Infectious Complication in Relation to the Prophylactic Mesh Position: The PRIMA Trial Revisited

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BACKGROUND: Prophylactic mesh reinforcement has proven to reduce the incidence of incisional hernia (IH). Fear of infectious complications may withhold the widespread implementation of prophylactic mesh reinforcement, particularly in the onlay position.

STUDY DESIGN: Patients scheduled for elective midline surgery were randomly assigned to a suture closure group, onlay mesh group, or sublay mesh group. The incidence, treatment, and outcomes of patients with infectious complications were assessed through examining the adverse event forms. Data were collected prospectively for 2 years after the index procedure.

RESULTS: Overall, infectious complications occurred in 14/107 (13.3%) patients in the suture group and in 52/373 (13.9%) patients with prophylactic mesh reinforcement ($p = 0.821$). Infectious complications occurred in 17.6% of the onlay group and 10.3% of the sublay group ($p = 0.042$). Excluding anastomotic leakage as a cause, these incidences were 16% (onlay) and 9.7% (sublay), $p = 0.073$. The mesh could remain in-situ in 40/52 (77%) patients with an infectious complication. The 2-year IH incidence after onlay mesh reinforcement was 10 in 33 (30.3%) with infectious complications and 15 in 140 (9.7%) without infectious complications ($p = 0.003$). This difference was not statistically significant for the sublay group.

CONCLUSIONS: Prophylactic mesh placement was not associated with increased incidence, severity, or need for invasive treatment of infectious complications compared with suture closure. Patients with onlay mesh reinforcement and an infectious complication had a significantly higher risk of developing an incisional hernia, compared with those in the sublay group. (J Am Coll Surg 2021;232:738−745. © 2021 The Author(s). Published by Elsevier Inc. on behalf of the American College of Surgeons. This is an open access article under the CC BY-NC-ND license [http://creativecommons.org/licenses/by-nc-nd/4.0/].)

Incisional hernia (IH) remains one of the most frequent complications after open abdominal surgery. Incidences of incisional hernia after midline laparotomy may be well over 30% in high-risk patients (ie with obesity or an abdominal aortic aneurysm).[1] Given this high prevalence of incisional hernia in high-risk patients, measures to prevent this complication are essential to improve patient care.

Two main techniques may substantially reduce the incidence of incisional hernia after open abdominal surgery. These include use of the small bites closure technique in the general patient population and prophylactic mesh reinforcement in patients with an increased risk for development of incisional hernia.[1,2]

Prosthetic meshes have proven to substantially reduce the occurrence of incisional hernia in a therapeutic setting and may reduce the incidence of incisional hernia when applied prophylactically.[1] However, fear of increased risks of infectious complications, associated with the use of foreign body material in general, may withhold the

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widespread implementation of prophylactic mesh reinforcement, particularly in the onlay position.

A disadvantage of prosthetic meshes is that if the operation field is contaminated, a surgical site infection (SSI) may occur in combination with a mesh infection. This is one of the most devastating complications that can occur after hernia surgery.[3] Proven mesh infections may require removal of the mesh, and SSIs are known to raise the risk of the development of an IH by negatively affecting the remodelling of the linea alba.[4,5]

Many previous studies have assessed the effect of mesh reinforcement with reference to infectious complications in a therapeutic setting.[3,6-10] However, little is known about the effects of prophylactic mesh reinforcement with reference to SSIs. Therefore, we aimed to reassess data of the 3-armed randomized "Prevention of incisional hernia with prophylactic onlay and sublay mesh reinforcement versus primary suture online midline laparotomies" (PRIMA) trial, in which high-risk patients were treated with either primary suture closure, prophylactic onlay, or sublay mesh reinforcement. The objective of this additional analysis was to assess the incidence, treatment, and outcomes of patients with infectious complications.

METHODS

The medical ethics board of the Erasmus University Medical Centre approved conduction of the PRIMA trial. A waiver for ethical approval was obtained for additional analyses. This retrospective observational study was conducted according to the STROBE (Strengthening the Reporting of Oservational studies in Epidemiology).[11]

Study design

The methods and study design used for the PRIMA trial have been described earlier.[1] In brief: after informed consent, patients from 3 different countries and 11 medical centers were scheduled for an elective midline laparotomy. Before surgery, patients were randomly assigned to a primary suture group, onlay mesh reinforcement group, and sublay mesh reinforcement group for closure of the midline incision. Only adult patients (aged 18 years or older) with an increased risk for developing an IH were included. Patients who were considered were either previously diagnosed with an abdominal aortic aneurysm (AAA) or had a BMI of 27 kg/m^2 or higher. The primary outcomes of the trial have been published.[1]

