Clinical Study Protocol

Randomized controlled trial

Umbilical hernias – Suture versus Mesh repair

The SUMMER Trial

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Trial Title

Randomized double-blind controlled multicenter trial comparing suture and mesh repair in small umbilical hernias in adults

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Trial Code

SUMMER trial

Trial Registration Number

ClinicalTrials.gov Identifier: NCT04231071

Trial Centre's

Departments in Surgery in; Södertälje Hospital, Danderyds Hospital, Norrtälje Hospital, Enköping Lasarett, St Görans Hospital, Mora Lasarett and Frölunda Hospital

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Trial Period

Estimated date of start inclusion: January 2020

Estimated date of last inclusion: January 2022

Ethics

Approval of the study protocol was obtained 12 December 2018 by the Regional Ethics Review Board in Stockholm, Sweden (DNR 2018/22-65). Completion of the trial centre´s before recruitment of participants were obtained 31 January 2020 (DNR 2019/05-608). All procedures performed in the study involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participating investigators have the responsibility to give both an oral and a written patient information about the trial. Obtained signed informed consent from all patients are maintained before including them in the trial.

Introduction

Umbilical hernia in adults is relatively common and its underlying cause is still unknown. Approximately 5.000 repairs are performed annually in Sweden [1]. The ventral hernia register in Sweden started in year 2010, but still only covers a minority of the ventral hernia repairs. This makes it difficult to study incidence, risk factors and recurrence rates of umbilical hernias in Sweden.

Small umbilical hernias have traditionally since 1740 been repaired either with an open Mayo's technique or using a simple suture [2]. In classic literature over the years the recurrence rates has been described up to 30%, which have been taken for granted since there were no alternative treatments [3]. Mesh repair seems to have been reserved for larger umbilical hernia defects. However, similar results to groin hernia repairs and incisional hernia repairs have also been described for small umbilical hernias to lower the recurrence rates when mesh have been used [4]. Data from retrospective observational studies [5-11], randomized controlled trials [7, 12] and meta-analyses [13, 14] have demonstrated lower recurrence rates using mesh reinforcement in open repair for small umbilical hernias. These limited hand-full published studies in this research area, reports recurrence rates for suture repair between 4-15 % and much lower for mesh repair, between 0-5 %. Two RCT: s are well known in this field; whereas one of them only consisted of total 50 patients with a mean follow up of 22 month [7]. Although, the other one from 2001 consisted of 200 patients with a follow-up of 64 months, the authors included hernias both over and under 3 cm with different mesh positioning [12]. The recurrence rate was ten times higher after suture repair than after mesh repair in this trial [12]. The differences in recurrence in this study were related to the technique (mesh versus suture repair) rather than the size of the hernia. These results support that the size of the defect may not be decisive in the risk of recurrence. Similar results have been published in a Danish nationwide register based study with collected data from the Danish Ventral Hernia Database (DVHD) consisting of a large amount of hernias (4.786) [15]. The reoperation rate for recurrence in small umbilical (and epigastric hernias) ≤ 2 cm were 2.2 % for mesh and 5.6 % for suture repair, $p = 0.001$ [15]. There were no significant differences between the different types of suture material or different positioning of the mesh. In the second Danish cohort study, the authors investigated the total recurrence rate [16]. The total recurrence rates were surprisingly high, demonstrating 21 % (reoperation 9 % + clinical 12%) for suture repair and 10 % for mesh (reoperation 3 % + clinical 7%) [16]. This confirms that reoperation for recurrence really underestimates the total recurrence rate.

Recently, a large, randomized, double-blind, controlled trial with 300 patients where published in Lancet, 2018, comparing suture to mesh repair in umbilical hernias of 1-4 cm [17]. The study is the first in modern literature with high level evidence of small umbilical hernias to demonstrate that mesh reinforcement (4%) has a significant reducing effect on recurrence compared to only suture repair (12%). However, the larger hernia defects (2-4 cm) in this study may affect the increase in recurrence risk in the suture repair group. Also, the role of mesh in these very small umbilical hernias of less than 1 cm remains uncertain.

