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Use of icodextrin 4% solution in the prevention of adhesion formation following general surgery: from the multicentre ARIEL Registry

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ABSTRACT

INTRODUCTION Intra-abdominal adhesions occur in many patients following major abdominal surgery and represent a serious burden to patients and healthcare providers. The multicentre ARIEL (Adept® Registry for Clinical Evaluation) Registry was established to gather clinical experiences in the use of icodextrin 4% solution, an approved adhesion-reduction agent, during routine general surgery.

PATIENTS AND METHODS General surgeons from five European countries completed anonymised data collection forms for patients undergoing laparotomy or laparoscopy. Surgeons recorded patient demographics, use of icodextrin 4% solution and adverse events, and made subjective assessments of ease of use and patient acceptability with the agent.

RESULTS The general surgery registry included 1738 patients (1469 laparotomies, 269 laparoscopies). Leakage of fluid from the surgical site did not appear to be affected by icodextrin 4% solution and was classified as 'normal' or 'less than normal' in most patients (laparotomies 86%, laparoscopies 88%). Overall, satisfaction with ease of use was rated as 'good' or 'excellent' by the majority of surgeons (laparotomies 77%, laparoscopies 86%). Patient acceptability was also good, with ratings of 'as expected' or 'less than expected' in most cases for both abdominal distension (laparotomies 90%, laparoscopies 91%) and abdominal discomfort (laparotomies 91%, laparoscopies 93%). Adverse events occurred in 30.6% of laparotomy patients and 16.7% of laparoscopy patients; the most common events were septic/infective events (4.2% and 3.4% in the laparotomy and laparoscopy groups, respectively). Anastomotic wound-healing problems were reported in 7.6% of patients in the subset of laparoscopy patients undergoing anastomotic procedures (n = 66).

DISCUSSION Volumes of icodextrin 4% solution used as an irrigant and instillate were in line with recommendations. Surgeons considered the agent to be easy to use and acceptable to patients. The reported frequencies of adverse events were in line with those published in the literature for surgical procedures, supporting the good safety profile of this agent.

CONCLUSIONS Icodextrin 4% solution can be used in a wide range of surgical procedures. In combination with good surgical technique, it may play an important role in adhesion reduction.

KEYWORDS
Adhesions – Registries – Surgery – Laparoscopy – Postoperative complications – Icodextrin

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Intra-abdominal adhesions occur in more than 90% of patients following major abdominal surgery[1] and account for about 60–70% of cases of small bowel obstruction (SBO).[2] Adhesions have significant implications for both patients and healthcare providers; they have been implicated in female secondary infertility[3,4] and chronic pelvic pain[5] and result in reduced patient quality of life. Furthermore, adhesions are associated with repeated, lengthier and more complex surgery,[6–8] higher surgical costs[7,9–11] and a propensity to reform,[12] with adhesion re-formation occurring at a rate of

85% following adhesiolysis, regardless of the method of adhesiolysis or the type of adhesion.[13] Despite these factors, patients are often not informed prior to surgery about the risks of adhesion formation or what measures can be used to try to reduce these risks.[14]

Until recently, the extent of adhesion formation following abdominopelvic surgery had not been known and the burden of adhesions remained largely unacknowledged. Two landmark epidemiological studies addressed this issue. The Surgical and Clinical Adhesions Research (SCAR) Study investigated the burden of postsurgical adhesions in Scottish patients who underwent initial abdominopelvic laparotomy in 1986.[15,16] Over the following 10 years, 5.7% of all re-admissions were directly attributable to adhesions and 3.8% required further abdominal surgery.

The subsequent SCAR-2 study re-assessed the burden of adhesions in a cohort of patients undergoing laparotomy in 1996 who were followed up for 4 years, and evaluated the risks of an adhesion-related re-admission during this period. The study found little change with persistently high re-admission rates, particularly in high-risk groups such as colorectal surgery patients, with up to one in five of these patients being re-admitted for adhesion-related events within 4 years of initial surgery. The risks of re-admission were even higher in those who had undergone previous surgery.[17]

The adoption of good surgical technique is critical in order to minimise adhesion formation and re-formation. Recommended strategies include the use of minimally invasive surgical procedures, maintenance of haemostasis, minimal handling of peritoneal organs, avoidance of desiccation and infection, minimal suturing and cauterisation, and the avoidance of foreign bodies in the peritoneal cavity.[4,18–20] Data from the SCAR and SCAR-2 studies indicate, however, that such strategies are proving largely ineffective in the prevention of adhesion-related complications. An analysis performed using a cost-effectiveness model based on the SCAR database, and published in 2002, estimated that the annual UK cost of adhesion-related re-admissions within the first year after initial surgery, was in excess of £24.2 million.[21] Such data serve to highlight the high economic, as well as personal burden of postsurgical adhesions and the need for effective adhesion-reduction agents.

