



Robotic versus open primary ventral hernia repair: A randomized controlled trial (Robovent Trial)



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ABSTRACT

Background: The objective of the present study is to compare the outcomes open PVHR and robotic PVHR. **Methods/Design:** The present study will be a randomized single-blinded controlled trial with intention-to-treat analysis comparing robotic PVHR to open PVHR in adult patients undergoing elective PVHR with a defect ranging between 1–5 cm. Patient refusing to participate, not able to give informed consent, with history of intra-abdominal surgery contraindicating a robotic surgical approach will be excluded. The intervention will consist in laparoscopic robotically assisted trans-abdominal pre-peritoneal epigastric or umbilical PVHR with closure of fascial defect and non-adsorbable mesh reinforcement. The control will be open pre-peritoneal epigastric or umbilical hernia repair with closure of fascial defect and non-adsorbable mesh reinforcement. The primary outcome will be the incidence of wound-related complication within 1 month. The secondary outcomes will be esthetic satisfaction, pain, pain-killers consumption, general complications, costs, operative time and early hernia recurrence.

Discussion: Open PVHR is potentially associated to more wound-related complications, but has the advantages of cost-effectiveness, short operative time and totally extra-peritoneal repair. Laparoscopic PVHR has lower wound-related complications but implies placing the mesh in intra-peritoneal position, requires advanced laparoscopic skills, usually does not allow the closure of the defect, and can lead to excessive pain and pain-killers consumption. Robotic PVHR uses the same laparoscopic access as laparoscopic PVHR, but thanks to the extended range of motion given by the robotic system, allows defect closure, pre-peritoneal placement of the mesh and requires less technical skills.

In the present randomized controlled trial, we expect to show that robotic PVHR leads to better wound-related outcomes than open PVHR.

Trial registration: The present randomized controlled trial was registered into clinicaltrials.gov under registration number NCT04171921.

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1. Background

Primary ventral hernia repair (PVHR) is a very common general surgery procedure, with 270'000 performed annually in the United States [1]. Standard open PVHR approach with pro-peritoneal or retro-muscular mesh placement is associated with rate of surgical complications up to 25% led by surgical site infections (SSI), and 6 months recurrence rate up to 13% according to large scale, multicenter or nationwide studies [2–4]. Yet often benign, open PVHR complications lead to significant re-admissions and follow-up costs [5]. Alternatively, intra-peritoneal onlay mesh (IPOM) laparoscopic approach for PVHR reduces SSI rate [6] and has gained pop-

ularity for incisional ventral hernia repair, especially in overweight patients [7]. For routine PVHR and small sized hernias, however, laparoscopic PVHR with intraperitoneal mesh placement is controverted. Intraperitoneal meshes are known to cause adhesions and potentially severe complications, port-site hernia may occur, primary defect closure can be challenging and is not systematically performed despite its proven effect in reducing seroma and hernia-site events [8–10]. In addition, poorer results can be observed after laparoscopic PVHR compared to open repair in terms of quality of life, long-term pain and functional disabilities, which may be explained by use of tackers to hold the mesh in place [11]. Laparoscopic transabdominal pre-peritoneal (TAPP) PVHR technique has been described and may address complications related to intra-abdominal mesh placement [12]. It combines the advantages of both open (no use of tackers, no intra-peritoneal

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material) and laparoscopic (minimally invasive access reducing SSI risk) approaches, but remains technically demanding and time consuming even in expert hands, especially if defect closure is performed.

The daVinci Xi robotic system (Intuitive Surgical, Sunnyvale, CA, USA) helps to overcome technical limitations such as difficulty to perform upside-down suture or precise dissection in limited workspace. Moreover, this device allows using only 8 mm trocars; reducing concerns about port site hernia, which occurs on 12 mm ports in about 2.5% laparoscopic PVHR [8]. Data from recent retrospective studies of TAPP robotic PVHR established the feasibility and safety of robotic approach for ventral hernia surgery [13,14]. The authors underlined its potential advantages over standard laparoscopic approach in terms of recurrence rate, surgical site complications and ability to perform primary defect closure [15,16].