Despite the above mentioned advantages with mesh reinforcement, surgeons have remained reluctant to use mesh in small ventral hernias. It could be due to fear of higher risk of postoperative complications after mesh repair. A meta-analysis found an increased risk for seroma and SSI (surgical site infection) in the mesh group compared to the suture repair group (7.3 % SSI rate and 7,7 % seroma rate in mesh group compared to 6,6 % SSI rate and 3,8 % seroma rate in the sutured group) [14]. The other meta-analysis showed a clear favor of mesh repair in reducing recurrence rates without any difference in complication rates between mesh and suture repair [13]. The risk of developing mesh-related infection overall is very uncommon. After an open small umbilical hernia repair with or without mesh, it is described as low as about 1-4 % [12]. The presence of seroma and SSI could seem to be slightly too high in the meta-analysis and the explanation could be that the studies are heterogeneous to hernia size and other factors as mesh positioning. For example, the risk of developing a seroma is theoretically higher in larger hernia repairs with a retromuscular technique, rather than in very small defects repaired with a small onlay mesh.

As in groin hernia repair, chronic pain has also become an important issue in ventral hernia repair. However, it has only been investigated in retrospective studies, demonstrating an incidence of chronic pain 4-20% without any differences regarding different surgical techniques [18, 19]. In the Danish cohort study the incidence of chronic pain was similar, 6 % after mesh repair and 5 % after suture repair [16].

Taken together, many studies argue that mesh reinforcement offers an advantage also in small ventral hernias to lower the risk of recurrence. However, there are limited published studies of the subject. Therefore it is difficult to estimate recurrence rates, whether with or without mesh reinforcement. Also, the optimum anatomical mesh position repair technique for small ventral hernias ≤ 2 cm is still not well documented.

At the Department of Surgery, at Södertälje Hospital, 37 patients during 1 year (2015-2016) underwent open hernia repair with suture repair with an onlay lightweight mesh for small (≤2 cm) elective umbilical and epigastric hernias. Three patients reported a seroma, which was managed conservatively. No patient has yet reported chronic pain or recurrence after 12 months of follow-up.

In order to assess whether mesh reinforcement in smaller elective primary umbilical hernias (≤2 cm) reduces the risk of recurrence rates without increasing postoperative complications and chronic pain compared to suture repair, we are planning to perform a randomized controlled trial. We want to compare routine suture repair (control group) with routine suture repair adding a small overlapping onlay mesh (intervention group).

Study objectives

Primary endpoint:

- To evaluate whether an onlay mesh in the repair of primary small umbilical hernias ≤ 2 cm reduces the risk of recurrence compared to suture repair 1 year and 3 year after surgery.

Secondary endpoints:

- To compare the two groups of patients with regard to surgical postoperative complication rate 30 days after surgery.

- To compare the two groups of patients with regard to postoperative pain rate 1 year after surgery assessed by the Ventral Hernia Pain Questionnaire.

Method

1. Trial design

The study is a randomized, double-blind, controlled, multicenter trial with patients undergoing open repair for small elective primary umbilical hernias ≤ 2 cm. The name of the trial is; the SUMMER trial (**S**ture**UM**bilical**ME**sh**R**epair). Patients are either randomized to a repair with only traditionally suture repair or to a traditionally suture repair with an onlay mesh. At each participating unit, all patients who fulfill the inclusion criteria and none of the exclusion criteria are invited in the study. After oral and written consent, the patients are included and are eligible for the study. Patients are then randomized

intra-operatively to one of the groups. The patients are blinded and so are the postoperative clinical investigators. The web-based database REDcap will be used for registration and randomization of the study.

2. Definition of a umbilical hernia

Umbilical hernia is in this study defined according to the European Hernia Society definition as a primary midline abdominal wall defect from 3 cm above to 3 cm below the umbilicus [20]. This definition is commonly used in previous studies, which allows comparison of results with earlier and future publications on these hernias.

3. Selection of the study population

All adult patients referred for an umbilical hernia to outpatient clinical are eligible to the study. Those who are undergoing an elective open repair of a primary umbilical hernia with a defect ≤ 2 cm at the participating units are screened for inclusion. Patients with umbilical hernia defects but not included in the SUMMER trial will be counted at each centre and reason will be documented for not being included.

Inclusion criteria

- Elective surgery of a primary umbilical hernia with a defect ≤ 2 cm that is measured clinically or with radiology.