Mesh reinforcement

For the onlay mesh reinforcement group, a lightweight polypropylene mesh (Optilene mesh LP, 6×35 cm; B Braun Surgical SA) was fixated to the anterior rectus fascia with an overlap of 3 cm. Fixation was accomplished with 4.0 mL of fibrin sealant (Tisseel; Baxter Healthcare). The edges and the centre of the mesh were glued to the tissue and fixated with the back of a pair of forceps on the entire surface. Subcutaneous tissue and skin were closed by suture preference of the surgeon.[1,12]

For the sublay mesh reinforcement group, a posterior plane was established between the rectus muscle and posterior rectus sheath, and caudally to the arcuate line between the rectus muscle and peritoneum. The mesh used was a lightweight polypropylene mesh (Optilene) that was placed on the posterior rectus fascia, with a 3-cm overlap. The mesh was fixated as described for onlay mesh reinforcement as well as adjustments made to the mesh. The subcutaneous tissue and skin were closed by suture preference of the surgeon.[1,12]

Data extraction

In this study, the available study data and adverse event forms were retrospectively assessed. The severity, treatment, and outcomes of patients with infectious complications were specifically extracted. Infectious complications were classified as either superficial surgical site infections (SSI) (with involvement of subcutaneous tissue), deep SSI (if fascia and muscle tissue were involved), or intra-abdominal abscesses. Primary treatment of infectious complications was classified in 5 categories: conservative (if no invasive intervention was performed), debridement, drainage and lavage, mesh removal (if this was the primary treatment), or relaparotomy. For patients receiving sublay and onlay mesh reinforcement who developed an infectious complication, the incidence of IH within 2 years after the index procedure was assessed. Additionally, in all patients who had the mesh removed during the 2 years of initial follow-up, the reason for mesh removal was assessed. These were classified into 4 categories: fascial dehiscence, relaparotomy unrelated to mesh, IH repair, or infectious complications. The latter included preventative mesh removal if an intra-abdominal infectious focus was present.

Primary and secondary objectives

The primary objective was to assess whether prophylactic mesh reinforcement was associated with more infectious complications or an increased severity (ie the need for invasive treatment) of these complications. Secondary objectives were to assess the 2-year IH incidence in patients with prophylactic mesh reinforcement who were diagnosed with an infectious complication. Outcomes were compared to the suture group and between the onlay and sublay mesh reinforcement groups.

Statistical analysis

Discrete variables were reported as absolute numbers and percentages, continuous variables were reported as mean and standard deviation (SD). Baseline characteristics of the 3 study arms were reported without formal statistical testing. Discrete outcomes were compared with a chi-square test or Fisher's exact test, as appropriate. The frequency of infectious complications was compared within the 3 treatment arms; additionally, the frequency of infectious complications after sublay and onlay mesh reinforcement was compared. The 2-year incidence of IH was compared between patients with and without infectious complications, for patients with onlay or sublay mesh reinforcement. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of included patients were previously described by Jairam and colleagues.[1] For illustration purposes, baseline characteristics of the 3 treatment arms are depicted in Table 1. The 3 randomized groups were well balanced based on collected data.

Frequency of infectious complication

Frequencies of postoperative infectious complications are summarized in Table 2. Overall infectious complications occurred in 14 (13.3%) of patients in the suture closure group, and in 52 (13.9%) patients who had received prophylactic mesh reinforcement ($p = 0.821$). Superficial surgical site infections occurred in 4 (3.7%) patients in the suture closure group, and in 23 (6.2%) patients who had received prophylactic mesh reinforcement ($p = 0.337$). Deep surgical site infections, including the subcutaneous tissue, occurred in 2 (1.9%) patients in the suture closure group and in 20 (5.4%) patients who had received prophylactic mesh reinforcement ($p = 0.108$). Intra-abdominal abscesses occurred slightly more frequently in the suture group ($n = 8$, 7.5%), as compared with patients who had received prophylactic mesh reinforcement ($n = 11$, 2.9%, $p = 0.021$). A confirmed mesh infection was reported in only 6 (1.6%) patients treated with prophylactic mesh reinforcement. When comparing onlay with sublay mesh reinforcement, onlay mesh reinforcement was associated with a statistically significant increased incidence of patients with overall infectious complications (onlay mesh: $n = 33$, 17.6% vs sublay mesh: $n = 19$, 10.3%, $p = 0.042$). No significant

