Article:
Chapman, SJ orcid.org/0000-0003-2413-5690, Wood, B, Drake, TM et al. (2 more authors) (2017) Systematic review and meta-analysis of prophylactic mesh during primary stoma formation to prevent parastomal hernia. Diseases of the Colon and Rectum, 60 (1). pp. 107-115. ISSN 0012-3706

https://doi.org/10.1097/DCR.0000000000000670

Systematic review and meta-analysis of prophylactic mesh during primary stoma formation to prevent parastomal hernia

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Article type: Systematic review and meta-analysis

Abstract word count: 294 Words

Manuscript word count: 3,062 Words

MeSH Keywords: stoma, parastomal hernia, prophylactic mesh

Acknowledgments: The authors acknowledge assistance from Leeds NIHR Healthcare Technology Cooperative (HTC) in Colorectal Therapies in design and execution of the study. Also acknowledged is the assistance of corresponding authors of included studies for their responses to data enquiries.

Competing interests: None to declare. The work was unfunded.

Contributions: DGJ and NY conceptualised the idea and had input to the study design. SJC and BW performed searches and collected data. SJC and TD performed statistical analysis. All authors contributed to the final writing of the manuscript. DGJ is the study guarantor.

Abstract

Background: Implantation of mesh at the time of stoma formation may reduce the rate of parastomal hernia. Until recently the evidence has been limited to only a few small randomised controlled trials.

Aim: We present an updated systematic review and meta-analysis to assess the effect of mesh prophylaxis on rates of parastomal hernia. We examine ongoing and unpublished trials via online registries and propose recommendations for future research.

Data Sources: MEDLINE, EMBASE and the Cochrane Library were searched up to March 2016 for published randomised controlled trials. Sixteen international trial registries were inspected for ongoing and unpublished trials.

Study Selection Randomised controlled trials comparing mesh versus no mesh on the incidence of parastomal hernia after colostomy or ileostomy formation.

Main Outcome Measures: The primary outcome measure was rate of parastomal hernia at least 12 months after stoma formation. Secondary outcomes included rates of stoma-related complications.

Results: Of 3005 studies identified, 7 RCTs (432 patients) were eligible for inclusion in the final analysis. All were at high risk of bias. Mesh reduced the incidence of clinically detected parastomal hernia (10.8% versus 32.4%; P=0.001) (RR 0.34, CI 0.18 to 0.65, I^2=39%) and the rate of radiological detected parastomal hernia (34.6% versus 55.3%; P=0.01) (RR 0.61, CI 0.42 to 0.89, I^2=44%). No increase in the incidence of stoma-related complications was observed with the use of prophylactic mesh. Results from ongoing and unpublished RCTs are expected, but few will report on alternative mesh types or surgical techniques.

Limitations: Heterogeneity of interventions, small patient populations and a high risk of bias seen in all studies implicate cautious interpretation of the results.

Conclusion: Mesh prophylaxis at the time of stoma formation appears safe and effective in preventing parastomal hernia, however limitations of the primary evidence justify larger, more rigorous RCTs.

Introduction

Parastomal hernia is a common complication after gastrointestinal stoma formation, with incidences of 4-48% after end-colostomy and 1.8-28% after end-ileostomy formation[1]. The risk of parastomal hernia is increased by obesity, steroid use and greater age. Although parastomal hernias may be asymptomatic, they frequently cause morbidity through poor implantation, with leakage and dermatitis, intermittent obstruction, strangulation, and perforation[2].

Local repair of parastomal hernias is associated with high rates of recurrence (46% - 100%), which is reduced when combined with a prosthetic mesh (0 - 33%)[1]. Recently, there has been a focus on hernia prophylaxis with the placement of mesh at the time of stoma formation. This was originally described by Bayer and colleagues in 1986[3] and has developed with the use of various meshes and techniques for implantation. Whilst attempts to reinforce the stomal defect are logical, concerns exist regarding the efficacy, safety and cost-effectiveness of mesh implantation[4, 5].

A previous, small meta-analysis of three randomised controlled trials (RCTs) suggested a favourable effect of mesh prophylaxis, but small participant populations, heterogeneous study selection and a high risk of bias across all cohorts limited the results[6]. New evidence from recently published RCTs has emerged and justifies an updated review. This may help to clarify the evidence for mesh prophylaxis, facilitating better clinical decision-making and more informed patient choice.

