

Adhesion-related readmissions after surgery for deep endometriosis with the use of icodextrin—long-term results

Jyrki Kössi^{1,2} · Kristiina Julkunen³ · Marjaleena Setälä⁴ · Markku Luostarinen⁵

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Abstract Icodextrin (Adept®) has been shown to prevent postoperative adhesions in experimental and laparoscopic adhesiolysis surgery. However, the role of icodextrin in the prevention of adhesions in extensive gynecological surgery is unclear. The present study evaluated the effect of icodextrin on adhesion-related readmissions after extensive gynecological surgery. The hospital readmissions of 140 endometriosis patients operated on at Päijät-Häme Central Hospital in 2004–2008 with the use of icodextrin were retrospectively reviewed. The evaluation of readmissions focused on adhesion-related disorders and reoperations. If an abdominal or pelvic reoperation was performed, the extent of the adhesions was classified. The mean follow-up time was 6.53 years (range 0.21–9.83). After initial surgery, one patient (0.7 %) had adhesive small bowel obstruction. Another directly adhesion-related readmission occurred in two patients (1.4 %). The number of readmissions possibly related to adhesions was 3 (2.1 %). Abdominal or pelvic reoperation was performed on 54 patients (38.6 %): 4 in the open surgery group and 50 in the laparoscopic surgery group. The extent of the adhesions among the 54 reoperated patients was as follows: not mentioned in 16 patients, no adhesions in 14, mild in 18, moderate

in 5, and severe in 1. There were two (3.7 %) bowel injuries (one enterotomy and one serosal lesion) in reoperations. The incidence of adhesion-related readmissions after the use of icodextrin is relatively low. This favorable result may be partly related to the laparoscopic technique. Despite the use of an anti-adhesion agent, in some patients, the extent of postoperative adhesions is severe.

Keywords Endometriosis · Surgery · Adhesions · Adhesion prevention · Icodextrin · Follow-up study

Background

Peritoneal adhesions are a natural consequence of peritoneal trauma regeneration. After intra-abdominal open general surgery, more than 90 % of patients develop peritoneal adhesions, and the corresponding figure for major gynecologic surgery is 60–90 % [1, 2]. Fortunately, most of the patients are asymptomatic. However, peritoneal adhesions can lead to complications such as chronic abdominal pain, female infertility, and small bowel obstruction. As a result, peritoneal adhesion-related readmissions create a significant surgical and socio-economic burden, as shown by Ellis et al. [3]. Strategies to decrease adhesion formation can be broadly divided into those directly associated with the surgical technique and those involving the use of a specific anti-adhesive regimen. Because the surgical technique has limited value in preventing adhesion formation, a number of anti-adhesion agents have been developed. One of them is a 4 % solution of the glucose polymer icodextrin, which has been shown to reduce adhesion formation in experimental studies [4–7]. Data from the Adept Registry for Clinical Evaluation (ARIEL) has shown that the use of icodextrin is safe and easy in both open and laparoscopic gynecological surgery [8]. Clinical randomized studies have

✉ Jyrki Kössi
jyrki.kossi@khshp.fi

¹ Department of Surgery, Kanta-Häme Central Hospital, Ahvenistontie 20, 13530 Hämeenlinna, Finland

² Department of Surgery, University of Turku, Turku, Finland

³ Department of Surgery, University of Helsinki, Helsinki, Finland

⁴ Department of Obstetrics and Gynecology, Päijät-Häme Central Hospital, Lahti, Finland

⁵ Department of Surgery, Päijät-Häme Central Hospital, Lahti, Finland

further confirmed the safety of icodextrin in laparoscopic gynecological surgery with some efficacy in the reduction of peritoneal adhesion formation [9–12]. However, there have been no long-term studies evaluating the clinical advantage of icodextrin in high-risk gynecological surgery. The aim of the present study was to evaluate the clinical effect of icodextrin (Adept®) on adhesion-related hospital readmissions after open and laparoscopic extensive endometriosis surgery.

