the participating centre via RedCap®. Only the physician responsible for the study, the anaesthetist and the surgeons will be informed about the treatment arm.

7.4 Criteria for withdrawal / discontinuation of participants

Participants are withdrawn from the study in case of informed consent not signed or non-compliance to the treatments.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products

8.1.1 Experimental Intervention

After patients select and randomization:

Group A will undergo pudendal nerve block under ultrasonographic control with injection of 10 mls of ropivacaine 0.75. Group B will receive no treatment.

8.1.2 Control Intervention

In the postoperative period all the patients will receive metronidazole 500 mg x3 + paracetamol 1 gr x4 + NSAID + opioids as needed for at least 24 hours. Opioids used will be “strong opioids” (Pethidine 50 mg sc or Oxycodone Kaps 5 mg)

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The pudendal nerve block will be done as follow before the spinal anaesthesia:

Ultrasonography allows the visualization of important landmarks: the ischial spine, pudendal artery, sacrospinous ligament, sacrotuberous ligament and pudendal nerve. It also allows real-time needle advancement and confirmation of injectate spread within the interligamentous plane. A low frequency 2-5 MHz curved array ultrasound probe is used. After skin preparation with Povidoneiodine and sterile probe preparation within a transparent plastic sheath, scanning is performed in transverse planes to visualize the ischium forming the lateral border of the sciatic notch. By moving the ultrasound probe in a cephalad-caudal direction, the ischium appears as a progressively lengthening hyperechoic line that is widest at the ischial spine level. The ischium is initially seen as a curved line as it forms the posterior aspect of the acetabulum. When the probe is at the ischial spine level, the ischium will appear as a straight line. At this level, a colour Doppler is used to localize the internal pudendal artery pulsations in close proximity to the ischial spine. Another arterial pulsation is often seen lateral to the tip of the ischial spine and is accompanied by the sciatic nerve. This is the inferior gluteal artery. Mistaking this artery for the pudendal artery will result in sciatic nerve block. The sacrospinous ligament appears as a hyperechoic line in continuity with the ischial spine, with lower echogenicity than bone. Similarly, the sacrotuberous ligament is seen as a light hyperechoic line deep within gluteus maximus muscle and appears parallel and superior to the sacrospinous ligament in ultrasound images. Localization of the pudendal nerve is targeted in the plane between these 2 ligaments. Under ultrasound guidance, a peripheral nerve stimulating needle is inserted from the medial aspect of the probe. It is advanced in line with the ultrasound probe to the medial aspect of the internal pudendal artery. Once the needle passes through the sacrotuberous ligament, a “click” is usually felt and a small volume (1 – 2 mL) of local anaesthetic is injected. The solution appears as a hypoechoic collection, in order to identify the plane between the sacrotuberous and the sacrospinous ligaments and to accentuate the pudendal nerve appearance (pudendal nerve however is not always visible). The needle is inserted medially toward the pudendal artery as the pudendal nerve is principally located medial to this artery. 10 mls of ropivacaine 0.75% are injected within this fascial plane, after negative aspiration. The procedure is than repeated identically on the contralateral side[10].

This procedure is usually a quite painful technique; thus, it is important to perform it after the spinal anaesthesia. It would be necessary to do it before the spinal anaesthesia just in case the pain would be associated to a nerve lesion. In this study the infiltration is not done on the nerve but in a muscular plane, thus is not needed the patient’s sensibility[11].

The procedure will be performed at our institution by one of the three expert anaesthesiologists in the peripheral nerves’ blockage. Those anaesthesiologists are:

- Dr. Med. Luciano Anselmi, Primario di Anestesia ORBV
- Dr. Med. Andrea Saporito, Caposervizio Anestesia ORBV, board member of the Swiss Society of Loco-regional Anaesthesia
- Dr. Med. Fabrizio Beretta, Caposervizio Anestesia e responsabile terapia del dolore ORBV

8.2.2 Control Intervention

The control group will not undergo the pudendal nerve block.