To date, no study investigated in a prospective randomized design the performance of robotic PVHR compared to open PVHR.

The present study protocol aims to determine if robotic PVHR reduces surgical site complications when compared to standard open technique, and if its cost-benefit balance is favorable.

1.1. Methods/design

The present randomized controlled trial was registered into clinicaltrials.gov under registration number NCT04171921.

1.2. Study design

The study will be a randomized controlled single-blinded monocentric superiority study comparing robotic PVHR with open PVHR in adult patients with primary umbilical or epigastric hernia between 1 cm and 5 cm (± 5 mm) of diameter.

1.3. Study setting

The study will take place at the Division of Digestive Surgery, University Hospitals of Geneva, Geneva, Switzerland.

1.4. Eligibility

Adult patients scheduled for primary umbilical or epigastric hernia (between 1 cm and 5 cm of diameter) repair will be considered as eligible for the study.

1.5. Inclusion criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Informed written consent.
- Aged 18 years or older.
- Undergoing primary umbilical or epigastric hernia repair of size between 1 cm and 5 cm (± 5 mm), with mesh reinforcement.

1.6. Exclusion criteria

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- Patients under corticosteroids or other immunosuppressive treatment.
- Women who are pregnant or breast-feeding.
- Intention to become pregnant during the course of the study.
- Lack of safe contraception, defined as: Female participants of childbearing potential, not using and not willing to continue

using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or appropriate use of condoms, or who are not using any other method considered reliable by the investigator in individual cases.

- Female participants who are surgically sterilized/hysterectomized or post-menopausal for longer than 2 years are not considered as being of child bearing potential.
- Incisional hernia and/or history of intra-abdominal surgery contraindicating a robotic surgical approach.
- Another concomitant hernia requiring treatment.
- Upon anesthesiologist evaluation, clinically significant concomitant disease states which require to shorten operative time.
- Upon anesthesiologist evaluation, clinically significant concomitant disease states being a contra-indication to laparoscopic approach and/or general anesthesia.
- Known or suspected non-compliance, drug or alcohol abuse.
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant.
- Previous enrolment in the current study.
- Enrolment of the investigator, his/her family members, employees and other dependent persons.
- Emergency repair.
- Patients unable to give informed consent.

2. Intervention and control

2.1. Intervention: Robotic PVHR with defect closure and preperitoneal mesh

The DaVinci Xi robotic system is CE marked, authorized for clinical use in abdominal surgery in Europe and Switzerland, and used in daily practice in the Department of Surgery of the University Hospitals of Geneva, Switzerland.

The surgical procedure will be carried on as follows:

- Patient is under general anesthesia in supine 0° position, legs closed, right arm abducted for anesthesiologists
- Robotic and laparoscopic carts are situated at patient's feet
- Antibioprophylaxis using a second-generation cephalosporin
- Standard skin disinfection and draping
- Surgical team stands on the left side of the patient
- Cables installation along the left leg
- 8 mm daVinci trocar (port n°3) Optiview access with 30° 5 mm optics in proximal part of the upper left quadrant
- Creation of pneumoperitoneum at 12 mmHg pressure
- Intra abdominal assessment and verification of the feasibility of the procedure
- 2 × 8 mm robotic ports placement under visualization: port n°1 in lower left quadrant for arm n°1 (left hand), port n°2 in left flank as lateral as safely possible for arm n°2 (camera)
- Xi robot is approached from the right side and perpendicular to the patient.
- Docking of the robot in the afford-mentioned trocars.
- Switch for robotic camera in port n°2.
- Bipolar Maryland grasper in port n°1, monopolar scissors in port n°3
- Surgeon goes to console, assistant or scrub nurse stays on the left side of the patient to assist
- If necessary, adhesions are taken down and hernia is reduced
- Incision of peritoneum on ipsilateral side of trocars at least 3 cm from the port n°3 and 5 cm from edge of defect
- Peritoneum is pulled towards the trocar with left hand and abdominal wall is pushed away from the peritoneum using blunt dissection of the scissors with right hand

