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Study protocol

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Postsurgical pain outcome of vertical and transverse abdominal incision: Design of a randomized controlled equivalence trial [ISRCTN60734227]

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Abstract

Background: There are two ways to open the abdominal cavity in elective general surgery: vertically or transversely. Various clinical studies and a meta-analysis have postulated that the transverse approach is superior to other approaches as regards complications. However, in a recent survey it was shown that 90 % of all abdominal incisions in visceral surgery are still vertical incisions. This discrepancy between existing recommendations of clinical trials and clinical practice could be explained by the lack of acceptance of these results due to a number of deficits in the study design and analysis, subsequent low internal validity, and therefore limited external generalisability. The objective of this study is to address the issue from the patient's perspective.

Methods: This is an intraoperatively randomized controlled observer and patient-blinded two-group parallel equivalence trial. The study setting is the Department of General-, Visceral-, Trauma Surgery and Outpatient Clinic of the University of Heidelberg, Medical School. A total of 172 patients of both genders, aged over 18 years who are scheduled for an elective abdominal operation and are eligible for either a transverse or vertical incision. To show equivalence of the two approaches or the superiority of one of them from the perspective of the patient, a primary endpoint is defined: the pain experienced by the patient (VAS 0–100) on day two after surgery and the amount of analgesic required (piritramide [mg/h]). A confidence interval approach will be used for analysis. A global α-Level of 0.05 and a power of 0.8 is guaranteed, resulting in a size of 86 patients for each group. Secondary endpoints are: time interval to open and close the abdomen, early-onset complications (frequency of burst abdomen, postoperative pulmonary complications, and wound infection) and late complications (frequency of incisional hernias). Different outcome variables will be ranked by patients and surgeons to assess the relevance of possible endpoints from the patients' and surgeons' perspective.

Conclusion: This is a randomized controlled observer and patient-blinded two-group parallel trial to answer the question if the transverse abdominal incision is equivalent to the vertical one due to the described endpoints.

Background

The choice of surgical incision to open the abdominal cavity can be based on patient, surgeon, or health care system criteria. From a patient's point of view pain and restriction of ingestion are important [1]. Considering prior surgical studies, these probable main interests of patients have not been examined systematically [2-8]. Surgeons' main interests, aside from the quick and optimal exposure of the operative field, are: time to open and close the abdomen and frequency of burst abdomen, wound infection, postoperative pulmonary complications, and incisional hernias [2-8]. For health economy, parameters such as duration of operation, length of hospital stay, and full physical and mental activity are relevant [9].

The results of a number of prior randomized controlled studies (RCT) [2-8] and a meta-analysis [9] in this field have shown the transverse approach to be superior to other incisions as regards complications. However, in surgical practice the midline incision is still mainly used [10]. One reason for this discrepancy may be the deficits in study design of these trials, reducing their internal validity. Main problems are: underpowered studies (sample size too small) to estimate the real difference sufficiently, lack of standardization and/or missing data for the surgical technique of the abdominal wall closure [5,9,11], no blinding of patients and assessors [2,3], study inhomogeneities in the meta-analysis [9], and lack of standardized postoperative analgesia and postoperative treatment [9,12,13].

The one available meta-analysis [9] concludes that the transverse incision is superior to the midline incision, leading to a reduction in early-onset complications (burst abdomen, pulmonary disorders) and late complications (incisional hernia) that is attributed to anatomical and physiological advantages. However, the occurrence of these complications not only depends on the type of incision but also on the closure technique. The studies included were retrieved in their original form and examined again separately according to their endpoints. Only one RCT focussed on the frequency of burst abdomen and could not find an advantage for the transverse approach [2]. Pulmonary early-onset complications were assessed in a RCT and were equally distributed in both groups [3]. None of the reviewed studies showed a significant difference in the occurrence of wound infections [9]. In the original data of Greenall et al. [2] the number of incisional hernias is similar with both approaches. Furthermore, retrospective and prospective study data were pooled in the meta-analysis [9] and led subsequently to a non-conclusive result.

To date, no clear evidence exists that the transverse incision is superior to other incisions for the endpoints early and late postoperative complications. It is therefore justified to focus on such a comparison from the patient's perspective. To do this in a scientifically valid manner, a randomized controlled observer and patient-blinded study is required under standardized conditions for the closure technique, pain therapy, and postoperative treatment.

The purpose of this trial is to show that there is no significant difference in pain intensity as experienced by the patient or in the amount of piritramide required between the two abdominal incisions, assuming similar complication rates. Additionally, early and late postoperative complications will be assessed for a follow-up time of 1 year.