Icodextrin 4% solution (Adept®, Baxter Healthcare S.A.) is a high-molecular-weight α-1,4-glucose polymer that is approved in Europe for use as an intra-operative lavage and a postoperative instillate to reduce adhesion formation following abdominopelvic laparotomy or laparoscopy. Due to the high molecular weight of icodextrin and the absence of amylase – the enzyme by which it is metabolised – within the human peritoneal cavity, the agent has a prolonged peritoneal residence time of at least 4 days.[22] This enables it to function by a process of hydroflotation,[23] keeping the peritoneal organs apart during the critical postsurgical period when adhesion formation occurs.

Preclinical and preliminary clinical studies have demonstrated that icodextrin 4% solution is an effective treatment for the reduction of adhesion formation following surgery.[23,24] ARIEL (Adept® Registry for Clinical Evaluation) is a Europe-wide registry that was established to collate feedback on the clinical experiences of general and gynaecological surgeons regarding their use of icodextrin 4% solution during routine laparotomy and laparoscopy. The registry aimed to provide an information source for surgical centres on the optimal usage and safety of icodextrin 4% solution in routine surgery.

In this paper, we present findings from ARIEL in terms of the safety, ease of use, handling, and patient acceptability of icodextrin 4% solution during laparotomy and laparoscopy in general surgery.

Patients and Methods

ARIEL was initiated in a number of general surgical and gynaecological centres in the UK and was then expanded to involve 253 centres (103 general-surgery and 150 gynaecological-surgery centres) in France, Germany, Italy, Spain, Greece (gynaecology only), and the UK. National co-ordinators for the registry were identified in each participating country and were involved in the finalisation of the registry.

Participating surgeons were asked to complete prospectively anonymous, 4-page general-surgery or gynaecological-surgery data collection forms for patients undergoing laparotomy or laparoscopy who had an associated risk of adhesion formation and in whom the use of icodextrin 4% solution was planned as an adhesion-reduction agent. The data collection forms were designed to be simple to complete and were provided in five European languages (English, French, German, Italian and Spanish). Icodextrin 4% solution is contra-indicated in patients who demonstrate allergic reactions to starch; therefore, such patients were excluded from the registry. Surgeons were advised to administer icodextrin 4% solution as a lavage at a rate of at least 100 ml every 30 min with a final wash and removal at the end of surgery, followed by a 1-l instillation, in accordance with instructions for use of the agent. Data were collected between February 2000 and December 2003.

Participating surgeons were requested to provide anonymised data concerning: patient demographics and presenting symptoms; surgical history; type of surgery undertaken (emergency/elective); presence/absence of adhesions; surgical procedure undertaken (laparoscopy/laparotomy); type of surgical closure; and surgical, clinical and post-discharge observations. Surgeons' experience with icodextrin 4% solution was recorded (as an irrigant and instillate plus the volumes used). A subset of laparotomy patients in whom drains

Table 1 Demographics of patients in the ARIEL general surgery registry (*n* = 1738)

	Laparotomy (*n* = 1469)	Laparoscopy (*n* = 269)
Age, mean ± SD (years)	60 ± 18	49 ± 17
Previous laparoscopy (%)	4	14
Previous laparotomy (%)	47	34
Surgery performed[a] (number of patients; % of total)		
Adhesiolysis[b]	679 (46.2)	117 (43.5)
Cholecystectomy	59 (4.0)	87 (32.3)
(Pan-)proctocolectomy	25 (1.7)	0 (0.0)
Hernia repair	62 (4.2)	17 (6.3)
Bowel resections with anastomosis	907 (61.7)	61 (22.7)
Bowel resections without anastomosis	226 (15.4)	4 (1.5)
Emergency repair to perforated viscera	22 (1.5)	2 (0.7)