Table 1. Baseline Characteristic

Characteristic	Total	Primary suture	Onlay mesh	Sublay mesh
Sex, n (%)				
Male	288 (61)	68 (64)	116 (62)	108 (58)
Female	188 (39)	39 (36)	72 (38)	77 (42)
Age, y, mean (SD)	64.5 (11.2)	65.2 (10.5)	64.2 (12.3)	64.4 (10.4)
BMI, kg/m^2, mean (SD)	30.6 (5.3)	29.8 (4.4)	30.8 (5.9)	30.8 (5.2)
Smoking, n (%)	102 (21)	17 (16)	41 (22)	44 (24)
Diabetes mellitus, n (%)	94 (20)	19 (18)	36 (19)	39 (21)
COPD, n (%)	52 (11)	9 (8)	24 (13)	19 (10)
ASA class, n (%)				
I	44 (9)	10 (9)	21 (11)	13 (7)
II	234 (49)	55 (51)	90 (48)	89 (48)
III	150 (31)	35 (33)	54 (29)	61 (33)
IV	6 (1)	1 (1)	3 (2)	2 (1)
Unspecified	46 (10)	6 (6)	20 (11)	20 (11)
Previous midline incision, n (%)	21 (40)	3 (3)	10 (5)	8 (4)
Other hernia, n (%)	50 (10)	13 (12)	19 (10)	18 (10)
Type of operation, n (%)				
Vascular	159 (33)	39 (36)	64 (34)	56 (30)
Upper gastrointestinal	65 (14)	18 (17)	22 (12)	25 (14)
Lower gastrointestinal	162 (34)	29 (27)	67 (36)	66 (36)
HPB	21 (4)	3 (3)	8 (4)	10 (5)
Gynecologic	66 (14)	15 (14)	24 (13)	27 (15)
Urologic	7 (1)	3 (3)	3 (2)	1 (<1)

ASA, American Society of Anesthesiologists; HPB, hepato-pancreato-biliary surgery.

differences were present for the subtypes of infectious complications (Table 2). Additionally, when excluding anastomotic leakage as a cause for intra-abdominal infections, the incidence of overall infectious complications was not significantly different between onlay and sublay mesh reinforcement (onlay mesh: n = 30, 16.0% vs sublay mesh: n = 18, 9.7%, p = 0.073).

Primary treatment of infectious complication in patients with prophylactic mesh reinforcement

The primary treatment of postoperative infectious complications is summarized in Table 3. In patients who received prophylactic mesh placement, treatment of infectious complications was not complicated by the mesh in the majority of cases. The mesh could remain in-situ in 40 of 52 (77%) patients with an infectious complication.

In the patients in whom the mesh was removed, this concerned an onlay mesh in 10 cases (5.3%) and a sublay mesh 2 cases (1.1%), p = 0.172. Mesh removal was reported as primary treatment in only 7 of 52 (13%) cases with an infectious complication. In another 5 of 52 (9.6%) cases, the mesh was removed as a preventive measure to avoid possible infection of the prosthesis.

Patients with a surgical site infection were treated conservatively (n = 22), received a debridement (n = 13), underwent surgical mesh removal (n = 6), had received relaparotomy and debridement (n = 2), or no treatment as palliative care was initiated (n = 2). Patients with an intra-abdominal abscess were treated conservatively (n = 3), received relaparotomy for an anastomotic leakage (n = 4), or received abscess drainage and lavage (n = 3).

Outcomes of cases with infectious complication and prophylactic mesh placement

The 2-year IH incidence was 13 of 52 (25%) for patients with an infectious complication vs 45 of 276 (16%) for patients without an infectious complication (p = 0.115) (Table 4). For onlay mesh reinforcement, significantly more patients who had an infectious complication developed an IH as compared with patients without an infectious complication (infectious complications: 10 of 33 [30.3%] vs no infectious complication: 15 of 140 [9.7%], p = 0.003). Of the 10 patients who had an infectious complication and IH in the onlay group, 4 had undergone previous mesh removal and 2 had mesh replacement (Fig. 1). This difference in IH incidence was not present for sublay mesh reinforcement (infectious complications: 3 of 19 [16%] vs no infectious complication: 20 of 136 [22%], p = 0.532). Of the 3 patients who had an infectious complication and IH in the sublay group, 1 had undergone previous mesh removal and 1 had mesh replacement (Fig. 1).

