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Seprafilm® and adhesive small bowel obstruction in colorectal/abdominal surgery: an updated systematic review

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Abstract

Background The efficacy of Seprafilm® in preventing clinically significant adhesive small bowel obstruction (ASBO) is controversial and deserves further review. The aim of this review was to assess the utility of Seprafilm® in preventing clinically significant adhesive bowel obstruction after abdominal operations, with separate focus on colorectal resections. The secondary aim was to provide an updated literature review on the safety profile of this implant.

Methods An up-to-date systematic review was performed on the available literature between 2000 and 2023 on PubMed, EMBASE, Medline, and Cochrane Library databases. The main outcome measures were rates of adhesive bowel obstruction, as well as rates of intervention. The secondary outcome was the clinical safety profile of Seprafilm® as described in current literature.

Results A total of 17 observational studies were included, accounting for 62,886 patients. Use of Seprafilm® was associated with a significant reduction in adhesive bowel obstruction events (OR 0.449, 95% CI: 0.3271 to 0.6122, $p < 0.001$), with preserved efficacy seen in laparoscopic cases. This did not translate into a reduced rate of reintervention. Clinicians should also be aware of isolated reports of a paradoxical inflammatory reaction leading to fluid collections after Seprafilm® use, although they appear uncommon.

Conclusion Seprafilm® can be considered in select patients although further study to determine which patients will benefit most is required.

Keywords Seprafilm®, Adhesive small bowel obstruction, Abdominal surgeries, Colorectal

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Introduction

There is a need to reduce morbidity from postoperative adhesions. Patients undergoing abdominal surgery have a risk of up to 90% of developing intra-peritoneal adhesions with incidence of re-admissions directly related to these estimated to be in the order of 5–20% [1–3]. These adhesions can cause chronic abdominal pain, female infertility, difficult re-operative surgery [4], and remain the leading cause of adhesive small-bowel obstruction (ASBO) in the developed world [4].

In addition to meticulous surgical technique and tissue handling, various approaches have been used to prevent adhesions [5]. Adhesion barriers are theorized to separate the damaged surfaces of the peritoneum and promote the healing of these wounds without the formation of fibrinous attachments, thus reducing the formation of adhesions [6].

Seprafilm® adhesion barrier (Baxter, Deerfield, IL) is a sterile, bioresorbable, hydrophilic adhesion barrier composed of two anionic polysaccharides: modified sodium hyaluronate (HA) and carboxymethylcellulose (CMC) [7]. Described as non-toxic and non-immunogenic, it has been marketed as an effective way to reduce the incidence and extent of severe postoperative adhesions [8]. It turns into a hydrophilic gel approximately 24 h after placement and provides a protective coat around traumatized tissue for up to seven days during the process of re-mesothelialization [7].

Animal studies and randomized controlled trials have shown efficacy and safety in preventing postoperative abdominal adhesion [9–11]. However, reduction in postoperative adhesions have not always resulted in a lower risk of bowel obstruction, nor a clinically significant reduction in need for reoperation.

Previous reviews have also yielded conflicting results with multiple criticisms. The predominant use in pelvic gynaecological surgeries raised questions about its generalizability in other forms of abdominal surgery. Thus the role of adhesion barriers in reducing postoperative adhesion remains controversial [12, 13].

This is our updated systematic review looking at the efficacy of Seprafilm® in preventing clinically significant ASBO after elective abdominal and colorectal surgery. Our secondary aim was to provide an up-to-date review on the safety profile of this implant to weigh up its role in surgery today.

Methods

Literature search strategy

A review was systematically conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was prospectively registered in the PROSPERO database.

A computer-assisted search of electronic databases Medline, Pubmed, Embase and Cochrane Central was performed. The search query combined medical subject headings (MeSH) terms and keywords related to 'Seprafilm®', 'adhesion' and 'obstruction.' Additional articles were captured using manual hand-searching of reference lists of captured articles to ensure that all publications relevant to this study were captured. The last search date for this study was 30 June 2023.

Inclusion and exclusion criteria

Full text peer-reviewed publications available in English language were assessed for eligibility. Papers that evaluated the use of Seprafilm® anti-adhesive barriers for outcomes including obstruction in abdominal surgery were included.

Papers were excluded if they were (a) not available in full text or English language, (b) pre-clinical studies including lab-based, cell-based or animal-based studies, (c) were of inappropriate study type including conference papers, letters, commentaries, posters, editorials or (d) included anti-adhesive barriers or technologies that were not Seprafilm®.