[a] Patients may have undergone more than one operation. Only the most frequently performed operations are listed.
[b] This was either the main reason for surgery or undertaken to enable another procedure.

were inserted was evaluated in order to assess levels of drainage and compare them with levels that the surgeon would have expected. Surgeons were also required to make subjective assessments of the following parameters: levels of leakage of peritoneal fluid/icodextrin 4% solution from patients' abdomens at closure; overall satisfaction, ease of handling and viewing of the surgical field with icodextrin 4% solution; and levels of abdominal discomfort and abdominal distension as indicators of surgeon and patient acceptability of the agent. All peri- and post-procedural complications and adverse events were recorded, and all cases involving serious adverse events were reported immediately.

Once submitted, the anonymous patient records were captured in a central database. To enable patient identification for future follow-up, the forms were precoded centrally, and surgeons retained a confidential 'patient details' form for each case. In order to ensure quality of the data, case providers were contacted for further information if records were incomplete or outcomes or adverse events were unclear.

Table 2 Presenting conditions/symptoms of patients undergoing general surgery in the ARIEL general surgery registry

Presenting symptom/condition[a]	Number of patients (%) Laparotomy	Laparoscopy
Anaemia	73 (5.0)	1 (0.4)
Change of bowel habit	121 (8.2)	5 (1.9)
Cancer	492 (33.5)	26 (9.7)
Bleeding	112 (7.6)	9 (3.3)
Fistula	81 (5.5)	5 (1.9)
Hernia	49 (3.3)	13 (4.8)
Nausea/vomiting	97 (6.6)	7 (2.6)
Obesity	22 (1.5)	19 (7.1)
Bowel obstruction/occlusion	334 (22.7)	22 (8.2)
Pain	413 (28.1)	134 (49.8)
Peritonitis/sepsis	60 (4.1)	1 (0.4)

[a] Patients may have more than one presenting symptom or condition; only the most frequently reported presentations are listed.

Results

Patient demographics

Patient demographics are presented in Table 1. In total, 1738 patients were included in the general surgery registry, the majority of whom (1469, 85%) underwent laparotomy (this included 33 patients for whom an initial laparoscopy was converted to a laparotomy). Overall, the mean age of patients in the general surgery registry was 58 ± 18 years; those undergoing laparotomy tended to be older. Bowel resections with anastomosis comprised a large proportion of laparotomies (61.7%), while adhesiolysis was commonly performed in both laparotomy and laparoscopy surgical groups (46.2%, and 43.5%, respectively). The most common presenting symptoms and conditions are shown in Table 2;

Table 3 Incidence of key adverse events that occurred in patients in the ARIEL general surgery registry (n = 1738). The published adverse events rates are included for comparison where available

Type of adverse event	Number of events (%) Laparotomy (n = 1469)	Laparoscopy (n = 269)	Published adverse event rate (%)
Cardiac events	22 (1.5)	0 (0.0)	1–39[42–44]
Fluid imbalance problems	11 (0.8)	1 (0.4)	2.3–4.5[45,46]
Haematological events	20 (1.4)	3 (1.1)	–
Ileus	53 (3.6)	5 (1.9)	2.3–17.6[32,39]
Pain	15 (1.0)	3 (1.1)	–
Predicted irrigation/instillation events	16 (1.1)	2 (0.7)	–
Respiratory events	56 (3.8)	3 (1.1)	–
Septic/infective events	61 (4.2)	9 (3.4)	2–40[40,47]
Peritonitis	4 (0.3)	4 (1.5)	2.8–5.1[40]
Surgical/technical events	43 (2.9)	6 (2.2)	–
Anastomotic wound-healing problems	27 (2.7)*	5 (7.6)*	1–39[31–36]
Non-anastomotic wound-healing problems	56 (3.8)	2 (0.7)	0–6.5[47]
Other	69 (4.7)	5 (1.9)	–

*Percentage of patients undergoing anastomotic procedures (laparotomy, n = 983; laparoscopy, n = 66).

cancer, pain and bowel obstruction/occlusion occurred with the highest frequencies in both the laparotomy and laparoscopy cohorts. A total of 518 patients in the general surgery registry presented with cancer.