Methods

An anti-adhesion strategy including the use of icodextrin was established at Päijät-Häme Central Hospital during 2004, since when the agent has been routinely used in operations expected to carry a high risk of adhesion formation. At the same time, the intention to use laparoscopic technique for all endometriosis operations was established. A prospective database of these patients was created for investigational purposes. At the initial operation, the severity of endometriotic lesions was graded according to the revised American Fertility Society (rAFS) classification (stage). A detailed evaluation of patient files was carried out retrospectively during November 2014. The hospital readmissions, with or without surgery, were categorized according to Ellis et al. [3]: Readmissions directly related to adhesions, readmissions possibly related to adhesions, and repeat surgery potentially complicated by adhesions

(abdominal or pelvic surgery). The diagnostic criteria for intestinal obstruction were as follows: abdominal pain, vomiting, absence of defecation, splashing, metallic intestinal sounds, and radiological evidence of bowel obstruction (plain abdominal radiograph, small bowel contrast study, or abdominal CT). Readmissions with abdominal pain without radiological evidence of intestinal obstruction were classified as readmissions possibly related to adhesions when no other definite diagnosis could be made. For patients who underwent repeat surgery due to an intestinal obstruction or other reason, the description of the extent of adhesions was recorded (no adhesions, mild, moderate, severe, extreme). However, a validated protocol for adhesion grading was not used. After cesarean section, the follow-up of the patients was continued since the incidence of small bowel obstruction after this operation is very low (0.5–1.0/1000 cesarean sections) [13, 14]. If a patient moved out the Päijät-Häme region, follow-up was terminated on the day of emigration. The flowchart of the study is shown in Fig. 1.

The study was approved by the Ethics Committee of the Joint Authority for Päijät-Häme Social and Health Care.

Findings

Altogether, 144 patients operated on for deep endometriosis with the use of icodextrin were identified from the database between 2004 and 2008 at Päijät-Häme Central Hospital. Four

Fig. 1 Flowchart of the study

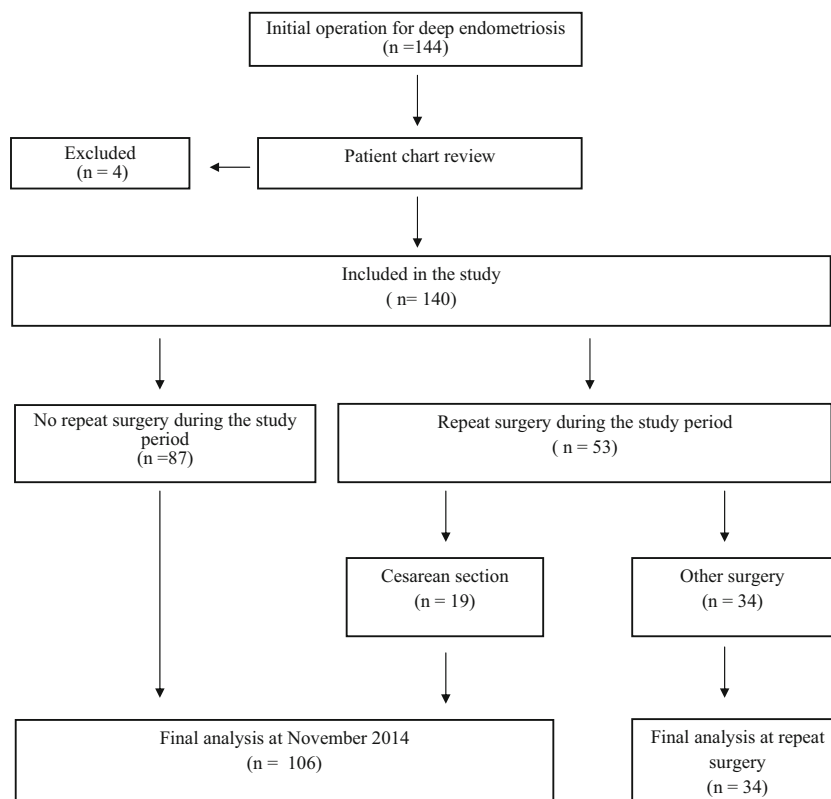


Table 1 The number of different procedures performed on endometriosis patients

Gynecological procedures		
Enucleation of endometrioma	89	
Uterosacral ligament resection	53	
Salpingectomy	34	
Vaginal resection	19	
Ovariectomy	18	
Hysterectomy	16	
Extirpation of endometriosis	8	
Ovarial resection	3	
Other gynecological operations	4	
Gastrointestinal procedures		
Appendectomy	15	
Segmental rectal resection	13	
Sigmoid resection	1	
Ileocecal resection	1	
Cecal resection	1	
Urological procedures		
Urinary bladder resection	5	
Total	230	

patients underwent an early reoperation due to a surgical complication and were excluded. The mean age of the patients was 31.7 years (range 19–63). The mean follow-up time was 6.53 years (range 0.21–9.83).

Table 1 shows the procedures performed on the endometriosis patients. The mean number of simultaneous procedures was 2.1, and the most common gynecological procedures were enucleation of endometrioma and resection of uterosacral ligaments. Adhesiolysis was performed on 105 patients (75.0 %) in the primary operation. The rAFS endometriosis stage distribution of patients was as follows: stage I 23 (16.4 %), stage II 23 (16.4 %), stage III 45 (32.1 %), and stage IV 49 (35.0 %).