Exclusion criteria

- Incisional hernia: previous surgery in the area of the operation
- Recurrent umbilical hernia
- Epigastric hernia (a defect from 3 cm below the xiphoid till 3 cm above the umbilicus) [20]
- Another operative procedure at the same time (i.e. cholecystectomy)
- Multiple defects
- An umbilical hernia with a defect > 2 cm measured clinically, with radiology or intra-operatively
- Pregnancy
- Age < 18 years
- Infected wounds
- Acute operation (incarcerated hernia)

- BMI>35
- Ascites
- Immunosuppression
- Anticoagulant treatment (Warfarin, NOAK)
- Connective tissue disease

4. Randomization process

Patients will be recruited to participate in the study during the clinical outpatient meeting with the surgeon if there is an indication for surgery. At each participating unit, all patients who fulfill the inclusion criteria and none of the exclusion criteria are invited in the study. After oral and written consent (see attachment 4.1, 4.2), the patients are included and eligible for the study with directly a registration in the web-based database REDcap. The randomization takes place intra-operatively in each hospital by the operating surgeon directly after the measurement of the hernia defect. If the hernia defect is ≤ 2 cm, the patient have meet the inclusion criteria's and none of the exclusion criteria's, the patient will be randomized to either one of the operation technique via the web-based database REDcap (see attachment 12 for Registration Trial profile). The patient is allocated to one of the groups, either to only suture repair or suture with an onlay mesh repair. Each hospital will receive the same relationship (1:1, block randomization) between suture repair and onlay mesh repair. The randomization will be stratified for participating centre and for size of the hernia defect.

5. Double-blinding

The patient is blinded and will not be informed about the choice of technique after the repair and the following follow-up time. The surgeon will record in the patient's hospital record the procedure that has been done according to the Umbilical SUMMER trial without specifying if a suture repair or a suture repair with an onlay mesh has been performed. The operation code that is going to be used is;

- Diagnos: K42.9 – Navelbråck utan inklämning eller gangrän
- Åtgärdskod: JAF80 – Annan operation av navelbråck

The repair that was performed (mesh or suture repair) is then registered in REDcap intra-operatively. The intraoperative information registered in REDcap will be locked for the postoperative clinical investigators. This means that also the postoperative clinical investigators are blinded, since they only have access to the patient's hospital record.

6. Sample size estimation

The sample size is *extraordinary* difficult to predict in this study. Recurrence rates in previous hand-full studies are inconsistent ranging from a few percent up to 20 %. We believe that the onlay mesh should at least decrease the risk for hernia recurrence with 50%. Taking previous reports recurrence rates in consider; we have predicted a 12 % recurrence rate in the suture repair group and 3 % in the mesh group at 3 year after surgery. The sample size for each group would then be 131 patients. In any case, the number of patients in each group must be increased by 10% to cover the expected patient drop off. The estimated total amount of patients in each group would then be 144 patients to achieve a chance of 80% to detect a difference at the p- level <0.05 with 95 % confidence interval (CI).

7. Multicenter trial

The study is a multicenter trial. The minimum number of included patients per hospital for authorship (one investigator per unit) is 30 patients during a 2-year inclusion period together with a substantive contribution to the work according to the ICMJE recommendations for authorship.

8. Type of Mesh

The onlay mesh that will be used in the intervention group is Ultrapro Advanced®. It is a lightweight composite polypropylene mesh with an absorbable monofilament poliglecarpone-25 component. The weight is 71 g/m² at implantation and ~39 g/m² after absorbable. The shrinking of the mesh is ~5 %. The size that is going to be used is 4x4 cm.

9. Surgical technique – Suture repair vs Onlay mesh repair

At study initiation, all surgeons that will be participating in the study to include and operate patients will be given an oral presentation of the study and the web-based database REDcap. The surgeons will also be demonstrated the surgical technique by the principal investigators with a detailed presentation of the technique to ensure they all use the same standardized techniques for suture repair or mesh repair. Surgeons attending this presentation will be given "green light" to perform the repairs in the trial.
The operation is performed under general anesthesia. No antibiotics will be given in any group. Mayo reconstruction of the umbilical hernia defect is not permitted in this study.

In the Sutured group the surgeon will perform an open incision in the umbilical area of the small umbilical hernia followed by dissection of the hernia sac. Resection of the hernia sac is avoided. The hernia defect diameter is then measured with a sterile ruler (size expressed in mm) and patients are randomized intra-operatively either to suture or mesh repair. The defect in size of the largest diameter in millimeter is measured and recorded in the patient´s hospital record and in REDcap. In this group the surgeon will perform a suture repair with continuous non – absorbable monofilament suture 2/0 of the aponeurosis defect. The defect will be sutured in transversal direction, starting with a start knot and ending with a stop knot.