Methods

Study Objectives

The primary objective of this study is to compare the transverse and the vertical abdominal approach under consideration of the abdominal pain intensity experienced by a patient and the amount of analgesic drugs used in a number of common surgical procedures.

The primary endpoint is the abdominal pain intensity experienced by a patient, quantified with the Visual Analogue Scale (VAS), and the amount of analgesic required (piritramide [mg/h]) on the second postoperative day.

Secondary objectives are the frequencies of early- and late-onset complications such as burst abdomen, postoperative pulmonary complications, wound infections and incisional hernias (as given in Table 1). In addition, pain is quantified according to the Pain-Sensation-Scale by Geissner, a modified McGill Pain Questionnaire, designed for studies conducted in Germany [14]. To assess the relevance of the possible endpoints from the patient's and surgeon's perspective, the following aspects are ranked from 1 (= most important) to 9 (= least important) by patients and surgeons: postoperative complication, intraoperative complication, duration of hospital stay, starting with standard enteral nutrition, death, postoperative pain, postoperative fatigue, restoration of complete physical maximum resilience, and cosmetic result [1]. The

surgeon ranks each aspect once before the operation. Patients rank the aspects twice: once at inclusion and again at discharge to investigate whether their main perioperative interest changes during the hospital stay.

Table 1: Definition of early-onset and late complications

Complication	Definition
Burst abdomen	Postoperatively missing continuity of the abdominal fascia in combination with a wound dehiscence with subsequent relapse operation.
Wound infection	Redness, wound dehiscence with secretion either of putrid or caliginous, smelly fluid or requiring antibiotic treatment or surgical intervention.
Postoperative pulmonary complications	Infection of the lung with either evidence of increased infection parameters (CRP > 2 mg/dl and/or leukocytes > 10 0000/ml) that are not caused by a different pathologic process or evidence of pulmonary infiltration in the chest x-ray requiring antibiotic therapy.
Incisional hernia	Postoperative evidence of a fascia dehiscence after completed superficial wound healing with or without prolapse of abdominal organs, confirmed by abdominal sonography.

Design of Study

A controlled intraoperatively randomized observer and patient-blinded trial has been deemed appropriate. A parallel group equivalence design was selected because, based on prior studies and knowledge, great differences cannot be expected. The randomization is stratified according to the type of operation planned.

Setting

The setting of the study is the Department of General-, Visceral-, Trauma Surgery and Outpatient Clinic of the University of Heidelberg, Medical School.

Participants

A total of 172 patients over 18 years will be included who are scheduled for an elective abdominal operation and are eligible for either a transverse or vertical incision.

Eligibility criteria

Inclusion Criteria

• Age equal or greater than 18 years

• Expected survival time more than 12 months

• Patients scheduled for the following procedures:

1. Whipple procedure (classic or pylorus-preserving)

2. Duodenum-preserving resection of the pancreatic head

3. Gastrectomy (partial or total gastrectomy)

4. Colon resection (left or right or transverse / classic or extended)

5. Ileocecal resection

• Primary and elective laparotomy

• Patient must be able to give informed consent

• Patient has given informed consent

Exclusion Criteria

• Permanent therapy with a opioid equivalent drug for any reason within 12 months before operation (duration longer than 2 weeks)

• Incompatibility of metamizole

• Recurrent opening of the abdominal cavity (**not** laparoscopic appendectomy, laparoscopic cholecystectomy, laparoscopic adrenalectomy, diagnostic laparoscopy or appendectomy), including prior cesarean section and Pfannenstiel incision (e.g., hysterectomy)

• Participation in another intervention trial that would interfere with the intervention and outcome of this study

• Severe psychiatric or neurologic diseases

• Lack of compliance

• Drug and/or alcohol abuse according to local standards

• Current immunosuppressive therapy (more than 40 mg of a corticoid per day or azathioprine)

• Chemotherapy within 2 weeks before operation

• Radiotherapy of the abdomen completed longer than 8 weeks before operation (except for neoadjuvant therapy, e.g., for pancreatic cancer)

• Liver, gallbladder, spleen, and rectum surgery

Ethics, Informed Consent

The final protocol was approved by the independent ethics committee of the University of Heidelberg, Medical School. Informed consent will be obtained from the patient in oral and written form before inclusion in the trial.