Use of icodextrin 4% solution

The mean volumes (± SD) of icodextrin 4% solution administered as an instillate were 999 ± 254 ml, and 959 ± 319 ml, during laparotomy and laparoscopy, respectively; when administered as an irrigant, 871 ± 490 ml and 864 ± 454 ml, respectively. This was in accordance with recommended volumes (1-l instillation and 100 ml every 30 min for irrigation).

Drains were inserted in a subset of laparotomy patients (n = 698, 47.5%). The proportion of cases in which drains were used varied considerably by country: 96% in Italy, 75% in Germany, 53% in Spain, 42% in France, and 37% in the UK. Drainage was rated as 'normal' in 63% of patients (mean estimated loss, 279 ± 312 ml of 1013 ml instillate within 9 h), and 'greater than normal' in only 20% of patients (mean estimated loss, 543 ± 288 ml of 1101 ml instillate within 6.6 h), the latter representing a mean excess fluid loss of 264 ml more than expected; drainage was not recorded in the remaining 17% of patients.

Leakage of peritoneal fluid/icodextrin 4% solution from the surgical site at closure was rated as 'normal' (*i.e.* as expected) or 'less than normal' in the majority of cases (86% of laparotomies, 88% of laparoscopies). Suturing of port sites in the laparoscopic cohort did not appear to have an effect on leakage. Viewing and handling of tissues – parameters used to assess surgeons' satisfaction with ease of use of the agent – were rated as 'good' or 'excellent' during both laparotomy and laparoscopy by the majority of clinicians. These parameters were not given a rating of 'bad' on any occasion. Overall satisfaction was rated as 'good' or 'excellent' by surgeons in 77% of laparotomies and 86% of laparoscopies.

Abdominal discomfort and abdominal distension, parameters used to evaluate patient acceptability of the agent, were rated as 'as expected' or 'less than expected' for most patients (discomfort 'as expected'/'less than expected', 91% of laparotomies and 93% of laparoscopies; distension 'as expected'/'less than expected', 90% of laparotomies and 91% of laparoscopies). Few patients experienced abdominal discomfort or distension rated as 'more than expected' or 'of clinical concern'.

Adverse-event profile

A small proportion of patients experienced adverse events during laparoscopic procedures (incidence, 16.7%; this value includes all reported adverse events). Adverse events occurred more frequently in patients undergoing laparotomy procedures (incidence, 30.6%). The reported frequencies for adverse events were in line with expected frequencies for surgical procedures as published in the literature (Table 3).

The main categories of adverse events are shown in Table 3. The most common adverse events during laparotomy were septic/infective events (4.2%), respiratory events (3.8%), non-anastomotic wound-healing problems (3.8%) and ileus (3.6%). In the laparoscopic cohort, the most common adverse events were anastomotic wound-healing problems (7.6%), septic/infective events (3.4%), surgical/technical events (2.2%) and ileus (1.9%). Overall, 56 patients in the general surgery registry presented with symptoms of peritonitis, while only eight postoperative incidences of peritonitis were reported as adverse events (laparotomy, and laparoscopy cohort incidences, 0.3%, and 1.5%, respectively). Patients presenting with peritonitis showed a slightly higher incidence of wound-healing problems (5.4% versus 3.4% for those without peritonitis).

The incidence of anastomotic leakage among patients undergoing anastomotic procedures (n = 1049) was 3.1%; anastomotic leakage occurred in 2.7% (n = 27) of 983 patients who underwent laparotomy and in 7.6% (n = 5) of 66 patients who underwent laparoscopy (patients may have undergone more than one anastomotic procedure). When anastomotic procedures were subdivided according to surgical site, the incidence of anastomotic leaks was as follows: colon (number of anastomotic procedures, n = 321), 1.9%; rectum (n = 176), 4.0%; small intestine (n = 155), 1.9%; colorectal – not specified (n = 149), 3.4%; gastric (n = 83), 1.2%; pancreatic/biliary (n = 46), 4.3%; oesophageal (n = 17), 17.6%; and other – not specified (n = 64), 3.1%. The incidence of leakage associated with laparoscopic surgery, according to the number of surgical site procedures, was also reported: colon (n = 19), 21.0%; rectum (n = 12), 8.3%; small intestine (n = 1), 0%; colorectal – not specified (n = 4), 0%; pancreatic/biliary (n = 6), 16.7%; and not specified (n = 3), 0%.