Literature screening and data extraction

Initial screening by title and abstract was performed independently by two investigators (KC, KL). Eligible studies were selected for full text-analysis by the same two investigators for inclusion into this review. Disagreement during this process was resolved by consensus.

Outcomes

Our primary outcome was to assess the efficacy of Seprafilm® in preventing ASBO after elective abdominal/colorectal surgery. Clinically significant ASBO was defined as requiring surgical intervention. Further subgroup analysis aimed to remove potential confounders by separating laparoscopic and open surgeries. Finally, the association with clinically significant ASBO, defined as requiring intervention, was studied.

The secondary outcome was to provide an up-to-date review on the safety profile of this implant. All studies assessing the clinical safety profile of Seprafilm® in current literature were reviewed to weigh up its role in modern surgical practice.

Data extraction, analysis and quality assessment

Data was systematically extracted from included articles based on parameters as outlined by our outcomes of interest. For homogeneous studies comparing outcomes of interest such as measures of rate of bowel obstruction and re-operation, a meta-analysis was conducted. Finally, methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results

Search results

Study characteristics

Our search identified 804 non-duplicate and relevant studies from electronic databases. After screening titles and abstracts, 47 were identified for full-text reading and 17 of these articles were eventually included in our study cohort (Fig. 1).

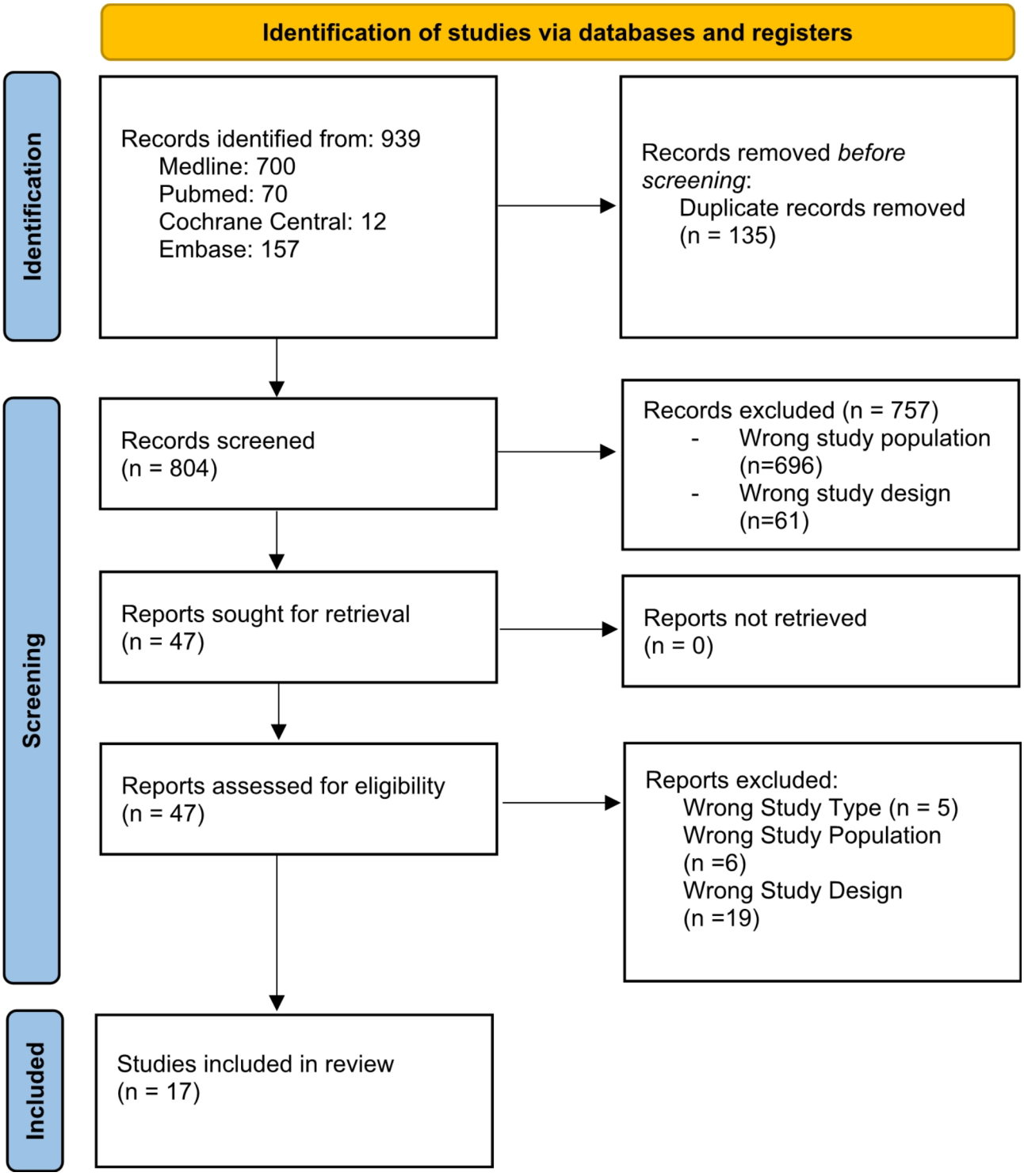

Fig. 1 PRISMA 2020 flow diagram. *From*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