Safety

Burst abdomen, pulmonary infection, and wound infection are secondary endpoints, but are also defined as adverse events. Burst abdomen and postoperative pulmonary infection will even always be considered a serious adverse event. The term *adverse event* covers any sign, symptom, syndrome, or illness that appears or worsens in a patient during the period of observation in the clinical trial and that may impair the well-being of the patient. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant. A *serious adverse event* is any adverse event that occurs at any time during the period of observation that results in death, is immediately life-threatening, requires or prolongs hospitalization, or results in persistent or significant disability or incapacity.

Safety-related data will be analyzed with respect to frequency of:

• Serious adverse events and adverse events stratified acorrding to the organ-systems

• Adverse events stratified by severity

• Adverse events stratified by causality

Statistical analysis

The alternative hypothesis for the primary endpoint is that there is no relevant difference in the postsurgical pain outcome. Postsurgical pain has two essential components: The pain experienced by patients measured on the second postoperative day by VAS and the amount of analgesic drug required (piritramide [mg/h]). Thus, two equivalence tests have to be analyzed confirmatively. For both tests the confidence interval approach will be used. The global significance level must be 0.05. The Bonferroni-Holm Procedure will be used to analyze this multiple test problem. Since the randomization will be stratified by operation class, the analysis also has to be stratified. Thus, an analysis of variance with the two factors incision type and operation class will be performed. A switch to a superiority design is planned if one of the equivalence tests does not give a significant result.

The analysis will be performed on the basis of an intention-to-treat (ITT) population and with respect to ITT principles. A patient belongs to the ITT population after the incision. The primary endpoint will also be analyzed on the basis of a "per protocol" population. Descriptive methods will be used to assess the quality of data, homogeneity of treatment groups, endpoints, and safety of the transverse versus the vertical approach.

Sample Size

The sample size calculation is based on $\alpha = 0.025$ (Bonferroni-Holm) and a desired power of 0.80. The calculation is done separately for each primary variable using Query Advisor Version 4.0, Statistical Solutions Ltd., Cork, Ireland. The maximum of the calculated sample sizes should be taken as sample size. That result is 86 patients per group (see below).

Experienced pain

1. Equivalence design: Assuming no difference between group means, a standard deviation of 20 [VAS], and an equivalence margin of $\delta = 10$ [VAS], 86 patients per group are required. 2. Superiority design: Assuming a minimal clinically relevant difference of $\Delta = 10$ [VAS] between group means and a standard deviation of 20 [VAS], 78 patients per group are required.

Amount of piritramide

1. Equivalence design: Assuming no difference between group means, a standard deviation of 1 [mg/h], and an equivalence margin of $\delta = 1$ [mg/h], 23 patients per group are required. 2. Superiority design: Assuming a minimal clinically relevant difference of $\Delta = 1$ [mg/h] between group means and a standard deviation of 1 [mg/h], 21 patients per group are required.

To achieve 86 patients per group, about 300 patients should be screened.

Based on the hospital volume data of 2002, we can expect to randomize 15 patients per month. To achieve the calculated sample size the enrollment will last at least 12 months, until October 2004. The follow-up time is 1 year. Patients excluded, not randomized, or lost to follow-up will be documented and a specific explanation for withdrawal from the study provided, according to the CONSORT statement (see Fig. 1) [15].

Randomization

Randomization lists will be generated for all strata by computer (SAS Version 8.2, SAS Institute Inc., Cary, USA). The sealed randomization list will be stored in the investigator file. Patients are randomized using sealed envelopes in the operating room after the abdomen has been surgically prepared.