The primary aim of this review was to determine the effect of prophylactic mesh during primary stoma formation on the incidence of parastomal hernia. Secondary aims included assessments of stoma-specific complications. In addition, we examined ongoing and unpublished studies to identify gaps in the evidence base, understand current research priorities and guide future research efforts**.**

Methods and Materials

Study Design and Outcomes

A study protocol was developed in accordance to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines[7]. The study was registered prospectively on the PROSPERO database of systematic reviews (CRD42016033679) and results reported according to PRISMA guidelines[8].

Searches

A systematic search strategy was designed to identify studies assessing the effect of prophylactic mesh during gastrointestinal stoma formation to prevent parastomal hernia (Supplement 1). The search was initially performed on 15th November 2015, and updated on 25th March 2016 in light of newly published evidence. Two investigators independently performed systematic searches of MEDLINE (via OvidSP), EMBASE (via OvidSP), and the Cochrane Database of Systematic Reviews. Study titles were screened for relevance prior to full inspection of abstracts and full texts. Discrepancies were addressed by re-examination and discussion, with involvement of a third investigator if necessary. Reference lists from relevant systematic reviews were inspected for eligible studies. All “primary registries” endorsed by the World Health Organisation International Clinical Trial Registry Platform were inspected for relevant ongoing and completed, but not yet published, trials using a modified search strategy. This included 16 international trial databases which comply with requirements set out by the International Committee of Medical Journal Editors (ICMJE)[9] (Supplement 2).

Inclusion Criteria

All RCTs including adult patients (18 years and older) undergoing primary lower gastrointestinal stoma formation via open or laparoscopic approaches were eligible for

inclusion. Studies assessing outcomes following formation of colostomy or ileostomy (including loop or end stomas) were included. Trials had to include at least one arm assessing the impact of mesh prophylaxis for prevention of parastomal hernia with at least 12 months follow up, measured by either clinical or radiological examination. Manuscripts published online or in print up to March 2016, were included. Other study types, including retrospective and prospective observational studies, technical notes, letters and study protocols were excluded. Grey literature, such as conference proceedings, was excluded due to the high likelihood of incomplete data.

Outcomes

The primary outcome was the rate of parastomal hernia. Identification of parastomal hernia through clinical and radiological examination were handled and analysed separately. Other planned secondary outcomes were the rate of stomal complications, including haematoma, seroma, stoma-related infection, stomal stricture, stomal prolapse and re-operation.

Definitions

For this study, stoma formation was defined as creation of an artificial opening to the external environment on any section of the lower gastrointestinal tract. Ostomies associated with the urogenital tract were excluded. According to definitions set out by the United States National Institutes of Health, ongoing RCTs were defined as those “Recruiting or “Active but not yet recruiting”[10]. “Completed” RCTs were considered ongoing if less than two years since the recorded date of completion to allow for active clinical follow. According to the same definitions, unpublished RCTs were defined as those “Terminated”, “Withdrawn” or “Completed” with greater than two years since completion. Several surgical techniques for placement of mesh are recognised: “onlay” implantation refers to mesh placed on the external oblique fascia if performed by an open technique, or to the peritoneum if performed by a laparoscopic technique;

“sublay” refers to mesh placed in the retro-muscular layer of the abdominal wall; and “inlay” refers to mesh placed under the peritoneum. Techniques were determined as described in the primary trials.

Data Extraction

Data extraction was performed by a single investigator and checked by a second investigator. Clinical data fields extracted included: stoma type (ileostomy vs. colostomy and loop stoma vs. end stoma), mesh type (synthetic vs. biological), mesh position (onlay vs. inlay vs. sublay), operative approach (open vs. laparoscopic), primary outcome measure (clinical vs. radiological), Body Mass Index (BMI) and time of follow up. Other descriptive data extracted included: study population size, country of origin and year of publication. Corresponding authors were contacted to seek missing data relevant to primary and secondary endpoints.

Study Quality and Bias

Assessment of quality and risk of bias was performed by two independent investigators with discrepancies addressed by discussion. The Cochrane Risk of Bias Tool[11] was used to assess included RCTs. The tool assesses multiple domains of bias, including selection, detection, attrition, reporting and other biases. All domains were assigned an overall status of “high” or “low” risk of bias, with “unclear” elements regarded as a source of “high” risk.

