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Vascular response in leg and arm muscles to injection of spinal analgesic in addition to general anaesthesia during laparoscopic gynecologic surgery

Submission date
27/12/2017

Recruitment status
No longer recruiting

Registration date
05/01/2018

Overall study status
Completed

Last Edited
20/05/2024

Condition category
Surgery

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Background and study aims:
The insufflation of gas into the abdominal cavity during laparoscopic (keyhole) surgery negatively affects cardiovascular (heart and blood vessel) function, for example by increasing blood pressure and pulse rate and depressing heart function. Anaesthesiologists face these changes on daily basis and take action to reduce these effects. This study aims to study any influence of spinal analgesia (a pain treatment approach) on cardiovascular function during laparoscopic gynaecological surgery. In addition to standard anaesthesia monitoring, cardiovascular function is examined by a vascular occlusion test and the use of two electrodes, which are put over the left lower arm and right calf muscles. The vascular occlusion test has been previously used for exploring cardiovascular function in certain areas of medicine and has been linked to better treatment adjustment (e.g. in intensive care units, in the field of cardiovascular surgery, etc). In addition to cardiovascular function the researchers examine any influence of spinal analgesia on the body's stress response to laparoscopy by measuring some blood molecules, and pain after the operation is also assessed. The study findings should help to ascertain whether blood pressure changes during laparoscopy are associated with target tissue changes in oxygen delivery/extraction and whether the addition of spinal analgesia is beneficial. Hence the results could guide anaesthesia management in gynaecologic laparoscopic surgery from cardiovascular and pain management perspectives.

Who can participate?
All adult female patients aged between 18 and 65 without major systemic disease, scheduled for elective laparoscopic surgery at University Medical Centre Maribor (Slovenia), and with expected duration of laparoscopy time of at least 20 minutes.

What does the study involve?
Participants are randomly allocated to one of three groups to be treated with either general anaesthesia alone,
general anaesthesia combined with a lower dose of spinal analgesia, or general anaesthesia

combined with a higher dose of spinal analgesia. The vascular occlusion test is performed by inflating a standard pressure cuff on the left upper arm and right thigh. After three minutes, the pressure is released. During the first vascular occlusion test the patients can feel some paresthesia (tickling sensation) and/or mild pain below the pressure cuff's location. These sensations gradually subside after the pressure is released followed by a warm feeling in the limb. The test is repeated two more times during the surgery (that is when the patients are at sleep and receiving pain medication). Additionally, two blood samples are taken. The first one is taken at the time of intravenous cannula (tube) placement (which is standard and necessary for anaesthesia management), hence it does not represent an additional invasive procedure. The second sample is taken with an additional venipuncture on patients right arm at 20 minutes after the beginning of surgery (that is still during the sleep and pain medication, i.e. general anaesthesia). After the first blood sample is withdrawn, the anaesthesia technique is started. In case of allocation to any of spinal analgesia groups, the spinal analgesic drug is first administered in a sitting position. This is a common anesthesia technique in general and is used on a daily basis for different surgeries (e.g. labour pain management, surgery on lower limbs, on or in lower abdomen, etc). Five minutes after the drug application (or entrance to the operating room for a control group patient), the first vascular occlusion test is performed. In all cases general anaesthesia induction then proceeds via the previously inserted intravenous cannula.

What are the possible benefits and risks of participating?
The expected benefits for patients treated with spinal analgesia in addition to general anaesthesia are: decreased stress response to laparoscopic surgery (which is due to increased abdominal pressure and cannot be prevented/reversed by general anaesthetic drugs), improved heart and vascular function, including improved blood flow in lower limbs during the surgery with decreased risk for venous thromboembolic (blood clot) events, decreased pain after the operation and lower opiate drug use which could lead to addiction and can have several side effects (e.g. respiratory depression after surgery, constipation, urinary retention, nausea, vomiting, dizziness, etc), a reduced need for increased levels of anaesthetic gas during surgery and improved abdominal wall relaxation (better conditions for surgeon at lower dose of muscle relaxants - which is beneficial to patients after the operation). In addition, neuraxial techniques (which include spinal analgesia) have been reported to reduce the risk of chronic pain after the operation and reduce the need for transfusion due to decreased bleeding. Risks of spinal analgesia are relatively low. After the dose application many patients feel warmth in their legs and abdomen, a transient tingling sensation and stiff legs. These are expected sensations and they differ among individuals. Sometimes the blood pressure can fall, which is monitored and acted upon by following the strict protocol for blood pressure management. Urinary retention and headache can also follow spinal analgesia. More serious complications, like bleeding, infection and nerve damage, are rare (about 1 in every 10,000 – 100,000 cases). The expected duration of spinal analgesic drugs is about three to five hours. A physician should be consulted If any lower body sensations persist after this time or if stiffness in the neck is noticed.