- When the sac is encountered it is pulled posteriorly and reduced or transected. If transected it is closed after completion of the dissection with VLCO 3–0 180. Completion of a peritoneal flap at least 5 cm from the edges of the defect.
- Introduction of a Quill PDO 0 barbed suture
- Decrease of pneumoperitoneum to 5–8 mmHg depending on workspace
- Defect closure.
- Soft graduate band is inserted, defect is measured, band is taken out.
- Macroporous polypropylene mesh prepared to ensure 5 cm coverage around the edges of the defect.
- Mesh is secured with VLOC 2–0 suture on the posterior fascia
- Peritoneal flap is sutured to cover the mesh with running suture of 3–0 vloc 180.
- De-docking, trocars removal, skin closure 3–0 Prolene, Steristrips

2.2. Control: Open umbilical or epigastric hernia repair with defect closure and preperitoneal mesh

The surgical procedure will be carried on as follows:

- Patient is under general anesthesia in supine 0° position, legs closed, both arms abducted for anesthesiologists
- Antibioprophylaxis using a second-generation cephalosporin
- Standard skin disinfection and draping
- Skin incision directly on hernia site
- Dissection of subcutaneous tissues
- (If umbilical hernia: desinsertion of umbilicus)
- Reduction of hernia
- Preparation of edges of defect
- Preparation of preperitoneal plane
- Macroporous polypropylene mesh is placed in the preperitoneal plane and attached to the aponeurosis with Maxon 2–0 sutures.
- Closure of defect with 2.0 Maxon
- (Re-insertion of umbilicus on aponeurosis with 2.0 Vicryl suture if umbilical hernia)
- Skin closure 3–0 Prolene, Steristrips

3. Randomization, allocation concealment and blinding

Fixed block randomization of blocks of 6 participants, on a 1:1 basis, will be generated using the RedCap software system. Block randomization is necessary for logistic reasons (management of operating room schedule, as the use of the robot needs to be spread throughout the year). As this study is single blinded, and as the patient doesn't have access to the operating room schedule and decisions made for previously included patients, there is no need for a varying block size randomization method.

Patients will be blinded from the chosen technique pre-operatively until post-operative day two. To ensure blindness, opaque wound dressing will be applied both on surgical wound(s) and on spot(s) where wounds would have taken place with the other procedure (open PVHR or robotic PVHR). Blindness will be maintained until wound dressing changing or removal at post-operative day two.

4. Definition of endpoints and outcome measures

The primary outcome will be the incidence of surgical site complication within 30 days after surgery. Surgical site complication is defined according to Clavien and Dindo (31) as any deviation from the normal postoperative course, and classified as follow:

- Grade 1: minor risk events not requiring therapy (with exceptions of analgesic, antipyretic, antiemetic, and antidiarrheal drugs or drugs required for lower urinary tract infection). For example, simple hematoma or abscess needing only nursing wound care.
- Grade 2: potentially life-threatening complications with the need of intervention or a hospital stay longer than twice the median hospitalization for the same procedure in a similar patient (1 day without comorbidity, 3 days with multiple or major comorbidities). Grade 2 is divided into 2 subgroups based on the invasiveness of the therapy selected to treat the complication; grade 2a require medications only, and grade 2b require invasive procedure.
- Grade 3: complications leading to lasting disability or organ resection. For example intestinal resection for perforation or major tissue loss due to severe wound infection.
- Grade 4: death of a patient due to a complication.

Primary outcome assessment will be based on physical examination of surgical wounds and former hernia site. Imaging techniques (ultrasound or computed tomography) may be required to confirm diagnosis, if clinically relevant (no imaging exam will be performed for the sole purpose of the study).

Follow-up period will be of 30 days after surgery and the study will end when the last included patient will complete this 30 days follow-up.