There were six prospective and randomized controlled trials and 11 retrospective studies. (Fig. 1). These compared 16,983 patients with Seprafilm® and 45,903 without, with a cumulative total of 62,886 (Table 1).

Of these 17 studies, eight studies focused solely on colorectal resections [11, 14–20], with four laparoscopic [16–20] and four open studies [11, 14, 15, 19] (Table 2). The remaining studies evaluated emergency and trauma laparotomies as well as open abdominal aortic aneurysm repair.

Quality assessment

Methodological assessment of quality was performed using the NOS and resulted in a median score of 7 with an interquartile range of 2. The range of quality was scores of 5 to 9. This overall indicates studies were of moderate quality (Table 3).

Rates of small bowel obstruction

All types of surgery

Application of Seprafilm® was associated with 55% reduction in small bowel obstruction rates. Overall, the overall odds ratio was 0.449 (OR 0.449, 95% CI: 0.3271 to 0.6122, $p<0.001$).

Colorectal resections

This sub-analysis yielded similar results, with an odds ratio of 0.5002 (OR 0.5002, 95% CI: 0.3275 to 0.7633, $p<0.001$).

Laparoscopic resections

To reduce the potential confounding of laparoscopic surgery which has been shown to be an independent factor that reduces adhesion formation, studies reporting on Seprafilm® use and adhesions after laparoscopic resections were compared. These studies still showed a significantly reduced OR of 0.425 (OR 0.425, 95% CI: 0.2452 to 0.7509, $p=0.003$).

Clinically significant small bowel obstruction

The reduction in clinically significant ASBO was not significant with a OR of 0.37 (OR 0.371, 95% 0.1514 to 0.9134, $p=0.051$). This was once again replicated among elective colorectal resection cases. In this subgroup analysis, the odds ratio of 0.35 was negated by the upper limit of 95% confidence interval crossing the 1.0 null effect line (OR: 0.353, 95% CI: 0.099 to 1.264, $p>0.05$).

Discussion

In this updated systematic review and meta-analysis, we show that Seprafilm® use in elective abdominal/colorectal surgery is associated with a reduction in postoperative adhesive small bowel obstruction but did not translate into a reduction in clinically significant adhesive bowel obstruction requiring surgical adhesiolysis.

This represents the first subgroup analysis of elective adominal surgery (both open and laparoscopic) which overcomes the heterogeneity brought about in previous systematic reviews, where most of the included articles studied gynaecology or pelvic surgery. Narrowing the focus onto clinically significant postoperative intestinal obstruction also allows us to answer the question on the utility of Seprafilm® in surgical practice today.

Adhesions are an inevitable consequence of intra-abdominal surgeries and complications associated with postoperative adhesions continue to challenge the health

Table 1 Demographics of all included studies

Year	Author	Study type	Country	No. with seprafilm	No. without seprafilm	No of sheets	Location of seprafilm
2001	Salum	Retrospective	USA	259	179	1 to 3	midline
2002	Vrijland	Retrospective	Netherlands	21	21	1 to 3	midline
2003	Beck	RCT	USA	91	92	1 to 2	midline
2004	Kudo	Retrospective	Japan	21	30	2	midline
2005	Mohri	Retrospective	Japan	184	183	1 or 2	midline
2005	Fazio	RCT	USA	840	861	4.4 (3 to 10)	all sites
2008	Hayashi	RCT	Japan	70	74	2	midline
2009	Park	Retrospective	S Korea	185	242	1	pelvic inlet/dissection area
2010	Kawamura	Retrospective	Japan	113	169	1	midline
2012	Hashimoto	Retrospective	Japan	60	63	1	midline
2013	Lee	Retrospective	S Korea	114	160	1	midline
2014	Stawicki	Prospective	USA	17	13	5	all sites
2015	Tsuruta	Retrospective	Japan	105	62	1 or 3	multi layered
2017	Fujii	RCT	Japan	270	270	NR	all sites
2018	Lee	Retrospective	S Korea	107	166	1	midline
2019	Saito	RCT	Japan	166	179	2 sheets	midline
2021	Nakashima	Retrospective	Japan	14,360	43,139	NR	NR