Discussion

Recent studies have demonstrated that adhesions continue to present a substantial burden following general surgery, despite careful attention to surgical techniques and the availability of adhesion-reduction strategies.[15–17] Both site-specific and liquid agents have been developed for the reduction of adhesions. The effective use of site-specific agents requires clinicians to perform positioning procedures and to predict sites of potential adhesion formation. However, many site-specific agents are difficult to apply, particularly during laparoscopy. In addition, Seprafilm® has been found to be associated with increased rates of anastomotic leakage,[25] and Interceed® requires meticulous haemostasis as efficacy of this agent is compromised by the presence of blood.[26,27] Preclinical and preliminary clinical studies of icodextrin 4% solution, a broad-coverage adhesion-reduction agent, indicate that it is effective in reducing adhesion formation throughout the peritoneal cavity without the need for accurate positioning. ARIEL was established to provide feedback on clinical experiences with icodextrin 4% solution during routine laparotomy and laparoscopy. The registry is, therefore, an important source of information on the safety and ease of use of icodextrin 4% solution collected prospectively from experienced surgeons.

The findings from ARIEL indicate that icodextrin 4% solution was well tolerated by patients who underwent laparotomy or laparoscopy, as the reported frequencies of adverse events were similar to those published in the literature. This finding is supported by previous reports of the low incidence of adverse events associated with the use of icodextrin 7.5% in patients receiving continuous ambulatory peritoneal dialysis (CAPD).[28,29] The ARIEL general surgery data also indicate that icodextrin 4% solution can be used in a wide range of surgical procedures and in patients with a wide range of conditions. Cancer, pain and/or bowel obstruction were the most frequent presenting symptoms or conditions reported in both cohorts. Data obtained from the large number of patients in ARIEL who underwent laparotomy for cancer suggest that icodextrin 4% solution was well tolerated by these patients. Animal models have shown that icodextrin 4% solution has no effect on intraperitoneal tumour-cell adhesion or the growth of free intra-abdominal tumour cells.[30] Indeed, the agent is separately approved in a number of European countries as an intraperitoneal carrier solution for the delivery of chemotherapeutic agents in cancer patients.

A key attribute of any effective adhesion-reduction product, particularly in colorectal surgery, is that it may be used during anastomotic procedures without an apparent increase in the risk of anastomotic leakage. A recent systematic review[31] revealed the median incidence of anastomotic leakage after gastrointestinal surgery to be 4–6% (range, 1–39%).[31–36] Preclinical studies with icodextrin 4% solution demonstrated that the use of this agent as an irrigant and a postoperative instillate resulted in no differences in bowel anastomotic healing in rabbits compared with treatment with lactated Ringer's solution (LRS) or untreated surgical controls.[37] The data presented here support this evidence and demonstrate that, within the ARIEL setting, the frequency of anastomotic leakage in patients undergoing bowel anastomoses was low (3.1%) and within the expected range. An assessment of leak rates by surgical site showed that the highest rates occurred in patients undergoing oesophageal, pancreatic/biliary or colorectal procedures. Assessment by type of surgery showed that the incidence of leakage was higher in patients who underwent laparoscopy (7.6%), compared with those who underwent laparotomy (2.7%). However, incidences were similar to those presented in the literature[31–36] and are likely to be related to open anastomotic procedures being a more established surgical technique in comparison to using laparoscopy.

Postoperative ileus is generally accepted as a normal physiological response to abdominal surgery.[38] In ARIEL, the incidence of postoperative ileus in the laparotomy and laparoscopy cohorts was 3.6% and 1.9%, respectively, which compares favourably with reported rates of 2.3–17.6%.[32,39]

The potential effects of adhesion-prevention products on peritonitis are also an essential concern when considering the use of such agents. Results from *in vitro* biocompatibility studies and preclinical models suggest that icodextrin 4% solution is unlikely to increase the risk of peritonitis.[22] A lower incidence of peritonitis in patients from ARIEL (laparotomy, 0.3%; laparoscopy, 1.5%), compared with previous reports of peritonitis after colorectal surgery (2.8–5.1%),[40] supports these findings. In addition, icodextrin 7.5% solution has been shown to neither increase the occurrence of peritonitis nor affect outcomes in patients with peritonitis, compared with glucose solution in patients receiving CAPD.[41] A slight increase in the frequency of wound-healing problems was observed in patients with peritonitis; however, this was unlikely to be a direct effect of icodextrin 4% solution.