5. Secondary endpoints

Secondary outcomes will be:

- detailed surgical site complications
- general complications (not directly relate to surgical site, Clavien-Dindo's scoring system)
- pain (Visual Analogue Scale (VAS), at every post-operative visit)
- painkillers consumption (recorded from patient's medical record for in-hospital stay and, for out-hospital period evaluated with consumption recall at each visit)
- esthetic satisfaction (qualitative appreciation by the patient, at wound dressing removal and at last visit)
- quality of life (EuraHS-QoL, at wound dressing removal, at threads removal and at last visit)
- in-hospital costs (hospitalization costs including medications, care and labs, cost of the procedure, diagnosis related group class, total amount billed to the insurance)
- out-hospital costs (derived using REKOLE method)
- early recurrence at 1 month (physical examination ± imaging)

Safety outcomes will be assessed in patients undergoing robotic PVHR :

- rate of device related adverse events
- rate and nature of robotic system malfunctions

5.1. Sample size

Sample size calculation is based on the literature and institutional data. With an estimated surgical site complication incidence of 20% for open PVHR and the objective of 5% surgical site complication incidence for robotic PVHR, 138 patients (69 in each group) will be required to reach 80% power and 5% alpha risk. To compensate for eventual drop-outs, 160 patients (80 in each group) will be included. Actually, 150 open PVHR are performed in the University Hospitals of Geneva; therefore, 1.5 year will probably be required to complete the study.

6. Data collection and management

A member of the study team will identify any eligible patient undergoing primary umbilical or epigastric hernia repair during pre-operative appointment. A member of the study team will give the patient the study information leaflet and discuss it. The patient will have an opportunity to read through the leaflet and ask any questions relating to the study. If the patient wishes to participate, a written agreement will be signed. Patients who do not wish to participate may also be offered robotic PVHR (as well as open PVHR or IPOM), as this technique is now part of the surgical armamentarium of our Division to treat ventral hernias. Included patients will be randomized using the RedCap system. Data of every included patient will be filled in an anonymized case-report form using the RedCap system.

Missing data will thus be managed depending on the cause of missingness. If missingness may directly or indirectly be related to the treatment, it may cause a bias even in intention-to-treat analysis. In such situation, the following measures will be taken: reporting of the missing data in the final report, missing data in intention to treat analysis will be analysed according to the worst case scenario method (failure). Pre-operative drop-outs will be replaced by new patient inclusion and will thus not lead to attrition bias. Post-operative drop-outs are unlikely to happen as post-operative study evaluations and schedule do not differ much from standard post-operative care. Eventual post-operative patients' drop-outs, however, are taken into account in the power calculation.

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

7. Statistical analysis

All study practices and statistical methods are based on the International Conference on Harmonization (ICH) document "Statistical Principles for Clinical Trials."

Baseline characteristics and safety outputs will be summarized overall and by intervention group.

In summary tables variables will be presented as follows. Continuous variables, the minimum and maximum values, the arithmetic mean and standard deviation will be presented to the same number of decimal places as the original data. Qualitative variables, absolute frequencies and percentages will be used. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

Chi2 test (or exact Fisher test when expected effectives are lower than 5) will be run on binary and categorical outcomes such as primary outcome (rate of surgical site complication). Student's t test will be run on continuous variables if they are normally distributed. With 80 patients per group, according to the central limit theorem, t test is applicable even if the data are not normally distributed.

Analysis will be carried in intention to treat.

Subgroup analyses are planned for the following subgroups: weight groups: obese ($BMI \geq 30 \text{ kg/m}^2$) / non-obese ($BMI < 30 \text{ kg/m}^2$), defect size groups: $\leq 2 \text{ cm}$ / $>2 \text{ cm}$.

All hypothesis testing will be carried out at the 5% (2-sided) significance level. P-values will be rounded to three decimals. P-values less than 0.001 will be reported as <0.001 in tables.

No interim analysis is planned for this study considering low risk of adverse events, short planned duration of the study and low risk of surgical failure as the type of repair is the same in both groups (preperitoneal repair with mesh), the only difference being the surgical access, and both surgical accesses are validated and commonly used in abdominal surgery.

8. Discussion

In the present trial, we expect to demonstrate that robotic PVHR leads to lower incidence of surgical site complication rate than the same procedure performed through standard open approach (open PVHR) while being an acceptable solution from economic, operative time and functional standpoints.