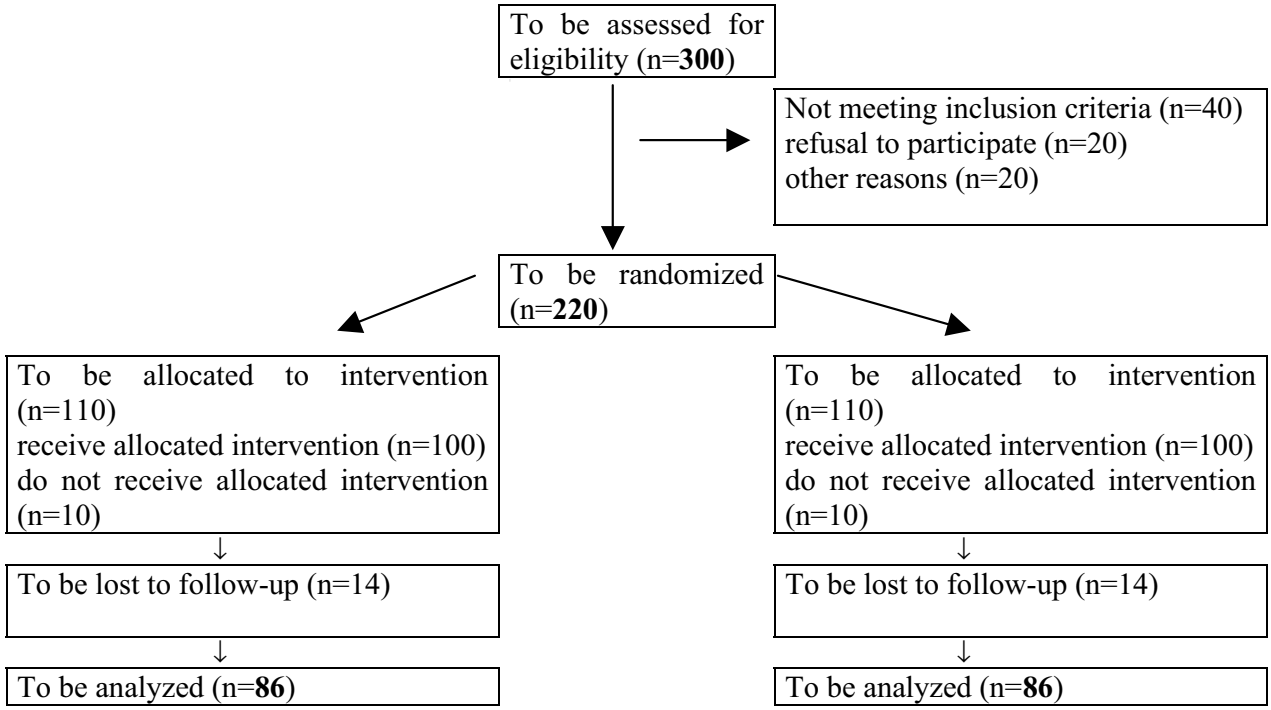

Figure 1
POVATI-Trial according to CONSORT.

Blinding

After surgery, in the operating room, the entire abdomen will be covered by a wound dressing to conceal the incisions type. The dressing will be first changed postoperatively after the primary endpoint has been assessed by a blinded study nurse on the second postoperative day. If necessary, the dressing will be changed before the second postoperative day and will be done by unblinded staff not involved in the trial with the patient blindfolded.

Treatment Program (Table 2)

Electrocauterization will be used for a standardized skin incision in all patients. In patients randomized to the median approach the abdominal fascia is separated in the median line. In the transverse group the rectus muscle is also dissected by cauterization. The time between the first incision in the skin and the placement of the retractor will be recorded in both groups.

The abdominal wall will be closed in a standardized way in both groups: Four Mikulicz clamps are placed at the edges of the abdominal fascia and a continuous, all-layer closure technique with two Mono Plus® loops (BBD Aesculap, Tuttlingen, Germany) performed, starting at both ends from the incision with a 4:1 ratio (suture : scar length). Neither a subcutaneous closure nor a subcutaneous drainage is to be inserted. The skin will be closed with skin clips. The length of the scar is measured in centimeters.

A wound dressing is placed so as to cover almost the entire abdomen, including the abdominal drainages.

The postoperative analgesia is standardized for both groups: piritramide (Dipidolor®[Janssen-Cilag]) at a dosage of 1 mg/ml without a basic rate is administered (patient-controlled analgesia). The dosage of the patient-controlled boli is either 2.0 mg, 2.5 mg, or 3.0 mg given as a single bolus over a period of 3 min. The lock-out time is 10 min and the maximum dosage within 4 h is 45 mg.

The total amount of pain medication is documented from the end of operation until the primary outcome assessment.

For concomitant standardized pain treatment, metamizole (Novalgin®[Aventis Pharma]) 1 g is given four times a day as i.v. infusion. If a patient has an adverse reaction

Table 2: Flow Chart

Visit	1 (=Screening)	2 (OP)	3 (day1 post OP)	4 (day 2 post OP)	5 (day 5 post OP)	6 (day of discharge)	7 (day 30 post OP) by phone	8 (1 year +/- 1 month post OP)	Extra-visit (secondary endpoint, AE or SAE)
Past medical history	X								
Informed consent	X								
Physical examination including personal data	X							X	X
Basic study-related examination (for each secondary endpoint, AE, SAE)	X (ranking by the patient)	X (ranking by the surgeon)	X	X (including survey and documentation of the amount of the analgesic drugs demanded, VAS and Pain-Sensation Scale)	X	X (incl. Second ranking by the patient)	X	X	X
Blinded changing of the wound dressing			X§						
Ultrasound of the abdominal wall								X	X
Lung function test	X							X	
Laboratory parameters	X		X		X				X
Medication	X							X	X