Other reasons for mesh removal

Throughout the follow-up period, the mesh was removed in 38 of 373 (10.2%) patients, and 28 of 38 (73.6%) patients underwent removal of the prophylactic mesh for other reasons than infection. Reasons other than infectious complications included burst abdomen (n = 9), unrelated redo surgery with concomitant removal of the mesh (n = 11), and IH occurrence (n = 8).

DISCUSSION

Based on the PRIMA-trial data, prophylactic mesh placement was not associated with an increased incidence of infectious complications as compared with suture closure. Onlay mesh reinforcement was associated with increased incidence of overall infectious complications compared to sublay mesh reinforcement. However, this difference did not reach statistical significance, excluding infections due to anastomotic leakage. In patients who developed infectious complications (n = 52), regardless of mesh location, the mesh could remain in-situ in the majority (n = 40, 77%) of cases. In 23% of patients with an infectious

Table 2. Infectious Complication

	Suture (n = 107)		Mesh (n = 373)			Onlay mesh (n = 188)		Sublay mesh (n = 185)		
Complication	**n**	**%**	**n**	**%**	**p Value**	**n**	**%**	**n**	**%**	**p Value**
Overall infectious complication*	14	13.3	52	13.9	0.821	33*	17.6	19	10.3	0.042†
Excluding anastomotic leakage*	11	10.2	48	12.9	0.472	30	16.0	18	9.7	0.0725
Superficial SSI	4	3.7	23	6.2	0.337	14	7.4	9	4.9	0.300
Deep SSI	2	1.9	20	5.4	0.108	13	6.9	7	3.8	0.125
Intra-abdominal abscess	8	7.5	11	2.9	0.021†	8	4.3	3	1.6	0.209
Confirmed mesh infection	–	–	6	1.6	–	5	2.7	1	0.5	0.215

p Values for chi-square test.
*Patients could present with multiple types of infection.
†Statistically significant.
SSI, surgical site infection.

Table 3. Primary Treatment of Infectious Complication in Patients with a Mesh

	Total (n = 373)		Onlay mesh (n = 188)		Sublay mesh (n = 185)	
Treatment	**n**	**%**	**n**	**%**	**n**	**%**
Total patients with infectious complication	52	13.9	33	18.6	19	10.3
Mesh stayed in situ	40	10.7	23	12.2	17	9.2
Mesh was removed	12	3.2	10	5.3	2	1.1
Primary treatment of infectious complication						
Intra-abdominal abscess	10	2.7	7	3.7	3	1.6
Conservative	3	0.8	3	1.6	0	0
Relaparotomy for anastomotic leakage	4	1.1	3	1.6	1	0.5
Drainage and lavage	3	0.8	1	0.5	2	1.1
Deep SSI	21	5.6	14	7.4	7	3.8
Conservative	7	1.9	5	2.7	2	1.1
Debridement	7	1.9	3	1.6	4	2.2
Mesh removal (primary treatment)	5	1.3	5	2.7	0	0
Other*	2	0.5	1	0.5	1	0.5
Superficial SSI	23	6.2	14	7.4	9	4.9
Conservative	15	4.0	7	3.7	8	4.3
Debridement	6	1.6	6	3.2	0	0
Mesh removal	1	0.3	0	0	1	0.5
Drainage and lavage†	1	0.3	1	0.5	0	0

*No treatment due to palliative care (n = 1), relaparotomy for simultaneous anastomotic leakage (n = 1).
†Concomitant intra-abdominal abscess was present.
SSI, surgical site infection.

complication, invasive treatment for the infection was necessary. However, this translates to only 3.2% of the total study population. Infection requiring mesh removal appears to be a relatively rare complication in a prophylactic setting, occurring in 5.3% and 1.1% of cases with, respectively, onlay or sublay prophylactic mesh reinforcement. Removal of the mesh does not occur solely after infectious complications; in fact, evacuation of the mesh was most often performed for other reasons, including burst abdomen, unrelated relaparotomy or IH.