Where is the study run from?
University Medical Centre Maribor (Slovenia)

When is the study starting and how long is it expected to run for?
October 2017 to December 2020

Who is funding the study?
University Medical Centre Maribor (Slovenia)

Who is the main contact?
Dr Marko Zdravkovic

Contact information

Type(s)
Scientific

Contact name
Dr Marko Zdravkovic

ORCID ID
https://orcid.org/0000-0002-0033-7071

Contact details
Ljubljanska ulica 5
Maribor
Slovenia
2000

Additional identifiers

Protocol serial number
KME 0120-603/2017/5

Study information

Scientific Title
Influence of spinal analgesia as addition to general anesthesia for laparoscopic gynecologic surgery on microvascular reactivity in musculus brachioradialis and musculus triceps surae

Study objectives
1. Improved microvascular reactivity (i.e. microhemodynamics) in study groups with spinal analgesia compared to controls
2. Improved postoperative pain control in study groups with spinal analgesia compared to controls
3. Lower surgery-related stress response in study groups with spinal analgesia compared to controls

Ethics approval required
Old ethics approval format

Ethics approval(s)
Republic of Slovenia National Medical Ethics Committee - NMEC, 14/12/2017, ref: 0120-603/2017/5

Study design
Single-centre prospective randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Planned laparoscopic gynecologic surgery with duration of pneumoperitoneum of at least 20 minutes

Interventions
Participants in the study will be randomly allocated to one of three groups based on computer generated list of random numbers by a non-investigator who also concealed the group allocation by putting the group assignments (in 1:1:1 ratio) in sequentially numbered opaque envelopes. Each envelope will be later opened by the principal investigator after the patient's consented enrolment and after placing the patients name sticker on the envelope.

The three groups are:
Group GA: General anaesthesia alone (control group)
Group GA+SA1: General anaesthesia combined with spinal analgesia with 3.75 mg of levobupivacaine and 2.5 mcg of sufentanil (volume: 2mL)
Group GA+SA2: General anaesthesia combined with spinal analgesia with 7.5 mg of levobupivacaine and 2.5 mcg of sufentanil (volume: 2mL)

All participants will be premedicated with midazolam one hour before surgery which is titrated according to their weight. After entrance to the operating theatre the standard anaesthesia monitoring will be applied and the first venous blood sample taken. Additionally for assessing microvascular reactivity in left m. brachioradialis and right m. triceps surae, pressure cuffs will be attached proximally to NIRS (Near Infra-Red Spectroscopy) electrodes over the corresponding muscles.

In the control group (Group GA), the first vascular occlusion test will be performed on the left arm and right leg by inflating the pressure cuffs to 30mmHg over the patients systolic blood pressure in 4 seconds. After 3 minutes the cuffs will be quickly released (in 2 seconds).

In the intervention groups (GA+SA1 and GA+SA2) the corresponding (hypobaric) spinal analgesic dose will be injected in the sitting position. After 5 minutes the first vascular occlusion test will be performed in the same manner as in the control group.

The second vascular occlusion test will be performed 5 minutes after intubation in all three groups, and the third test will be performed after 15 minutes of pneumoperitoneum duration. At this point the second venous blood sample will be taken for stress hormones levels determination.

At the time of each vascular occlusion test the following data will be collected: tympanic temperature, blood pressure, heart rate, peripheral saturation, EtCO2, mechanical ventilation parameters (inspiratory and plato pressures, tidal volume, respiratory frequency, positive end expiratory pressure, fraction of inspired oxygen), Sevorane concentration in inhalation and MAC, fresh gas flow, degree of table tilt, intrabdominal pressure.

All patients will be treated with the following general anaesthesia induction plan: initial fluid bolus of 10ml/kg of crystalloids, 0,25 mcg/kg of sufentanil (concentration 5 mcg/ml, rounded to nearest ml). After 2 minutes this will be followed by a clinically titrated bolus (loss of palpebral reaction) of etomidate (0.1-0.3 mg/kg). Then they will receive rocuronium 0.6 mg/kg

(concentration 10mg/ml, rounded to nearest ml) and will be intubated after 2 minutes. After tube placement confirmation the patients will be mechanically ventilated to target EtCO2 between 4.2 and 4.7kPa, with 5cmH20 positive end expiratory pressure (peak pressure should not exceed 35 cmH2O) and fraction of inspire oxygen of 40%. Anaesthesia will be maintained with sevoflurane 0.6 - 1.0 MAC. Three to five minutes before surgical incision the patients will all receive a further dose of 10 mcg of sufentanil.