8.3 Dose / Device modifications

No dose modification are planned

8.4 Data Collection and Follow-up for withdrawn participants

Results will be collected on specific printed formularies (CRFs). The Principal Investigator will preserve the sensitive data in his office in a closed cabinet key. Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians responsible for the study) will have the access rights and all changes on the database are trackable.

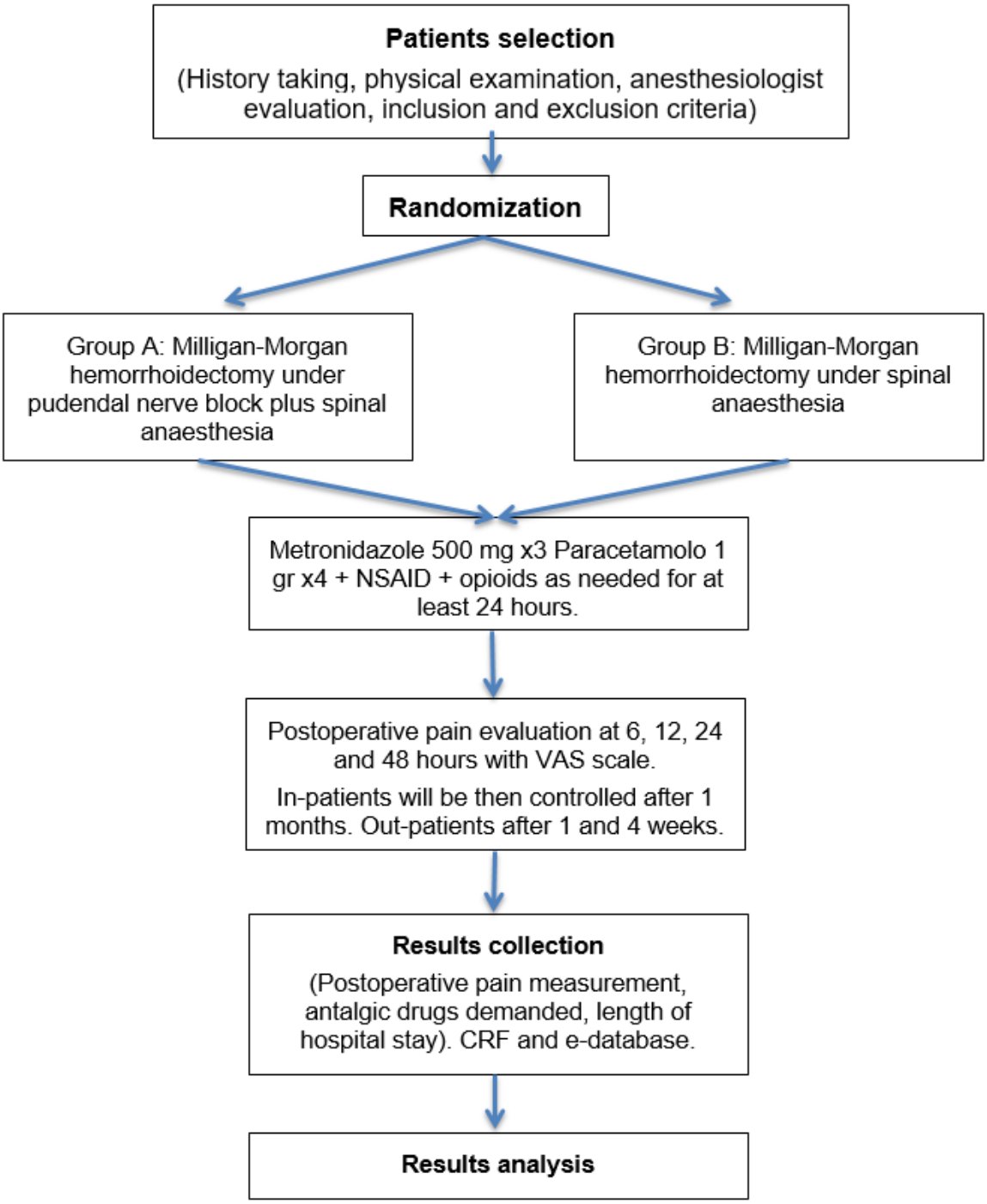
In-patients will be then controlled after 1 months and out-patients will be controlled after 1 and 4 weeks.