In the Onlay mesh group the operation will be performed initially as above. The subcutaneous tissue is then dissected from the aponeurosis so the surgeon can apply a 4x4 cm mesh on the site of the defect that has been closed. The mesh is fixated with single non – absorbable monofilament suture 2/0; *first* one in the center of the mesh and *then* one in each corner in a transversal direction to prevent the risk of nerve-entrapment. Totally five single sutures will attach the onlay mesh (Figure 1).

If the surgeon has created an opening in the umbilical skin during the procedure the patient is excluded from the study.

In both groups an absorbable monofilament suture 3/0 or 4/0 is used to adapt the umbilical skin down to the aponeurosis in the suture group and to the mesh in the mesh group. Closure of the skin will be done with the same type of suture with an intra-cutaneous running suture.

Operation time is registered.

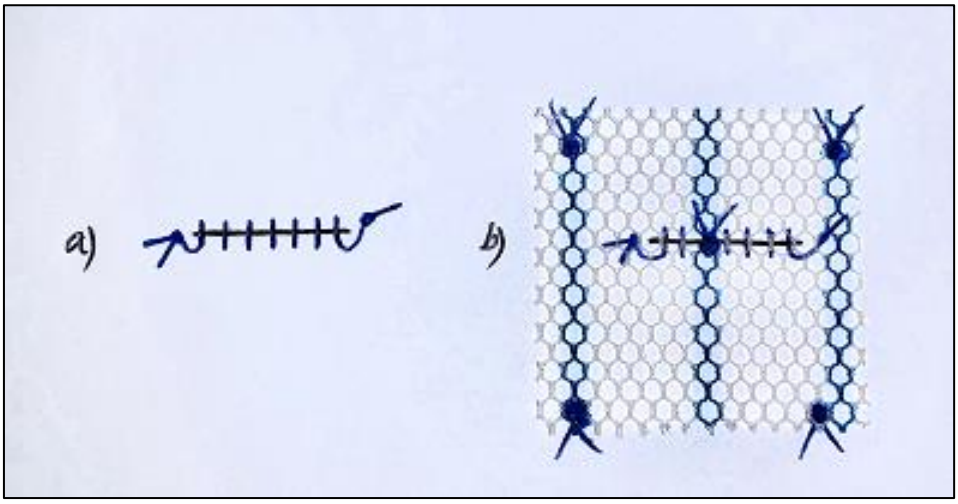

Figure 1 *a) Suture repair b) Suture repair with a 4x4 Onlay Ultrapro Advanced® mesh on the closed defect, illustrating the 5 single sutures.*

10. Postoperative follow-up

The postoperative regime is the same in the two groups. The patients can be operated either as outpatients or inpatients due to the patients' comorbidity.

All patients will be seen in the outpatient clinic at 30 days, 1 year and 3 years after surgery. If the operating department cannot perform all postoperative controls at their own department, the patients will be offered a free visit at Södertälje Hospital.

Postoperative complications

- Wound related complications

The patients are investigated for a seroma, haematoma or a wound infection.

A seroma is defined as an accumulation of clear fluid in the surgical field. A haematoma is defined as an accumulation of blood in the wound area. An infection is defined as a surgical site infection (SSI) which needs an intervention. The postoperative complication will be graded according to the *Clavien- Dindo classification* (see attachment 14) and registered in patient´s hospital record and in REDcap. These findings are investigated and *diagnosed clinically with a physical examination* by the investigated surgeon following an ordinary medical assessment. If there is an uncertainty of a postoperative complication a Computed tomography scan of the abdomen (*CT scan)* is being performed.

- Pain

Patients are requested to fill in Ventral Hernia Pain Questionnaire (VHPQ) after surgery at 1 year visit (see attachment 5).

- Recurrence

Patients are investigated for recurrence at each visit, *diagnosed clinically* with a physical examination by the investigating surgeon following a standard medical assessment. If uncertainty of a recurrence, a Computed tomography scan of the abdomen (*CT scan)* with a valsalva maneuver is being performed.

- Other postoperative complications

Other postoperative complications will be categorized in either pulmonary complications, cardiovascular complications or urinary tract complications.

11. Monitoring – web-based database REDcap

The investigators at each unit are responsible to record and register patients variables pre-, intra- and postoperatively at each follow-up in the patient´s hospital record and in the web-based database REDcap (Karolinska Institutet). A special demonstration of the database REDcap will be given to each unit and the involved surgeons by the principal investigator.