Statistical Analysis

The number of patients in each group was the primary unit of analysis and was used to construct risk-ratios (RR) or odds-ratios (OR) for relevant outcomes. Quantitative meta-analysis of pooled effect-estimates were calculated and presented using Forest plots. Results of each study and overall pooled effects are presented as ratios of risk or odds, alongside 95 per cent confidence intervals (95% CI). The level of statistical

significance was defined as $P<0.05$ a priori. Where an adequate number of events existed across trials (greater than 10 between experimental groups), a Mantel-Haenszel random effects model was used to construct risk-ratios and account for the anticipated heterogeneity contained in the included studies. Where there were fewer than 10 events across both experimental groups, the Peto model was used to estimate odds ratios (OR), which is more robust at extremes of power. Inter-study heterogeneity was measured using the I^2 statistic. Substantial statistical heterogeneity between studies was defined as I^2 greater than 50 per cent or a statistically significant Chi-squared value ($P<0.10$). In the case where statistical heterogeneity did occur, a qualitative synthesis of findings was planned through careful examination of bias and variation. All statistical analyses were performed using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen).

Sensitivity Analyses

Sensitivity analyses on the primary outcome (parastomal hernia) were pre-planned for the following groups as long as two or more respective RCTs existed: RCTs assessing the impact of biological mesh (as opposed to synthetic mesh), RCTs with low risk of bias (as opposed to high risk) and RCTs assessing the presence of hernia following colostomy formation (as opposed to ileostomy or mixed populations).

Results

Characteristics of Included Manuscripts

From a total of 3005 manuscripts identified, 12 RCTs met provisional inclusion criteria. Two were excluded as they reported less than 12 months follow up, one was excluded due to insufficient report quality, and two were excluded as they described multiple follow up periods of the same population (Figure 1). Seven manuscripts underwent final assessment of the primary outcome, including 464 randomised participants (432 undergoing analysis) across a range of multicenter and single-center settings[12-18]. Full characteristics of these trials are shown in Table 1.

Procedures and Mesh

Most procedures involved formation of an end-colostomy, apart from one trial that included a mixed population undergoing end-colostomy or end-ileostomy. There were no procedures involving loop stomas in any of the included studies. Six of the seven eligible trials used synthetic mesh, with one trial using porcine-derived biological mesh. Mesh was placed in the sublay position (retro-muscular) in four out of seven trials, with the remaining trials using an intraperitoneal onlay position. Full characteristics including fixation methods and surgical approach are shown in Table 2.

Assessment of Quality and Bias

All included studies were deemed to be high risk of bias. All seven trials provided adequate details of allocation concealment, and all but one described methods of random sequence allocation. One trial blinded both patients and assessors, three trials blinded assessors or surgeons, with no patient blinding and two trials were not blinded at all. Blinding in the remaining trial was not clearly reported. Other biases included one trial with significant loss to follow up and one trial terminated early due to strong early evidence supporting the use of prophylactic mesh (Figure 2).

Assessment of Outcomes

Parastomal hernia was assessed by clinical examination in five trials, of which three also included assessment by computer tomography (CT) as a secondary outcome. The remaining two trials assessed presence of parastomal hernia by CT as the primary outcome. Six trials (85.7%) provided definitions for parastomal hernia, but these varied considerably (Table 3).

Efficacy Outcomes

Of 464 randomised participants, 432 were available for analysis according to the intention to treat principle. Reasons for participant attrition across studies included: failed eligibility during or after surgery (n=21); withdrawal of consent before surgery (n=3); loss to follow up (n=5); and death prior to 12 months follow up (n=3). The incidence of clinical parastomal hernia was reduced by use of prophylactic mesh (19/176; 10.8%) versus no mesh (55/170; 32.4%) across five RCTs (RR 0.34, CI 0.18 to 0.65, I^2=39%, P=0.001). The same was true when assessed using CT, with incidences of 47/136 (34.6%) and 73/132 (55.3%) for mesh versus no mesh respectively across five RCTs (RR 0.61, CI 0.42 to 0.89, I^2=44%, P=0.01) (Figure 3). The number needed to treat (NNT) to prevent one parastomal hernia was 5 (CI 3.3 to 7.2).

Safety Outcomes

There were no significant differences in rates of stomal prolapse (0.6% versus 2.9%; P=0.09), stomal stricture (4.5% versus 1.8%; P=0.15) or stoma-site infection (2.0% versus 1.5%; P=0.71) between mesh and no mesh respectively. Mesh was associated with fewer re-operations within the follow up period (2.3% versus 8.4%; P=0.005). Full data from pooled analyses of all included studies are shown in Table 4. Data for haematoma or seroma formation were not available for analysis.