8.5 Concomitant Interventions (treatments)

No specific or relevant concomitant care or treatment are allowed.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments



9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Postoperative pain measured on VAS scale at 6, 12, 24, 48 hours. The data will be registered by the nursing personnel in the postoperative period on printed formularies (CRFs) or by the patient itself on a specific formulary.

9.2.2 Assessment of secondary outcomes

Opioids drugs as needed, length of hospital stay and complications data will be registered by the care providers in the postoperative period on specific printed formularies.

9.2.3 Assessment of safety outcomes

The type and the severity of AEs related to the pudendal nerve block will be recorded according to CTCAE Version 4.03 - June 14, 2010[12]. The evaluation will be done after the nerve block, during the hospital stay and 1 months (in-patients) or 1 and 4 weeks (out-patients) after the operation.

9.2.3.1 Adverse events

For adverse event the information collected are: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment. The evaluations will be done during the hospital stay and during the further planned clinical evaluations.

9.2.4 Assessments in participants who prematurely stop the study

Participants can be withdrawn from the study prematurely in case of adverse events after the pudendal nerve block.

9.3 Procedures at each visit

One pre-operatory visit is planned: history taking, physical examination, anaesthesiologist evaluation will be assessed.

All patients will be then controlled (history taking and clinical examination) after 1 months or 1 and 4 weeks (in- or out patients respectively).

10. SAFETY

10.1 Drug studies

During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period. For adverse event the information collected are: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment. The evaluations will be done during the hospital stay and the further planned clinical evaluations.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

SAEs will be followed until stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until stabilisation of the disease after termination.

The Principal Investigator will be informed on the randomization and will be available 24/24 hours, 365 days/year in case of complications related to the pudendal nerve block occur.

Assessment of Causality

The Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident

Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical

descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity day living.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity day living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

For a detailed description of EAs, we follow the CTCAE Version 4.03 - June 14, 2010[12].

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

All SAEs will be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days.

Reporting of SUSARs

A SUSAR needs to be reported to the local Ethics Committee (local event via local Investigator) and to Swissmedic for category B and C studies (via Sponsor-Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so-called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the local Ethics Committee

Periodic reporting of safety

An annual safety report is submitted once a year to the local Ethics Committee via local Investigator

10.1.3 Follow up of (Serious) Adverse Events

In case of SAE the patient will be followed up according the type and the severity of the complication developed, at least until stabilization.

11. STATISTICAL METHODS

11.1 Hypothesis

The hypothesis to be tested is that the spinal anaesthesia + pudendal nerve block is superior to the spinal anaesthesia alone in terms of postoperative pain.

11.2 Determination of Sample Size

Based on previous studies we will expect a 33% reduction in VAS scale. To detect a clinically relevant difference between groups with a type I error of 0.05 and a power of 0.80 we determined a sample size of 18 subjects per group. Taken into account a possible drop out for different reasons of 10% we calculated the definitive sample size in 20 patients per group.

11.3 Planned Analyses

Descriptive statistics will be presented as mean with standard deviation (SD) or as median with interquartile range (IQR) for quantitative data. Qualitative data will be presented as absolute numbers with percentages. Comparisons of postoperative pain measured on VAS scale at 6, 12 and 24 h after surgery between group A and group B will be performed with the non-parametric repeated measures analysis of variance (Friedman test). By statistically significant p-value, post-hoc tests will be performed taken into account the multiple comparisons. Qualitative data between groups of patients will be compared with the Chi-Square test, or the Fisher exact test as appropriate. By statistically significant result post-hoc comparisons were made with the appropriate critical level adjustment. Comparisons of quantitative data between groups will performed with the Student's t-test or with the Mann-Whitney test as appropriate. All tests will be conducted two-sided, and p-values < 0.05 will be considered statistically significant. Stata version 12.1 (StatCorp. LP, College Station, TX, USA) will be used for all statistical analysis.