Mesh infection is one of the most feared complications in hernia surgery, and may result in reinterventions and the possible removal of the mesh. After IH repair surgery, relatively high incidences of mesh infections have been reported in several studies.[13-16] However, based on the present data, these high incidences of infections complications do not occur after prophylactic mesh reinforcement. Placing a mesh in a prophylactic setting may differ from IH repair surgery. This difference could be due to poor previous cicatrisation of the linea alba after developing an IH. Furthermore, SSIs are more likely to occur in case of previous abdominal surgery.[17]

Even though in the PRIMA trial, 52% of included patients had undergone procedures related to the gastrointestinal tract, prophylactic mesh placement appeared not to be associated with increased rate of infectious complications or a more complicated course of these complications. Based on current data, infectious complications may usually be treated regardless of the prophylactic mesh, and without the necessity to remove the mesh. Therefore, prophylactic mesh reinforcement may compare better to primary

Table 4. Incisional Hernia Incidence after Infectious Complication

IH incidence	Onlay mesh	Sublay mesh	Total
No infectious complication, n	140	136	276
IH, n (%)	15 (12)	30 (22)	45 (16)
Patients with infectious complication, n	33	19	52
IH, n (%)	10 (30)	3 (16)	13 (25)
p Value	0.003	0.532	0.132

p Value for chi square test.
IH, incisional hernia.

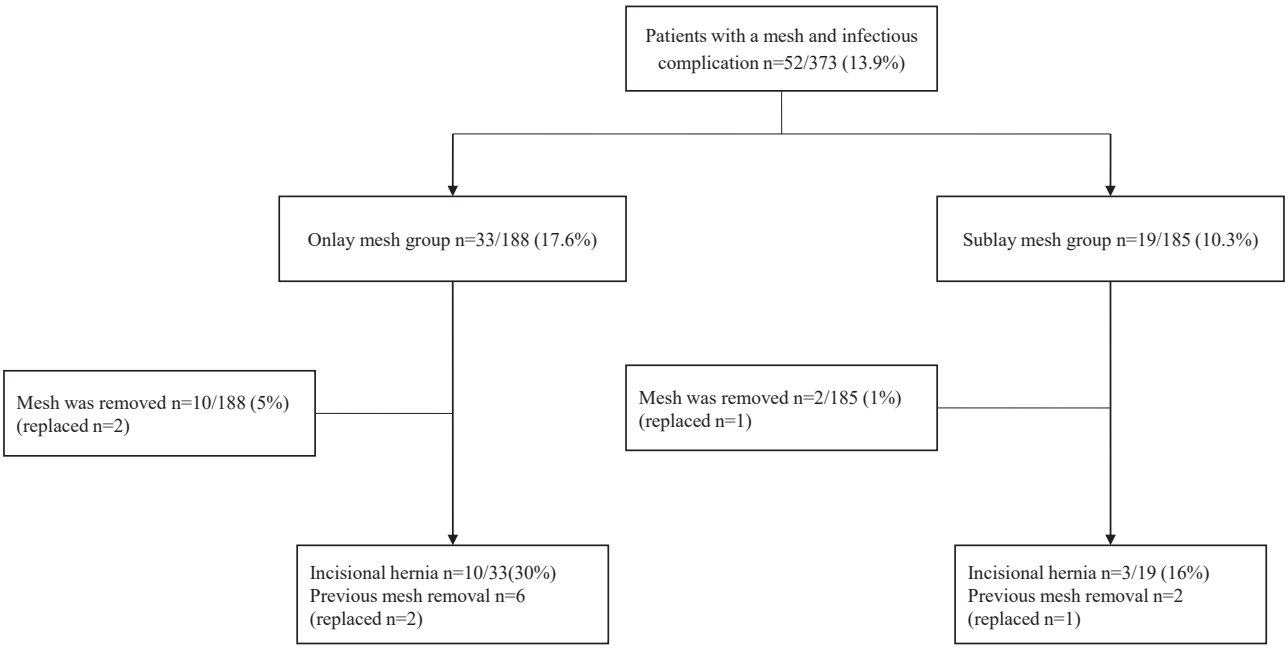

Figure 1. Flowchart representing incisional hernia occurrence after infectious complication in patients with prophylactic mesh placement.

ventral hernia repair. The mesh infection rates after primary ventral hernia repair are similar to the rates found in this study.[18,19]

In this series, occurrence of an infectious complication was usually not an argument for mesh evacuation. Nevertheless, in theory, any infection of subcutaneous tissue could be a mesh infection. However, these infectious complications were usually treated with the mesh in-situ, while obtaining satisfactory results. Moreover, if the mesh was removed, this was often as a preventative measure, with no sign of infection of the prosthesis itself. In only 6 of 52 patients with an infectious complication, mesh removal was the primary treatment. Furthermore, when assessing all patients in whom the mesh was removed or replaced (n = 38), this was due to noninfectious complications in the majority (73.7%) of cases. Therefore, it appears that prophylactic mesh placement was not associated with increased severity of infectious complications, or the necessity for a more invasive treatment.