The volumes of icodextrin 4% solution used by general surgeons in the ARIEL Registry were in line with volumes recommended for its use as an irrigant and as an instillate. In addition, abdominal discomfort and abdominal distension were rated as 'as expected' by the majority of patients, indicating good patient acceptability. Using appropriate volumes of icodextrin 4% solution as both a wash and an instillate during surgery is particularly important. In animal models, using the agent as a wash-only was less effective in reducing the incidence of adhesions than using a combination of washing and subsequent postoperative instillation of the agent.[22] It is, therefore, recommended that icodextrin 4% solution should be used as both an intra-operative irrigant and as a postoperative instillate in order to minimise the risk of adhesion formation.

The use of icodextrin 4% solution in patients with drains remains a subject of debate as, inevitably, some of the instillate will be lost during drainage. Furthermore, drain usage varies considerably between institutions and countries. ARIEL data indicate that drainage was rated as 'normal' in the majority (63%) of patients with drains and as 'greater than normal' in 20% of patients, in whom a mean volume of 264 ml of fluid was lost in excess of the expected volume (total fluid loss, 543 ml over 6.6 h; 49% of total instillate volume). However, as 1 l of instillate was used, it is likely that ≥ 50% of the solution remained within the peritoneal cavity in all patients.

Ease of use is a major factor in the uptake and effective use of an adhesion-reduction agent. The registry shows that most surgeons considered viewing of the surgical field and handling of tissues to be 'good' or 'excellent' while using icodextrin 4% solution, which indicates that the majority of surgeons found the agent easy to use. Indeed, none of the 103 centres reported viewing or handling as 'bad'. This is in contrast to some site-specific films that have been found to be difficult to apply.[25–27]

Conclusions

Preclinical and preliminary clinical studies have demonstrated that icodextrin 4% solution is an effective treatment for the reduction of adhesion formation following surgery. Data from ARIEL indicate that the agent is easy to use, can be used in a wide range of general surgical procedures without excessive leakage from the surgical site and does not adversely affect viewing of the surgical field or the handling of tissues. Furthermore, icodextrin 4% solution was well tolerated by patients undergoing laparotomy or laparoscopy and by those presenting with symptoms of peritonitis, and satisfaction with the agent was rated as 'good' or 'excellent' by the majority of surgeons. These findings suggest that icodextrin 4% solution may play an important role as part of an adhesion reduction strategy.

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- UNITED KINGDOM (total number of patients, 902)
  Parker M, Darent Valley Hospital, Dartford
  Galloway D, Gartnavel General Hospital, Glasgow
  Sunderland G, Southern General Hospital, Glasgow

- SPAIN (total number of patients, 440)
  Rivas Guerrero J, Hospital Virgen de la Victoria, Málaga
  Dávila Dorta D, Hospital 9 de Octubre, Valencia
  Alcántara Gijón F, Hospital Virgen del Rocío, Sevilla
- GERMANY (total number of patients, 167)
  Reijnen N, Kreiskrankenhaus Leer, Leer
  Klempa J, Klinikum Bremen Mitte, Bremen
  Schäffer M, Knappschaftskrankenhaus Bochum, Bochum
- FRANCE (total number of patients, 141)
  Descottes B, Hôpital Universitaire Dupuytren, Limoges
  Lehur PA, Hôpital Hôtel Dieu, Nantes
  Younes E, Centre Hospitalier François Quesnay,
  Mantes La Jolie
- ITALY (total number of patients, 88)
  Vita S, Fatebenefratelli Ospedale Villa S. Pietro, Rome
  Mazzoconi G, Ospedale SS. Benvenuto e Rocco, Osimo
  Martin F, Ospedale Generale Regionale di Bolzano, Bolzano