Sensitivity Analyses

Exclusion of a single RCT[15] with mixed stomas demonstrated a further reduction in the risk of clinical parastomal hernia after formation of end-colostomy (RR 0.27, 0.16 to 0.48, P<0.001; I^2=0%) (Figure 4). The excluded study included both end-colostomy and end-ileostomy procedures, but limitations of the data meant it was not possible to comment on outcomes relating to end-ileostomy specifically. Pre planned sensitivity analyses for RCTs assessing biological mesh and RCTs with low risk of bias were not possible due to insufficient data.

Ongoing and Unpublished Trials

Inspection of 16 international trial registers identified 38 unique studies. All seven studies included in the current meta-analysis were excluded. A further 18 studies were excluded due to non-mesh interventions (n=7), non-gastrointestinal stoma formation (n=6) and non-randomised study design (n=5), leaving 13 that were eligible. Eleven studies were ongoing or within two years following completion, with a total anticipated population of 1,603 participants (Table 5). The majority of these tested synthetic mesh, with a sublay position being the most common position of implantation. The surgical approaches used in these studies (laparoscopic versus open) were commonly not disclosed, but the limited data available suggested a broad mix of approaches in ongoing studies. Almost all of these studies (n=10/11; 90.1%) aimed to follow up patients at least 12 months after the primary procedure (range 6-120 months). Quality of life assessments were planned in 6/11 (54.5%) and assessments of cost effectiveness in 3/11 (27.3%). The remaining trials (2/11; 18.2%) were unpublished at ≥2 years after completion, with a total anticipated population of 340 participants.

Discussion

The results of this study show that placement of mesh at the time of stoma formation significantly reduces the incidence of parastomal hernia. This is evident when assessed using either clinical or radiological outcome measures. In addition, placement of mesh appears safe and does not increase the incidence of postoperative adverse events. These results must be balanced with inherent limitations of the primary evidence, including heterogeneous interventions and a high risk of bias seen across all included studies.

There are several approaches for parastomal hernia repair, including local tissue repair, stoma relocation and mesh reinforcement. All are associated with considerable rates of hernia recurrence (46-100% vs. 0-72.2% vs. 0-33% respectively), which has driven interest in mesh prophylaxis[1]. Risks of complications associated with this approach include stoma-site infection and stricture, which have contributed to a cautious uptake amongst surgeons. However, evidence from recent randomised controlled trials suggests good efficacy and safety for mesh prophylaxis in small study populations, and may represent a superior approach. The current meta-analysis demonstrates a reduction of parastomal hernia with prophylactic mesh, with no significant increases in stoma-related complications. The rate of stoma-site infections was similar between mesh and non-mesh groups, and whilst a small increase in stricture rate was identified (4.5% vs. 1.8% respectively), the difference was not statistically significant. The smaller incidence of parastomal hernia with mesh was detected using both clinical and radiological outcome measures. Notably, the overall rate of detection was far greater when assessed using CT, which is likely explained due to detection of clinically asymptomatic hernias. The number needed to treat in order to prevent one parastomal hernia was 5 according to both clinical and radiological outcomes, suggesting a good treatment effect.

Included in this study was an evaluation of ongoing and unpublished trials, which was performed to better understand current research priorities and to make recommendations for future research. A number of trials were identified from online registers, with a combined population exceeding 1,600 patients. One of these, the PREVENT study (NTR2018; trialsregister.nl)[19], is expected to publish outcomes in the next 12 months, with interim outcomes already reported[20]. Strengths of this study compared to current literature include a larger study population and patient blinding, but the absence of assessor blinding may be a limitation. Publication of other trials is expected in the next 12-24 months, with most expected to report outcomes relating only to synthetic mesh materials. This leaves a number of questions unanswered, including the efficacy and safety of alternative mesh types and positions of implantation. Biological and composite meshes have gained interest recently as concerns of comorbidity associated with synthetic polypropylene mesh have grown[4]. In addition, it has been suggested that mesh-related comorbidity such as contamination may be reduced by intraperitoneal placement of mesh, however others have raised concerns over the risk of intestinal obstruction related to this approach[4, 21]. Evidence from high quality RCTs to investigate these issues is lacking and future studies should broaden their scope to assess safety and efficacy of multiple materials and techniques. Future studies may also wish to extend their portfolio of outcomes, including patient-reported measures and evaluations of cost-effectiveness. Finally, identified within this assessment were a small number of completed trials with no published evidence after at least two years following primary completion. These represent hidden trial data and implicate wasted resources through unrealised data[22]. Investigators should aim for timely and complete dissemination of results to inform best current practice.