The onlay mesh position was not associated with a significant increase in infectious complications when excluding anastomotic leakage. However, given that this study was not powered to assess this relation, we cannot confirm any absence of this association. In fact, infectious complications occurred 1.5-fold more often after onlay mesh reinforcement. Given data has been sampled from randomization, this result cannot be discarded. Potentially, when including more patients, significant differences become apparent.

Position of the prophylactic mesh in the PRIMA trial was either in the onlay or sublay position. Based on current data, patients who received onlay mesh reinforcement and developed an infectious complication had a significantly higher incidence of IH compared with patients without an infectious complication. After sublay mesh reinforcement, the incidence of IH was not statistically different in patients with and without an infectious complication. Some operations have higher incidences of SSI than others. We do not yet know which prophylactic mesh reinforcement position is best for which type of surgery. However, based on these data, the sublay position could be preferred in patients with a high postoperative infection risk. In general, based on previous studies of randomized trials, both onlay and sublay mesh reinforcement are considered effective for preventing the development of IH.[20-22]

Causes for the difference in IH incidence in sublay vs onlay mesh reinforcement after infectious complications remain unclear. In addition to the majority of infectious complications involving the subcutaneous space, it could also be hypothesized that infection of the subcutaneous tissue may decrease the contact of an onlay mesh prosthesis against the abdominal wall. Additionally, the fibrin sealant used to fixate the mesh in the anterior plane could be prone to dissolvement after infection. This may

subsequently diminish the supportive effect on collagen remodelling and reinforcement. However, the majority of IH occurrences among patients with an infectious complication occurred among patients who had undergone mesh removal or replacement. Therefore, it appears that IH formation after prophylactic mesh placement in patients who developed infectious complications is, in part but not solely, caused by previous mesh removal related to the infection, but not necessarily due to the infection itself. Potentially, the surgeon is prone to prematurely evacuate the onlay mesh if a superficial infection is present. The onlay position makes it easy to remove the mesh, while the sublay position would require a more invasive procedure. This subsequently could be the reason why more onlay meshes have been removed, without increasing the level of proven mesh infections, and increased IH occurrence rates for the onlay position in patients with infectious complications.

In the original PRIMA trial, preference was given to the onlay mesh position. However, based on a recent meta-analysis, both onlay and sublay prophylactic mesh reinforcement are considered equally effective for the prevention of IH.[23] Potentially, the sublay position may be advantageous in patients with a high postoperative infection risk, whereas the technically less challenging onlay position is sufficient for the general population. The prophylactic mesh position in relation to the postoperative infection risk may warrant further exploration in future trials or additional reassessment of previous trials.

Limitations

This study has several limitations. The initial study was not powered to assess the incidence of individual types of infectious complications between the 3 study arms; therefore, a composite outcome was used. Differences between infectious complications after onlay and sublay mesh reinforcements could become apparent when including more patients and attaining sufficient study power. However, incidences were low in both mesh reinforcement groups. Another limitation is that infectious parameters including leukocytes, C-reactive protein, fever, and bacterial cultures were not collected and not retrievable. However, the severity of infectious complications could be estimated based on the treatment regimens required. Additionally, pre-inclusion selection bias may have occurred; potentially, patients with unfavorable risk profiles for infectious complications were not included in the original study. This may cause underestimation of the number and severity of infectious complications. However, obese patients are considered to be at an increased risk for infectious complications. Moreover, the majority of included patients received gastro-intestinal surgery similarly associated with higher infection risk. Therefore, the effect of pre-inclusion selection would likely be relatively minor.

CONCLUSIONS

Prophylactic mesh placement was not associated with increased incidence of infection compared with suture closure. In the majority of cases, infectious complications may be treated regardless of the in-situ mesh. Furthermore, prophylactic mesh placement appeared not to be associated with more severe infectious complications, a complicated treatment of infections, or high rates of mesh removal. Patients with onlay mesh reinforcement and an infectious complication had a higher risk of developing an incisional hernia compared with patients with onlay mesh reinforcement without an infectious complication, while this was not the case in the sublay group.

Author Contributions

Study conception and design: Van den Dop, Sneiders, Timmermans
Acquisition of data: Van den Dop, Sneiders, Timmermans
Analysis and interpretation of data: Van den Dop, Sneiders
Drafting of manuscript: Van den Dop, Sneiders
Critical revision: Kleinrensink, Jeekel, Lange, Timmermans

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