Data regarding hospital readmissions during the follow-up period are shown in Table 2. One patient (0.7 %) had an adhesive small bowel obstruction. This patient was operated on and the cause of the obstruction was adhesion. Details of the repeat surgery are shown in Table 3. Reoperation was performed on 54 patients (38.6 %). The most common operation was cesarean section ($n = 19$, 35.8 % of reoperations). The second most common indication for reoperation was endometriosis ($n = 15$, 28.3 % of reoperations). The extent of

adhesions in the 54 reoperated patients was as follows: not mentioned in 16 patients (29.6 %), no adhesions in 14 (25.9 %), mild in 18 (33.3 %), moderate in 5 (9.2 %), and severe in 1 (2.0 %). There were two bowel injuries (3.7 % of operated patients) in reoperations related to adhesiolysis: one serosal injury and one enterotomy.

Two patients were readmitted to hospital for another directly adhesion-related reason. Both patients suffered from chronic abdominal pain, and subsequent diagnostic laparoscopy with adhesiolysis resolved the pain completely. The number of readmissions possibly related to adhesions was 3 (2.1 %).

Taking into account adhesive small bowel obstructions and other disorders related to adhesions, 2.1 % of the entire patient population had directly adhesion-related readmissions.

Discussion

The well-known burden of postoperative abdominal adhesions has prompted intensive research to develop an agent capable of effectively preventing the formation of adhesions. The whole spectrum of formation and prevention of adhesions in gynecological surgery has been well described in an excellent review by DeWilde and Trew [15]. One of these agents is the broad-spectrum liquid regimen icodextrin. The safety and efficacy of icodextrin in reducing adhesion formation has been shown in many animal studies [4–7]. However, few human studies focusing on the efficacy of icodextrin on adhesion prevention have been published to date [9–12, 16]. There have been even fewer studies evaluating the clinical benefits of icodextrin after general surgery, the results of which seem to be somewhat conflicting [17, 18]. Thus, the overall clinical advantages of icodextrin, especially the long-term clinical results, are still questionable and further studies are warranted. To our knowledge, the current study is the first to evaluate the long-term clinical effect of icodextrin use in patients undergoing extensive surgery for endometriosis.

The SCAR study published in 1999, together with later published sub-group studies evaluating lower abdominal and gynecological surgery, revealed that after certain operations, the risk of adhesion-related admissions is high [3, 19, 20]. According to these studies, operations on the ovary, colon, and rectum can be regarded as high-risk surgery in terms of

Table 2 Readmissions after open and laparoscopic surgery with the use of icodextrin

Operation type (n)	Small bowel obstruction		Another disorder related to adhesions		Possible disorder related to adhesions		Reoperation	
	n	%	n	%	n	%	n	%
All operations (140)	1	0.7	2	1.4	3	2.1	54	38.6
Open (6)	0	0	0	0	0	0	4	66.7
Laparoscopic (134)	1	0.7	2	1.5	3	2.2	50	37.3

Table 3 Details of reoperations

	Number	Percent
Cesarean section	19	35.2
Reoperation for endometriosis	15	27.8
Hysterectomy	6	11.2
Adhesion division	4	7.4
Laparoscopic cholecystectomy	3	5.6
Appendectomy	2	3.7
Diagnostic laparoscopy	2	3.7
Myomectomy	1	1.9
Ileal resection	1	1.9
Laparoscopic ileocecal resection	1	1.9

adhesion-related complications. It is also well known that endometriosis itself promotes adhesions and surgery as it is associated with considerable reformation and de novo formation of adhesions [21]. The percentage of patients with stage III or IV endometriosis in our material was high (67.1 %), and up to 75 % of our patients needed adhesiolysis at the initial operation. Based on this, the patients in our study can be considered to be at high risk of developing adhesions.

The number of directly or possibly adhesion-related readmissions in our study is very low, 3 (2.1 %) and 3 (2.1 %), respectively. Unfortunately, we do not have a concurrent control group of similar patients treated without the use of icodextrin. Further, it was impossible to get a historical control group from our hospital because before the period covered by the current study, all the endometriosis operations were performed openly. Thus, the only remaining option is to compare our findings with results from previous studies. Although the patient populations are different, the best comparative studies are probably the SCAR studies, the latest of which also includes laparoscopic patients [22]. In these studies, a risk ratio per 100 initial procedures was calculated, and the main results of the SCAR studies are compared with those of the current study in Table 4. Compared to the SCAR figures, the rate of

readmissions directly associated with adhesions after endometriosis surgery in our study was indeed low, at least compared to open surgery. However, the difference was not so great when compared to laparoscopic operations. This is probably because the follow-up in the study by Lower et al. [22] was only 4 years and because our patients underwent more extensive surgery.