A previous meta-analysis of prophylactic mesh by Shabbir and colleagues reported outcomes from three RCTs[6]. Small patient populations, heterogeneous interventions

and a high risk of bias in the primary studies limited the conclusions drawn from this analysis. Notably, one study included patients undergoing temporary loop stomas, with most subjects undergoing reversal at a median time of 5-7 months after formation[23]. There are suggestions that herniae associated with loop stomas develop within three months[1], however this timescale is likely insufficient to ensure reliable and complete detection of all herniae[24]. The current updated meta-analysis excluded this study, according to a minimum follow up period of 12 months, and included five additional RCTs published during or after 2012. One of these included a mixed population of patients undergoing end-colostomy and end-ileostomy[15], which was included to maximise available evidence, whilst been subjected to an appropriate sub-analysis. Another study tested biologic meshes, whereas all others used synthetic materials. This is notable, as the biologic mesh series contributed approximately 25% of the overall pooled population, and unlike other studies, failed to demonstrate improved outcomes with mesh. Further investigation into the safety and efficacy of biologic mesh, and its performance compared to synthetic materials, is indicated. Finally, despite previous calls for a large, robust RCT[6], a high risk of bias persisted in all studies in the current review. A major source of bias arose from inadequate blinding, with most studies failing to blind both subjects and assessors. This was augmented by events such as early trial termination in one study due to strong interim evidence supporting prophylactic mesh, which may have introduced bias through falsely inflated effect sizes[25]. This topic remains a priority research area, acknowledged by both the American Society of Colon and Rectal Surgeons (ASCRS) and Association of Coloproctology of Great Britain & Ireland (ACPGBI).[26, 27]

Strengths of the current study include an outline of ongoing studies. This is important as, although the volume of evidence for prophylactic mesh has increased, the respective gaps in evidence still persist in ongoing research. The results should raise awareness of these issues and guide future trial designs and priorities. Limitations of

this meta-analysis are recognised and should be considered when interpreting the results. Firstly, a heterogeneous mix of synthetic and biological meshes placed in different anatomical planes is inherently problematic for meta-analysis due to heterogeneity of interventions. This is particularly notable in the absence of sufficient data to perform reliable sub-analyses for clinically important variables. Secondly, disparity in the clinical definition of parastomal hernia and variable follow up periods across all studies added further heterogeneity to the studies' outcome measures. We attempted to address this inherent heterogeneity by selecting models based upon their performance for meta-analysis, however residual error is likely to remain.

The data presented by this meta-analysis appears to support the safety and efficacy of prophylactic mesh to prevent parastomal hernia. However, inherent limitations of the primary evidence hinder reliable, unbiased assessment and ongoing trials still lack assessment of alternative mesh types and techniques. This study represents best current evidence, but there is a continued need for larger, higher quality RCTs with broader scopes of assessment. This may be achieved by more complex, multi-arm clinical trial designs.

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Table 1: Characteristics of all included trials (n=7)

Table 2: Characteristics of mesh, mesh position and fixation methods of all included trials (n=7)

Table 3: Definitions of parastomal hernia for all included trials (n=7)

Table 4: Meta-analysis of pre-planned secondary outcomes for all included trials (n=7)

Table 5 Characteristics of ongoing & unpublished trials identified from 16 trial registries (n=13)

Figure 1: Systematic process of Inclusion and exclusion of published RCTs

Figure 2: Cochrane Risk of Bias Assessment for all included trials (n=7)

Figure 3: (a) Meta-analysis of clinical parastomal hernia for mesh vs. no mesh interventions (n=5); (b) Meta-analysis of radiological parastomal hernia for mesh vs. no mesh interventions (n=5)

Figure 4: Sensitivity analysis of clinical parastomal hernia for mesh vs. no mesh according to stoma type

Supplement 1: Systematic **s**earch strategy applied to MEDLINE and EMBASE databases

Supplement 2: Clinical Trial Registries endorsed by the World Health Organisation International Clinical Trials Registry Platform (ICTRP) (n=16)