NR: Not Reported

Table 2 Rates of Adhesive small bowel obstruction and re-intervention rates

Year	Author	Open/Lap	Type of surgery	Bowel obst (S) (%, (*n*))	Bowel obs (no S) (%, (*n*))	Req Operation (S) (%, (*n*))	Req Op (no S) (%, (*n*))
2001	Salum	Open	Elective colorectal surgery (all sorts, inflammatory + non inflammatory)	4.6 (12)	6.7 (12)	1.5 (4)	3.9 (7)
2002	Vrijland*	Open	Emergency Hartmanns	NR	NR	NR	NR
2003	Beck	Open	IBD surgeries	NR	NR	NR	NR
2004	Kudo	Open	AAA repair (80% elective)	NR	NR	0	0
2005	Mohri	Open	Elective GI resections	NR	NR	1.6 (3)	4.4 (8)
2005	Fazio	Open	Elective GI resections	1.8 (15)	3.4 (29)	1.8 (15)	3.4(29)
2008	Hayashi	Open	Gastrectomy for cancer	5.7 (4)	9.5(7)	0	1.4(1)
2009	Park	Lap	Elective rectal cancer dissection (pelvis)	2.7(5)	4.6 (11)	NR	NR
2010	Kawamura	Open	Distal gastrectomy for cancer	0.9 (1)	6.5 (11)	NR	NR
2012	Hashimoto	Open	Laparotomies	17.7 (11)	44.4 (28)	NR	NR
2013	Lee	Lap	Elective colorectal cancer resections	4.3 (5)	6.9(11)	0	1 (2)
2014	Stawicki	Open	Trauma laparostomies	NR	NR	NR	NR
2015	Tsuruta	Lap	Elective colorectal cancer resections	5	9.7	NR	NR
2017	Fujii	lap	Elective colorectal cancer resections	2.6 (7)	7 (19)	1.1 (3)	1.9 (5)
2018	Lee	Lap	Elective colorectal cancer resections	7.1 (7)	18.7 (31)	0	0
2019	Saito	Open	Elective colorectal cancer resections	7.8(13)	10.6 (19)	0.03 (5)	0.04 (7)
2021	Nakashima	Lap	All Elective surgeries including gynae surgeries	1.1(158)	1.1 (474)	0.2 (29)	0.2(86)

NR: Not Reported

care system. In particular, colorectal surgery has been noted to have high rates of ASBO [21]. Apart from meticulous tissue handling and minimally invasive surgical techniques, physical barriers represent the only widely accepted methods of postoperative adhesion prevention [1].

With the increase in minimally invasive colorectal surgery performed today, our sub-analysis of laparoscopic operations is relevant. Our results support previous reports that Seprafilm® can reduce intestinal obstruction after laparoscopic surgery [17], where the reduced trauma from laparoscopic surgery has been shown to prevent adhesion formation in itself [22]. By removing this confounder, it gives us confidence that Seprafilm® will continue to remain relevant.

Much has been discussed around the technical difficulties in applying Seprafilm® laparoscopically [23]. The thin film understandably is difficult to insert via a laparoscopic port, being easily torn. Thereafter highly skilled laparoscopic skills required to unfold it in the abdominal cavity and accurately applied in the targeted area. when the Seprafilm® gets wet, its surface becomes sticky, so once it enters the abdominal cavity, it is extremely difficult to remove laparoscopically and separate from other organs. Because of these shortcomings in the application of Seprafilm® in laparoscopic surgery, some studies have improved the method of laparoscopic placement [23, 24]. These include the introduction of a reducer sleeve to protect the sheets as they are inserted, to dividing the Seprafilm® sheet into smaller pieces that can be more easily manipulated into its intended position without moistening.

The inability to show a significant reduction in clinically important small bowel obstruction episodes despite a reduced bowel obstruction incidence hint at the complex physiological pathways involved in producing adhesions. This is inevitably due to the interplay between individual patient, surgical and disease factors. Therefore, the authors hypothesize that while there is no evidence to support universal use of Seprafilm®, there could be a select group of patients such as recurrent small bowel obstruction patients, in whom Seprafilm® may prove to be useful. Further prospective research is required to evaluate this.

We acknowledge that our dataset spanned two decades which portends a degree of heterogeneity that deserves consideration. It follows that Seprafilm® is effective only at the site of placement, as the anti-adhesion properties of the film-based barrier depend on separation between the intra-abdominal organs and the mesothelium. Our studies yielded various placement strategies including amount of Seprafilm® and the location placed. This is a limitation and while we did not prove Seprafilm® as an adhesion barrier could translate into a reduction in reoperation rates, this deserves further study.