References

1. Menzies D, Ellis H. Intestinal obstruction from adhesions – how big is the problem? *Ann R Coll Surg Engl* 1990; **72**: 60–3.
2. Ellis H. The clinical significance of adhesions: focus on intestinal obstruction. *Eur J Surg* 1997; **163 (Suppl 577)**: 5–9.
3. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ, Wexner SD *et al.* Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg* 1996; **183**: 297–306.
4. Risberg B. Adhesions: preventive strategies. *Eur J Surg* 1997; **163 (Suppl 577)**: 32–9.
5. diZerega GS. Biochemical events in peritoneal tissue repair. *Eur J Surg* 1997; **163 (Suppl 577)**: 10–6.
6. Coleman MG, McLain AD, Moran BJ. Impact of previous surgery on time taken for incision and division of adhesions during laparotomy. *Dis Colon Rectum* 2000; **43**: 1297–9.
7. Beck DE, Ferguson MA, Opelka FG, Fleshman JW, Gervaz P, Wexner SD. Effect of previous surgery on abdominal opening time. *Dis Colon Rectum* 2000; **43**: 1749–53.
8. van der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, Schaapveld M, van Goor H. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. *Br J Surg* 2000; **87**: 467–71.
9. Ivarsson ML, Holmdahl L, Franzen G, Risberg B. Cost of bowel obstruction resulting from adhesions. *Eur J Surg* 1997; **163**: 679–84.
10. Menzies D, Parker M, Hoare R, Knight A. Small bowel obstruction due to postoperative adhesions: treatment patterns and associated costs in 110 hospital admissions. *Ann R Coll Surg Engl* 2001; **83**: 40–6.
11. Ray NF, Denton WG, Thamer M, Henderson SC, Perry S. Abdominal adhesiolysis: inpatient care and expenditures in the United States in 1994. *J Am Coll Surg* 1998; **186**: 1–9.
12. Kavic M. Adhesions and adhesiolysis: the role of laparoscopy. *J Soc Laparosc Surg* 2002; **6**: 99–109.
13. Diamond MP, Freeman ML. Clinical implications of postsurgical adhesions. *Hum Reprod Update* 2001; **7**: 567–76.
14. Parker MC. Adhesion-reduction in high-risk surgery – is there a need for consensus? *Colorect Dis* 2004; **6 (Suppl 2)**: 10.
15. Parker MC, Ellis H, Moran BJ, Thompson JN, Wilson MS, Menzies D et al. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. *Dis Colon Rectum* 2001; **44**: 822–9.
16. Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D *et al.* Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. *Lancet* 1999; **353**: 1476–80.
17. Parker M, Sunderland G, Wilson M, Menzies D, Thompson J, Clark D *et al.*, on behalf of the Surgical and Clinical Adhesions Research (SCAR) Group. Colorectal surgery: the risk and burden of adhesion-related complications. *Colorect Dis* 2004; **6**: 506–11.
18. Holmdahl L, Risberg B, Beck DE, Burns JW, Chegini N, diZerega GS *et al.* Adhesions: pathogenesis and prevention-panel discussion and summary. *Eur J Surg* 1997; **163 (Suppl 577)**: 56–62.
19. diZerega GS, Campeau JD. Peritoneal repair and post-surgical adhesion formation. *Hum Reprod Update* 2001; **7**: 547–55.
20. Ling FW, DeCherney AH, Diamond MP, diZerega GS, Montz FJ. *The Challenge of Pelvic Adhesions. Strategies for Prevention and Management.* Crofton, MD: Association of Professors of Gynecology and Obstetrics, 2002.
21. Wilson MS, Menzies D, Knight A, Crowe AM. Demonstrating the clinical and cost effectiveness of adhesion reduction strategies. *Colorect Dis* 2002; **4**: 355–60.
22. Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM. Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin. *Drug Deliv* 2001; **8**: 9–12.
23. diZerega GS, Verco SJ, Young P, Kettel M, Kobak W, Martin D *et al.* A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. *Hum Reprod* 2002; **17**: 1031–8.
24. Verco SJ, Peers EM, Brown CB, Rodgers KE, Roda N, diZerega G. Development of a novel glucose polymer solution (icodextrin) for adhesion prevention: preclinical studies. *Hum Reprod* 2000; **15**: 1764–72.
25. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG. A prospective, randomized, multicenter, controlled study of the safety of seprafilm adhesion barrier in abdominopelvic surgery of the intestine. *Dis Colon Rectum* 2003; **46**: 1310–9.
26. Wiseman DM, Gottlick-Iarkowski L, Kamp L. Effect of different barriers of oxidized regenerated cellulose (ORC) on cecal and sidewall adhesions in the presence and absence of bleeding. J *Invest Surg* 1999; **12**: 141–6.
27. Gynecare Women's Health Solutions. Gynecare Interceed® (TC7) Absorbable Adhesion Barrier Essential Product Information. <http://www.gynecare.com/content/backgrounders/www.womenhealth.info/www,gynecare.com/INTERCEED_Essential_Product_Information.pdf (accessed May 2006).
28. Mistry CD, Mallick NP, Gokal R. Ultrafiltration with an isosmotic solution during long peritoneal dialysis exchanges. *Lancet* 1987; **2**: 178–82.
29. Mistry CD, Gokal R. The use of glucose polymer (icodextrin) in peritoneal dialysis: an overview. *Perit Dial Int* 1994; **14 (Suppl 3)**: S158–61.
30. van den Tol MP, ten Raa S, van Grevenstein WMU, Marquet RL, van Eijck CHJ, Jeekel J. Icodextrin reduces postoperative adhesion formation in rats without