§ if necessary, Basic study-related Examination (= physical examination for each second endpoint or adverse event/severe adverse event), Physical examination (= including personal data, Height in cm, Weight in kg, vital signs); Laboratory Parameters (= serum chemistry, clotting, hematology).

to metamizole, paracetamol is given instead (Perfalgan®[Upsamedica GmbH]1 g i.v. 4 × a day given as i.v. infusion.). The patient will not be removed from the trial if the drug is changed.

Monitoring

An independent study nurse not involved in the trial or in completing the CRFs will monitor the patients. The surgical monitoring, i.e., ensuring that the standardized surgical procedures are performed correctly, will be done by an independent surgeon not involved in the trial.

Follow-up

Patients are observed for 30 days postoperatively for early-onset complications defined as secondary endpoints. The follow-up is completed 1 year after operation with a physical examination, including ultrasonography to exclude an incisional hernia.

Conclusions

The POVATI trial compares the two most common incision types in general surgery. A qualitative ranking by the patients and surgeons to assess the relevance of the primary endpoint is included. Central features of the study design are:

1. Patient's perspective as primary endpoint

2. Detailed calculation of an adequate sample size

3. Randomization stratified for the planned surgical procedures

4. Patient and observer blinded assessment of the primary endpoint

Abbreviations and Definitions

CRF Case Report Form

VAS Visual Analogue Scale

RCT randomized controlled trial

ITT Intention-to-Treat

Competing interest

None declared.

References

1. Nies C, Celik I, Lorenz W, Koller M, Plaul U, Krack W, Sitter H, Rothmund M: **[Outcome of minimally invasive surgery. Qualitative analysis and evaluation of the clinical relevance of study variables by the patient and physician].** *Chirurg* 2001, **72:**19-28.
2. Greenall MJ, Evans M, Pollock AV: **Midline or transverse laparotomy? A random controlled clinical trial. Part I: Influence on healing.** *Br J Surg* 1980, **67:**188-190.
3. Greenall MJ, Evans M, Pollock AV: **Midline or transverse laparotomy? A random controlled clinical trial. Part II: Influence on postoperative pulmonary complications.** *Br J Surg* 1980, **67:**191-194.
4. Ellis H, Coleridge-Smith PD, Joyce AD: **Abdominal incisions--vertical or transverse?** *Postgrad Med J* 1984, **60:**407-410.
5. Stone HH, Hoefling SJ, Strom PR, Dunlop WE, Fabian TC: **Abdominal incisions: transverse vs vertical placement and continuous vs interrupted closure.** *South Med J* 1983, **76:**1106-1108.

6. Garcia-Valdecasas JC, Almenara R, Cabrer C, de Lacy AM, Sust M, Taura P, Fuster J, Grande L, Pera M, Sentis J: **Subcostal incision versus midline laparotomy in gallstone surgery: a prospective and randomized trial.** *Br J Surg* 1988, **75:**473-475.
7. van 't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J: **Meta-analysis of techniques for closure of midline abdominal incisions.** *Br J Surg* 2002, **89:**1350-1356.
8. Armstrong PJ, Burgess RW: **Choice of incision and pain following gallbladder surgery.** *Br J Surg* 1990, **77:**746-748.
9. Grantcharov TP, Rosenberg J: **Vertical compared with transverse incisions in abdominal surgery.** *Eur J Surg* 2001, **167:**260-267.
10. **POI clinical practice preliminary data, Paris 13th April 2003 GlaxoSmithKline.** 2003.
11. Guillou PJ, Hall TJ, Donaldson DR, Broughton AC, Brennan TG: **Vertical abdominal incisions--a choice?** *Br J Surg* 1980, **67:**395-399.
12. Rucinski J, Margolis M, Panagopoulos G, Wise L: **Closure of the abdominal midline fascia: meta-analysis delineates the optimal technique.** *Am Surg* 2001, **67:**421-426.
13. Halasz NA, Torrance C: **Vertical versus Horizontal laparotomies.** *Archives of Surgery* 1964, **88:**911-914.
14. Geissner E: **Die Schmerzempfindungs-Skala (SES).** *Hogrefe, Verlag für Psychologie*; 1996.
15. Moher D, Schulz KF, Altman DG: **The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials.** *Lancet* 2001, **357:**1191-1194.

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