The study seeks primarily to determine the incidence of surgical site complication after robotic PVHR versus open PVHR. Secondary objectives are to assess general complications rate, early recurrence rate, pain, esthetic results and costs.

As a comparator against robotic PVHR, we chose open PVHR with mesh reinforcement, as this constitutes the gold standard procedure, IPOM being usually reserved for obese patients with small defects only. Moreover, functional results between laparoscopic IPOM and robotic PVHR are not likely to be the same as mesh reinforcement is not performed in the same anatomic plane, and defect closure is not performed in IPOM.

Conceptually, both approaches (open PVHR and robotic PVHR) lead to the same hernia repair involving closure of musculo-fascial defect with non-absorbable mesh reinforcement in the preperitoneal plane.

Essential difference comes from the minimally invasive approach to perform the procedure in the robotic group and the trans-abdominal approach. Some risk historically described as related to the laparoscopic approach (intra-abdominal organ lesions and adhesions creation), have to be balanced as they were described in the early days of laparoscopy and on small cohorts, and as a substantial number of open PVHR end up with peritoneal effraction too during hernia reduction. As such, a recent US based national quality database of more than 5000 patients over a 4 years course showed that rate of inadvertent enterotomies during ventral hernia repairs is not significantly different between open (2%) and minimally invasive approaches (1.8%, including robotic and standard laparoscopic cases) (29). The subject of adhesion formation is purely conceptual: any peritoneal penetration is likely to produce adhesions, but open ventral hernia repair induce most of the time an opening of the peritoneal sac, and in that way is not less traumatic for the peritoneum than a laparoscopic approach. More adhesions are seen in the IPOM technique than in open repair but this is not applicable to robotic PVHR technique as IPOM implicates an intra-abdominal synthetic material whereas robotic PVHR places the mesh extraperitoneally. No data, until now, allows expecting more adhesions after laparoscopic (or robotic) TAPP ventral hernia repair than after open PVHR.

Adverse events related to the robotic system itself may occur, but in our experience they are frequently related to mis-knowledge and mis-use of the system. In a recent review (30), it was clearly demonstrated that instrument malfunction occur rarely (13 malfunctions over 10 000 cases), and that they result in complication only in case of inappropriate management of the situation by the operating team. Thus, over more than 150 robotic cases performed last year in the visceral surgery department of the HUG, no complication directly related to system malfunction was observed. In addition, strong experience in using the robotic system and a dedicated surgical team allow dealing with eventual device malfunctions without causing any harm to the patient. To reduce these risks the surgical team, which will perform robotic procedures will be constituted of surgeons trained for this kind of procedure and experienced in using the daVinci robotic system. On the other way, to limit bias related to surgical team experience the following measures are deployed:

- at least one surgeon familiar with general surgery but not with the robotic surgery nor robotic PVHR procedure, will be taught to do the procedure under supervision in the robotic group.

- although open umbilical hernia repair is a very common procedure learned very early during surgical residency (often the first learned abdominal procedure), all procedures of the open group will be performed or at least supervised by an experienced surgeon.

Using this design, we are as close as possible from the “real life” conditions of surgical practice in a teaching hospital, with practice from trained surgeons as well as from trainees under supervision.

9. Trial status

Recruiting.

10. Disclosures

Dr. Douissard received a research grant from the Intuitive Foundation to support this study (<http://www.intuitive-foundation.org/clinical-research-grants/>). Outside the scope of this work, Dr. Douissard received personal fees from Verb Surgical Inc. and non-financial support from Intuitive Surgical Inc. Dr. Monika Hagen has no conflicts of interest or financial ties to disclose pertinent to this work. Outside the scope of this work Dr. Monika Hagen received personal fees from Intuitive Surgical Inc. and Ethicon Endosurgery and non-financial support from Intuitive Surgical Inc. and Ethicon Endosurgery. Dr. Meyer, Dr. Dupuis, Dr. Peloso, Mrs. Mareschal and Prof. Toso have no conflicts of interest or financial ties to disclose pertinent to this work.

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