affecting peritoneal metastasis. *Surgery* 2005; **137**: 348–54.
31. Bruce J, Krukowski ZH, Al Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg* 2001; **88**: 1157–68.
32. Hamel CT, Pikarsky AJ, Weiss E, Nogueras J, Wexner SD. Do prior abdominal operations alter the outcome of laparoscopically assisted right hemicolectomy? *Surg Endosc* 2000; **14**: 853–7.
33. Zorcolo L, Covotta L, Carlomagno N, Bartolo DC. Safety of primary anastomosis in emergency colo-rectal surgery. *Colorect Dis* 2003; **5**: 262–9.
34. Elton C, Makin G, Hitos K, Cohen CR. Mortality, morbidity and functional outcome after ileorectal anastomosis. *Br J Surg* 2003; **90**: 59–65.
35. Nakamura T, Pikarsky AJ, Potenti FM, Lau CW, Weiss EG, Nogueras JJ *et al*. Are complications of subtotal colectomy with ileorectal anastomosis related to the original disease? *Am Surg* 2001; **67**: 417–20.
36. Demetriades D, Murray JA, Chan LS, Ordonez C, Bowley D, Nagy KK *et al*. Handsewn versus stapled anastomosis in penetrating colon injuries requiring resection: a multicenter study. *J Trauma* 2002; **52**: 117–21.
37. Rodgers KE, Verco SJ, diZerega GS. Effects of intraperitoneal 4% icodextrin solution on the healing of bowel anastomoses and laparotomy incisions in rabbits. *Colorect Dis* 2003; **5**: 324–30.
38. Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg* 2000; **87**: 1480–93.
39. Nesbakken A, Nygaard K, Westerheim O, Lunde OC, Mala T. Audit of intraoperative and early postoperative complications after introduction of mesorectal excision for rectal cancer. *Eur J Surg* 2002; **168**: 229–35.
40. Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2003; 2: CD001544.
41. Gokal R, Mistry CD, Peers EM. Peritonitis occurrence in a multicenter study of icodextrin and glucose in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Dialysis. *Perit Dial Int* 1995; **15**: 226–30.
42. Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. *Am J Med* 2003; **115**: 515–20.
43. Stevens RD, Burri H, Tramer MR. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. *Anesth Analg* 2003; **97**: 623–33.
44. Struthers AD, Cuschieri A. Cardiovascular consequences of laparoscopic surgery. *Lancet* 1998; **352**: 568–70.
45. Klingler A, Henle KP, Beller S, Rechner J, Zerz A, Wetscher GJ *et al*. Laparoscopic appendectomy does not change the incidence of postoperative infectious complications. *Am J Surg* 1998; **175**: 232–5.
46. Hazzan D, Geron N, Golijanin D, Reissman P, Shiloni E. Laparoscopic cholecystectomy in octogenarians. *Surg Endosc* 2003; 17: 773–6.
47. van't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. *Br J Surg* 2002; **89**: 1350–6.