The main difference between the findings of the SCAR studies and our study seems to be in the readmissions possibly related to adhesions. The reason for this discrepancy is very likely due to the different settings of the studies. Our study is a detailed evaluation of patient files, while the SCAR study results are based on registry-derived data. Our study is more accurate and the figures presented by the SCAR study group very likely include admissions that eventually were not due to adhesions. However, the difference may also in part reflect the true beneficial effect of icodextrin. It may be assumed that adhesion-related problems, particularly mild ones, are alleviated by the anti-adhesive effect of icodextrin.

Reoperation was performed in 54 patients during the mean follow-up time of 6.5 years. Although the grading of adhesions is highly subjective and the reliability of a retrospective study is not the best possible, we focused on this important issue, too. It is noteworthy that in roughly 60 % of reoperated patients, there were no adhesions at all or the extent of adhesions was mild. Not surprisingly, in roughly 30 % of the patients, the extent of adhesions was not mentioned at all. It is, however, quite probable that these patients had a small number of adhesions since it tends to be that surgeon reports the presence of adhesions particularly if these hamper the operation. Regarding adhesion assessment, it is worth mentioning that roughly one third of reoperated patients had cesarean section. It may be assumed that the grading of adhesions is incomplete in this patient cohort due to insufficient visibility of the upper abdomen. However, in our sub-analysis of adhesion grading, there was no difference between reoperations (data not shown). Further, a relatively large part of the

Table 4 Comparison of the rate of readmissions per 100 initial procedures in the present study and SCAR studies including high-risk operations

	Site of initial surgery	Rate of readmissions (DRA)	Rate of readmissions (PRA)
Current study		2.1	2.1
Parker et al. [18]	Rectum	7.2	23.6
	Colon	5.7	27.4
Lower et al. [19]	Ovary	4.9	40.0
	Fallopian tubes	2.5	32.7
Lower et al. [21]	Open; ovary	7.0	43.6
	Open; fallopian tubes	3.2	35.0
	Laparoscopy; high risk	3.0	33.0
	Laparoscopy; medium risk	2.8	24.0

Data from SCAR studies estimated to represent 6-year [18, 19] or 4-year [21] follow-up figures
DRA directly related to adhesions, *PRA* possibly related to adhesions

abdomen can be seen during cesarean section and it is probable that there are no major adhesions in the upper part of the abdomen after laparoscopic pelvic surgery. The number of bowel injuries in repeat surgery is a good surrogate marker for adhesions. The 3.7 % incidence of bowel injury (including only one enterotomy) in the current study is low compared to the figure of 19 % presented by van der Krabben and colleagues [23]. This also suggests that the extent of adhesions in our patients was limited.

It seems that laparoscopic endometriosis surgery in combination with the use of icodextrin results in a low incidence of adhesion-related clinical problems. However, the exact roles of the good surgical technique, laparoscopic technique, and icodextrin on this are unclear; one reason for this uncertainty is that our study is not a randomized controlled trial. Further, a recent pilot study indicated that after 72 h, most of the instilled icodextrin was absorbed from the abdominal cavity suggesting the role of icodextrin in adhesion prevention may be minor than previously thought [24]. Although there are studies reporting less adhesion formation and fewer adhesive small bowel obstructions compared to open surgery [25–27], a recent review suggests that although the laparoscopic technique reduces adhesion formation, the clinical benefit has not yet been proven [28]. On the other hand, the preventive effect of icodextrin on adhesion formation in gynecological surgery has been only moderate according to some studies [9–12]. The low incidence of adhesion-related readmissions found in our study thus is very likely not attributable to the use of icodextrin only.

In conclusion, the incidence of adhesion-related readmissions after extensive laparoscopic endometriosis surgery with the use of icodextrin is low. The favorable result seen in this study is probably due to a combination of laparoscopic technique and use of an anti-adhesive agent. However, it was not possible to determine the exact roles of these two components in the present study. The findings at reoperation indicate that despite the use of an anti-adhesion agent, in some patients, the extent of postoperative adhesions is moderate or severe.

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Authors' contribution J. Kössi was involved in project development, data management, data analysis, and manuscript writing. K. Julkunen was involved in data collection and manuscript editing. M. Setälä was involved in project development, data collection, and manuscript editing. M. Luostarinen was involved manuscript editing.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was approved by the Ethics Committee of the Joint Authority for Päijät-Häme Social and Health Care. All procedures performed in the study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent According to the ethical standards of the institutional and national research committee, informed consent was not necessary in this kind of patient file-based study.

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