12. Patient baseline characteristics

See attachment 13 for detailed variables that will be recorded in the database REDcap.

13. Statistical analysis

The statistical analysis and presentation of the data will be described in detail using program R in collaboration with statistical expertise. See attachment of a statistical analysis plan (SAP).

14. Study period

The study will start including patients 2020. Collected patients are estimated to be done after maximum 24 months. The total follow-up is 3 year after surgery.

Ethical considerations

There is still no standard treatment for repair of small umbilical hernias due to reduce the recurrence rates. Traditionally, suture repair for small umbilical hernias (even up to 3-4 cm in some surgical units) is often still being used as the primary repair. However, surgeons are considered to use mesh reinforcement also in small umbilical hernias to reduce the recurrence rates. It is ethically very feasible to perform this kind of study when previous studies have shown the advantage of mesh reinforcement in small umbilical hernias. However, there are still not clinical trials that can response to our objectives in a good scientific way with high quality. A randomized control trial provides the highest level of evidence for the effect of the treatment and the aim is to describe the effect of an optimized standardized intervention in selected patients. The most cited RCT in the subject is from 2001 and it

has past more than 15 years with its outdated material. The most recent RCT from 2018 is well-designed with a sufficient amount of patients demonstrating the significant advantage of mesh reinforcement in small and medium (1-4 cm) umbilical hernias. Up to now, the study is the first and only in modern literature. More evidence is needed to establish the optimal anatomical placement of the mesh, especially in very small umbilical hernias. The study has a weakness that the flat mesh is placed under the fascia through a small defect with potentially a higher risk of complications. Also, the study includes medium umbilical hernia defects (2-4 cm) that could theoretically increase recurrence rates in the suture group. In our planned study, the mesh is placed on the outside of the fascia defect with a low risk of complications, and also includes those very small defects below 1 cm. Patients are also investigated for pain after the repair with a validated questionnaire as VHPQ.

None of the methods in the study are controversial techniques that haven't been used before. No danger is described in using them in patients with small umbilical hernias. The risk of using mesh in previous studies is considered not necessary to be higher than not using a mesh. This study aims to investigate this in an effective and safe way. It will determine the best surgical approach for open repair of elective small primary umbilical hernias due to risk of postoperative complications and recurrence. The study can lead to improved knowledge of the treatment of umbilical hernias.

Patient benefit

If we can show that mesh reinforcement in small umbilical hernias, just like in incisional and groin hernia repairs, also have an advantage in reducing recurrence, there is room for improve the surgical technique. The knowledge of umbilical hernia repair will be greater. It could mean that mesh reinforcement may have a new area of use. According to current traditional routines, mesh in small umbilical hernia defects is not used to a large extent. If this study can detect a decreased rate of recurrence when using mesh compared to using suture repair, it may lead to changed treatment recommendations for this patient group. Fewer patients will get recurrences and need to be re-operated in the future. It will reduce the patient suffering and it could have potential cost benefits for the care of these patients.

Data-Protocol protection

The investigators at each unit are responsible and will ensure the confidentiality of the clinical study protocol and data of the study. Each unit/surgeon will be given a login and password to REDcap. Only

the principal investigators will have access to all registered information in REDcap. Unidentified data will then be used in the final statistical analysis.

Revision Protocol History after ethical approval Dec 2018

22 January 2019:	Layout revisions
19 Mars 2019:	Small details in Section 9 about incision of the Surgical method was revised
19 Mars 2019:	Section 7: Minimum included amount of patients/centra is revised to 30
23 Mars 2019:	Section 10: Definition of postoperative wound related complication was revised
30 May 2019:	Addition of 30 days follow-up
24 August 2019:	Preliminary date of Data collection/Inclusion changed to 1 January 2020
7 October 2019:	Section 3: Addition of Connective tissue disease as an exclusion criteria
7 October 2019:	Section 3: Selection of the study population is more clarified regarding patients eligible to the study but not included in the trial

Version 1.0 – Dated after second Ethical approval 2020-01-31 before recruiting status.

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Participant Investigator Signature Page

Participant Centre: ……..

Trial Title

Randomized double-blind controlled multicenter trial comparing suture and mesh repair in small umbilical hernias in adults

I, as a Participant Site Investigator, agree to conduct the SUMMER study in accordance with the terms of this clinical study protocol and with the ethical standards of national research and with the latest version of Helsinki declaration and the ICH Good Clinical Practice.

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Site Investigator Name

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Signature

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Date

Notes