Our analysis did not yield any significant red flags about the safety of Seprafilm®, apart from the well-known association with anastomotic leaks when placed on anastomoses. Seprafilm® has the characteristics of non-immunogenicity and good biocompatibility but its effects on postoperative liver function, renal function, and other physiological indexes of gastrointestinal neoplasms patients remain unclear [10]. The significance of the temporary increase of serum creatinine in the early stage after Seprafilm® application seen in some patients remains unanswered [25, 26]. Reassuringly, there is no difference in the results of aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, which suggests that Seprafilm® does not cause a systemic inflammatory response [11].

Isolated case reports [27–31] have nonetheless described a paradoxically intense intra-abdominal inflammatory reaction at the site corresponding to Seprafilm® application which can make re-entry unsafe within the first seven days. This could potentially make a relook laparotomy in the event of complications such as an anastomotic leak even riskier. These accounts have described a foreign body reaction causing intense inflammation, with foreign body granulomas found on biopsy [29]. This dense, thick, glue-like mass can envelop the underlying small intestine and transverse colon with resultant high risk of iatrogenic enterotomy [30]. This process of aseptic peritonitis is usually accompanied by a fever and raised neutrophil counts within 4–7 days after receiving Seprafilm® during laparotomy [27].

This foreign body reaction can alternatively create collections of sterile intra-abdominal fluids were identified in three subjects following the use of Seprafilm® in colorectal surgery [29]. These case studies were included in the retrospective study at the Cleveland Clinic which found use of Seprafilm® in restorative proctocolectomy was associated with pelvic collections [32, 33]. Another 10-year observational retrospective study found a significant increase in postoperative fluid collections after colectomies and gynaeological debulking surgeries [26]. While reports of this kind remain uncommon in the two decades of Seprafilm® use, further attention is required to define the risk factors for such adverse effects.

Our study has a number of limitations – in the quality and heterogenous studies included in our analysis. However, to our knowledge, this could represent the first subset analyses with the subset evaluation of minimally invasive surgery – which is the mainstay of surgical approaches in today's practice. We also included a narrative review on the safety profile/complications around Seprafilm which is the first of its kind in the literature.

Table 3 Methodological quality assessment of included studies assessed using the Newcastle-Ottawa Scale (NOS)

Study	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at the start of the study	Cohorts comparable on basis of design or analysis	Study control for external confounders	Assessment of outcomes	Sufficient follow up	Adequacy of follow up	Total Score (/9)
Salum 2001	-	-	+	+	+	+	+	+	+	7
Vrijland 2002	-	+	+	+	+	+	+	-	+	7
Beck 2003	+	+	+	+	+	+	+	-	-	7
Kudo 2004	-	-	+	+	+	+	+	+	-	6
Mohri 2005	-	-	+	+	+	+	+	-	+	6
Fazio 2005	+	+	+	+	+	+	+	+	+	9
Hayashi 2008	-	+	+	+	+	+	+	+	+	8
Park 2009	+	+	+	+	+	+	+	+	-	8
Kawamura 2010	-	-	+	+	+	+	+	+	-	6
Hashimoto 2012	-	+	+	+	+	+	+	-	+	7
Lee 2013	+	-	+	+	+	+	+	+	-	7
Stawicki 2014	-	+	+	+	+	+	+	+	+	8
Tsuruta 2015	-	-	+	+	+	+	+	-	-	5
Fujii 2017	+	-	+	+	+	+	+	+	-	7
Lee 2018	+	+	+	+	+	+	+	-	-	7
Saito 2019	-	+	+	+	+	+	+	+	+	8
Nakashima 2021	+	-	+	+	+	+	+	-	-	6

Conclusion

There is much heterogeneity in current use of Seprafilm®. Our results support previous work in suggesting that while the overall rate of adhesion formation is reduced, his may not translate to clinically significant small bowel obstruction requiring adhesiolysis. It remains a safe option, but clinicians ought to be aware of the rare but significant adverse effects of a paradoxical intense inflammatory process which may make re-entry into the abdomen fraught with danger. Cost-effectiveness arguments aside, the utility of Seprafilm® deserves further study to identify selected patients in whom Seprafilm® is worth considering.

Author contributions

K.C. and K.L drafted the main manuscript text and prepared Fig. 1; Table 1, and 2. J.K. led the conceptualization and provided valuable supervision and oversight of the project. All authors reviewed the manuscript.

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Data availability

Data will be provided upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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