11.3.1 Datasets to be analysed, analysis populations

All randomized subject will be included in the analyses

11.3.2 Primary Analysis

The primary analyses will be conducted at the end of the study by Dr. Med Pagnamenta Alberto, OBV (Chief of the EOC Biostatistic Service)

11.3.3 Safety analysis

The analysis of the safety will be conducted at the end of the study by Dr. Med Pagnamenta Alberto, OBV (Chief of the EOC Biostatistic Service). Parameters analysed will be the type and severity of AEs, treatment and resolution or stabilization (according to CTCAE Version 4.03 - June 14, 2010[12]).

11.4 Handling of missing data and drop-outs

In case of missing data, the patient will be dropped-out. 2 drop-outs each arm is planned

12. QUALITY ASSURANCE AND CONTROL

The Principal investigator is responsible for maintaining quality assurance and quality control, he is also responsible for proper training of all involved study personnel.

12.1 Data handling and record keeping / archiving

All the data will be collected on specific printed Case report form for each patient. The Principal Investigator will preserve the sensitive data in his office in a closed cabinet key.

12.1.1 Case Report Forms

A paper Case Report Forms will be used. Participants will not be identified in the CRF by name or initials and birth date. Appropriate coded identification will be used and managed by the Principal Investigator.

The Principal Investigator, Coordinators, data collector, authorised representatives of the Sponsor (-Investigator), the monitor, a competent authority or an ethics committee may have direct access to parts of the medical records relevant to the study. They are authorized to CRF access.

Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians responsible for the study) will have the access rights and all changes on the database are trackable.

12.1.2 Specification of source documents

Source data on the CRF include the original documents relating to the study, as well as the medical treatment and medical history of the participant (demographic data, clinical data, participation in study and Informed Consent, VAS scale at 6, 12, 24, 48, drugs taken, length of hospital stay, complications).

12.1.3 Record keeping / archiving

The Principal Investigator will preserve the sensitive data in his office in a closed cabinet key, archiving for 10 years. The e-database Redcap® grants security standard according to the EOC sensible data system storage and security.

12.2 Data management

The Principal Investigator has the overall responsibility for the data management.

12.2.1 Data Management System

CRF paper will be used and secured by the principal investigator in his office in a closed cabinet key. Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians responsible for the study) will have the access rights and all changes on the database are trackable (double data entry).

12.2.2 Data security, access and back-up

CRF paper will be used and secured by the principal investigator in his office in a closed cabinet key. Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians

responsible for the study) will have the access rights and all changes on the database are trackable (double data entry).

CRFs and the electronic database will be accessible only by authorized personnel (physicians responsible for the study). Authorised representatives of the Sponsor/Investigator, the monitor, a competent authority or an ethics committee will have the access to sensible data.

12.2.3 Analysis and archiving

Results will be then collected on a Redcap® electronic database. The access to the database will require username and password. Only the authorized personnel (physicians responsible for the study) will have the access rights and all changes on the database are trackable. Sensitive data will be archived for 10 years.

12.3 Monitoring

The Monitor of the study will be:

- Dr. Med. Stephan Engelberger, Caposervizio Chirurgia Vascolare OCL Lugano. GCP statement I and II level

12.4 Audits and Inspections

The monitor will perform 2 inspections / year and will send to the Local Ethical Committee 1 report / year about safety data.

12.5 Confidentiality, Data Protection

The Principal Investigator has the overall responsibility for the data management. Data will be accessible only by authorized personnel (physicians responsible for the study). Authorised representatives of the Sponsor/Investigator, the monitor, a competent authority or an ethics committee may have direct access to parts of the medical records relevant to the study. They are authorized to CRF access.

13. PUBLICATION AND DISSEMINATION POLICY

The trial results will be communicated to the healthcare professionals, the public and other relevant groups via publication

14. FUNDING AND SUPPORT

None

14.1 Funding

None

14.2 Other Support

None.

15. INSURANCE

Not needed

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(v4.03: June 14, 2010)

17. APPENDICES

Other documents needed are listed:

1. Informed consent
2. Patient's formulary (CRF include all the clinical information to be collected in the trial)
3. Protocollo per pazienti ambulanti