All patients will be treated with the same antiemetic protocol before the end of surgery and after the last vascular occlusion test (dexamethasone 4mg, ondansetron 4mg) and paracetamol 1g.

In the post anaesthesia care unit pain will be assessed in still position and coughing at 30 minutes, 1 hour, 2 hours, 4 hours and 24 hours after extubation.

Rescue protocols for blood oxygen saturation and hemodynamics:
Rescue measurements in case of peripheral desaturation below 94%: increasing the fraction of inspired oxygen by 10% until corrected.
Rescue measurements in case of hemodynamic instability:
1. Bradycardia (<50 beats per minute for more than 30 seconds): bolus of atropine 0,5 mg, repeated up to three times and if needed ephedrine 5 mg up to three times
2. Tachycardia (>100 beats per minute for more than 1 minute): bolus of sufentanil 10 mcg max 3 times, if no correction additional bolus crystalloid infusion of 5mL/kg
3. Hypotension (MAP<60 mmHg): phenylephrine boluses of 50 mcg or ephedrine boluses of 5 mg plus additional bolus crystalloid infusion of 5mL/kg
4. Hypertension (MAP>110 mmHg): bolus of sufentanil 10mcg max 3 times

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Levobupivacaine, sufentanil

Primary outcome(s)
1. Microvascular reactivity in selected muscles (i.e. microhemodynamics): desaturation /resaturation rates in NIRS (measured by INVOS system) during/after vascular occlusion tests (before general anaesthesia, 5 minutes after intubation, 15 minutes after pneumoperitoneum)
2. Standard macrohemodynamic parameters (blood pressure measured non-invasively by arm cuff and heart rate measured by ECG) correlation with desaturation/resaturation rates in NIRS (measured by INVOS system) during/after vascular occlusion tests (before general anaesthesia, 5 minutes after intubation, 15 minutes after pneumoperitoneum)
3. Upper vs lower body desaturation/resaturation rates in NIRS (measured by INVOS system) during/after vascular occlusion tests (before general anaesthesia, 5 minutes after intubation, 15 minutes after pneumoperitoneum)

Key secondary outcome(s))
1. Other NIRS (measured by INVOS system) parameters: minimal tissue saturation, maximal tissue saturation and rate of return to baseline during/after vascular occlusion tests (before general anaesthesia, 5 minutes after intubation, 15 minutes after pneumoperitoneum)

2. Surgical stress response as assessed by stress hormone levels in venous blood samples taken at baseline and after the last vascular occlusion test
3. Postoperative pain (measured by Visual Analogue Scale at rest and during coughing) and analgesic consumption at 30 minutes, 1 hour, 2 hours, 4. hours and 24 hours after extubation
4. Sevoflurane consumption per minute between the the second and third vascular occlusion test
5. Vasoactive drugs and fluids consumption by the end of the last vascular occlusion test and during the whole surgery
6. Blood pressure measured non-invasively by arm cuff and heart rate measured by ECG and peripheral saturation at the three designated measurement points (before general anaesthesia, 5 minutes after intubation, 15 minutes after pneumoperitoneum)
7. Potential rescue managements during the study protocol and within the duration of surgery
8. Patient satisfaction collected via anonymous questionnaire 24 hours after the surgery

Completion date
31/12/2020

Eligibility

Key inclusion criteria
1. Aged 18-65 years
2. ASA Physical Status I or II
3. Planned laparoscopic gynecologic surgery with duration of pneumoperitoneum of at least 20 minutes

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
Female

Total final enrolment
102

Key exclusion criteria
1. Allergy or sensitivity to any medication used in trial
2. Alcohol or drug abuse
3. Body mass index higher than 35 kg/m2 or lower than 15 kg/m2
4. Pregnancy or breastfeeding status

5. Diabetic patients on insulin treatment
6. Untreated arterial hypertension
7. Peripheral arterial disease
8. Corticosteroid treatment
9. Coagulopathy or other contraindication for spinal analgesia
10. Known difficult airway management

Date of first enrolment
08/01/2018

Date of final enrolment
23/01/2019

Locations

Countries of recruitment
Slovenia

Study participating centre
University Medical Centre Maribor
Ljubljanska ulica 5
Maribor
Slovenia
2000

Sponsor information

Organisation
University Medical Centre Maribor

ROR
https://ror.org/02rjj7s91

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
University Medical Centre Maribor

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study (collected raw data, fully anonymised) will be available upon request from Marko Zdravkovic after the publication of the study results and up to five years thereafter.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	microcirculation results	01/10/2020	21/11/2019	Yes	No
Results article		16/04/2020	20/05/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes