Gynecol Surg (2007) 4:97–100
DOI 10.1007/s10397-006-0267-0

ORIGINAL ARTICLE

Adverse effects related to icodextrin 4%. Our experience

D. Doumplis · G. S. Majeed · K. Sieunarine · R. Richardson · J. R. Smith

Received: 26 August 2006 / Accepted: 13 December 2006 / Published online: 28 February 2007

Abstract Icodextrin 4% solution is a well established agent which prevents adhesion formation after gynaecological surgery. Its safe usage has been well proved with long term clinical trials. We present five cases where the adverse effects encountered were related to icodextrin 4%. In two cases painless vulval oedema developed after laparoscopy and resolved in the next four days. There were two cases of symptomatic pleural effusion formation after a laparoscopic and a laparotomy surgery, which both gradually subsided after the fourth postoperative day. The fifth case was an anaphylactoid reaction attributed to icodextrin. Surgeons who use icodextrin 4% solution should be aware of the composition and metabolism of the product in order to safely manage any potential adverse effects observed.

Keywords Icodextrin · Surgery · Adverse effects

D. Doumplis · G. S. Majeed · J. R. Smith
West London Cancer Center, Hammersmith Hospital NHS Trust,
London, UK

K. Sieunarine
West Middlesex Hospital,
London, UK

R. Richardson
Department of Gynaecology, Chelsea and Westminster Hospital,
London, UK

J. R. Smith (✉)
Gynaecologic Oncology Department,
Queen Charlotte's and Chelsea Hospital,
Du Cane Road,
W12 0HS London, UK
e-mail: jrsmithgynaecology@gmail.com

Introduction

Abdominal adhesions form as a result of the inflammatory response to peritoneal trauma, when the mesothelial lining, which separates tissues, is disrupted. Surgical trauma to the mesothelial layer of peritoneum leads to bleeding and leakage of plasma proteins and pro-inflammatory cytokines like interleukin-1, interleukin-6 and tumour necrosis factor-α. Fibrin is deposited at the site of tissue damage and either gets degraded or is transformed into a permanent connective tissue structure, namely, an adhesion. Adhesion prevention strategies have been developed by either using site-specific or more generally active adhesion reducing agents. Icodextrin 4% solution (Adept™) is now commonly used in gynaecological minimal access surgery and open procedures for prevention of adhesions. As Adept is retained in the peritoneal cavity for over 4 days after surgery, its safety record and effects on recovery, healing and post-operative infection are an important consideration. Here, we present five cases with post-operative adverse events related to Adept. In all five cases surgery was performed in Chelsea and Westminster and Lister Hospitals Hospital.

Case presentation

Case 1

LB, a 32 year old, P^{0+1}, underwent elective laparoscopy for resection of adhesions. A previous diagnostic laparoscopy had confirmed dense adhesions on the right side of the pelvis between the ovary, the caecum, the posterior aspect of the uterus and the sigmoid colon. They were attributed to a previous salpingectomy for right ectopic pregnancy. At

the end of the adhesiolysis a litre of Adept solution was left in the peritoneal cavity to reduce the risk of adhesion reformation. The patient stayed overnight as she developed urinary retention. The following day a marked unilateral labial swelling was noticed. Although unpleasant for the patient, the swelling was painless and it was gradually reduced in size and resolved after four days.

Case 2

PN, a 38 year old, P^{0+1}, with well-known endometriosis, underwent operative laparoscopy for endometriosis treatment. She had previously had ovarian cystectomy because of an endometrioma. At the end of the operation a litre of 4% icodextrin solution was left in the abdominal cavity. Postoperatively she developed urinary retention along with fluid leakage from the suprapubic entry port. She also developed unilateral vulval swelling which gradually subsided spontaneously over the next four days.

Case 3

AL, a 40 year old nulliparous woman with severe endometriosis resistant to medical treatment, was scheduled for operative laser laparoscopy. She had previously undergone a right ovarian cystectomy in 2001 when severe endometriosis was diagnosed. Previous laparoscopy via the left upper quadrant port (Palmer's point) showed extensive adhesions between small bowel and the anterior abdominal wall. The abdominal wall adhesions were resected to some extent by laser but it appeared that the pelvic adhesions were quite dense and extensive. Thus, laparotomy was performed and adhesions were resected to reconstitute a pouch of Douglas. A litre of Adept solution was left in the abdominal cavity and a drain was inserted in the pelvis, which was initially clamped. The patient was in Trendelenburg position for most of the operation which lasted nearly two hours. At that time she remained stable with normal pulse of 60–70 bpm and blood pressure 100–130/60–70. However, five hours later she became tachycardic (120 bpm), complained of shortness of breath and felt very hot. Her temperature was 37.8°C and the respiratory rate 20/minute. On examination there was reduced air entry on the base of right side of chest and a provisional diagnosis of atelectasis of the right lung was considered. It was noted that the pelvic drain contained only 170 ml of fluid. Full blood count, urea and electrolytes, and CRP were normal while chest X-ray showed right pleural effusion. Intravenous antibiotics were started. An hour later it was noted there were 450 ml of heavily blood stained fluid in the abdominal drain. She was assessed by both the anaesthetic and surgical teams during the night, internal bleeding seemed unlikely and the blood stained fluid from the drain was considered to be some of the Adept solution. Twenty-four hours later she had another episode of shortness of breath. The patient developed pyrexia of 37.9°C, tachycardia (94 bpm) and a further chest x-ray showed an increase in size of the pleural effusion. Blood gases showed alkalosis: pH 7.5↑, pCO_2 3.8↓, pO_2 8.4↓. A spiral chest CT excluded pulmonary embolism but confirmed right basal consolidation with pleural effusion. A chest drain was inserted at the right mid-axillary line under ultrasound guidance and blood stained fluid was aspirated. After drainage of 1300 ml the patient's condition was significantly improved. By day 5 there was no further drainage and repeat chest x-ray confirmed no further accumulation of effusion. No organisms were isolated from pleural fluid culture and cytology was also negative. The drain was removed and she was discharged home. She was reviewed in both gynaecology and respiratory outpatient clinics six weeks later recovering well.

Case 4

A 41 year old, while being investigated for primary infertility, was diagnosed to have stage IV endometriosis. Her ovaries were down regulated with Goserelin (Zoladex®, Astra Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK). A previous laparoscopy had shown a frozen pelvis involving both the bladder and the rectum but demonstrated that the Fallopian tubes were patent. Laser adhesiolysis with resection of a rectal nodule was performed. A litre of Adept was left in the abdominal cavity to prevent adhesions. On the second postoperative day she complained of sore throat and difficulty in breathing. Chest examination revealed a right sided pleural effusion, which was confirmed by chest x-ray. She had chest physiotherapy and was treated with antibiotics. She was given goserelin for another three months and re-laparoscoped in January 2003. Further adhesiolysis as well as resection of a bladder nodule was performed. A litre of Adept was instilled into the abdominal cavity at the end of the operation. The next day she complained of shortness of breath. Chest examination and a chest x-ray confirmed a right sided pleural effusion. She was treated with antibiotics and was discharged after resolution of pleural effusion. A defect in the right side of diaphragm was identified by further investigations. In March 2004 she had right hemicolectomy and anterior resection because of dense adhesions involving terminal ileum and rectum. This time Adept was omitted and postoperatively she did not develop any chest complaints.

Case 5

MP, a 28 year old woman, P^{0+1}, on OCP since 14 years of age underwent laparoscopy and hysteroscopy for dysmen-

orrhoea and dyspareunia. It was noted that in childhood she had bladder/ureteric surgery and also suffered from mild asthma (but did not use any medication over the last twelve months). Laparoscopy was performed through left upper quadrant entry port, endometriosis was treated with diathermy and a Mirena IUD was inserted. A litre of Adept solution was left in the peritoneal cavity. Four hours later she complained of shortness of breath and chest pain radiating to her back. Her pulse was 80 bpm, BP 110/70, temperature 35.5°C, oxygen saturation 100% on air and chest was clear. The pain settled with analgesia. On the next day she developed another episode of shortness of breath with wheezing, cyanosis, uncontrolled shaking and angio-oedema. Her respiratory rate went up to 24/minute, pulse 120 bpm, BP 90/40, oxygen saturation on air 92%. There was marked bronchospasm with reduced air entry to the base of both lungs indicative of anaphylactic/anaphylactoid reaction. Investigations which included blood gases, full blood count, urea and electrolytes, CRP and ECG were all normal. Her condition improved after administration of 2 mg of adrenaline, prednisolone and chlorphenamine. She had a chest X-ray which showed a raised right hemi-diaphragm. On the second post-operative day she started coughing and choking. There was now marked facial angio-oedema and shortness of breath. She had another hypoxic episode despite administration of 10 litres/minute of oxygen with oxygen saturation of 92% and pulse of 112 bpm. Adrenaline was administered again and her condition improved. A spiral CT and a V/Q scan excluded pulmonary embolism. She had a further episode of shortness of breath with tremors, which again responded to adrenaline. A neurologist attributed her tremors to possible hypoxia or hyperactivity reaction related to icodextrin (which has been reported in patients who are on chronic abdominal peritoneal dialysis with 7.5% icodextrin). She had one last episode of shortness of breath with tachycardia, which settled with adrenaline and no further episodes after the fourth postoperative day. She was referred to the Royal Brompton Hospital for further investigations of her allergic reactions.

Discussion

Abdominal and pelvic surgical procedures lead to adhesion formation, which can lead to small bowel obstruction, secondary infertility, chronic abdominal and pelvic pain. The Surgical and Clinical Adhesion Research Study (SCAR) followed 54,380 patients with abdominal or pelvic surgery for 10 years and observed the readmission rate related to adhesion formation was 527 per 100 initial surgical procedures and 3.8% required surgical intervention. The estimated cost of adhesion related procedures over 10 years was £83,065,324 [1, 2]. A number of adhesion-prevention products have been developed which use a physical method of separation in order to effectively separate all the traumatised peritoneal surfaces during the critical period of adhesion development particularly in the first 5 days after surgery. Both solid and gel barriers currently available are site-specific and they do not protect the entire field of surgery. 4% icodextrin solution (Adept™) has been proven to be very effective for adhesion reduction [3]. It is easy to use, protects the entire surgical area and is economical. There is no change to surgical time and can be used for both laparotomy and laparoscopy.

Icodextrin 4% solution (Adept™) causes temporary separation of peritoneal surfaces by hydrofloatation, thus providing a barrier during the critical period of fibrin formation and mesothelial regeneration. Hydroflotation by crystalloids like saline, Ringer's lactate or Hartmann's solution is not very effective as they are rapidly absorbed [4]. Icodextrin is a α-1, 4 linked glucose polymer which is capable of maintaining a reservoir of fluid within the peritoneal cavity for up to 3–4 days [5]. Thus most of the polymer is retained intraperitoneally and only a small amount is absorbed into systemic circulation and metabolised by amylase to oligosaccharides, maltose and finally glucose by the enzyme maltase.

Adept has been used at 7.5% concentration in peritoneal dialysis for many years with well documented effects and safety profile [6, 7]. It is clinically proven to have no adverse effect on recovery time and healing, and shows no difference in inflammatory cell infiltration, fibroblast density, blood vessel formation or collagen maturity. Additionally it has been shown that it doesn't increase the risk of infection or the formation of abscesses [8].

However, here we report five cases where adverse effects associated with Adept were observed. In all five cases, symptoms appeared just a few hours postoperatively and resolved by the fourth day. It is therefore possible, as the Adept solution remains in the peritoneal cavity for almost 4 days, that it can escape through orifices like the deep inguinal ring through the inguinal canal and following the round ligament into mons pubis (canal of Nuck), thus accounting for swelling around the mons in cases 1 and 2 [9]. Similarly, it can also tract down through orifices in the diaphragm near the aortic opening into the chest cavity (cases 3 an 4). Once the fluid was absorbed and metabolised after the third to fourth day, improvement was noted in all patients.

During laparoscopic procedures intraabdominal pressure is up to 15 mmHg due to CO_2 distension, which can make fluid solutions track down to areas of lower pressure through small orifices. Therefore, it is worth considering occluding the superficial/deep inguinal ring by pressure

over the groins, until CO_2 is removed from the abdominal cavity. It is also worth considering levelling the patient from the head down position before Adept is instilled so as to avoid its tracking to the chest.

The fifth case developed an anaphylactoid reaction, which could be due to allergy to amylase as mentioned by the manufactures, so she was referred to the Royal Brompton Hospital for further assessment. The fact that she developed tremors also suggested allergic reaction to icodextrin. A 7.5% solution of icodextrin has been widely used for peritoneal dialysis in chronic renal failure as mentioned above and a case report suggests similar tremors/fits associated with its usage.

The manufacturer, ML Laboratories PLC, Liverpool, UK recommend that ADEPT should not be used in patients with a known allergy to starch based polymers or in patients with maltose or isomaltose intolerance.

Conclusion

Although icodextrin 4% solution (Adept) is an effective and safe agent for prevention of abdominal adhesions, surgeons should be aware of some potential rare adverse effects that could be encountered. These rare adverse effects resolve after absorption and metabolism of the fluid usually by the fourth postoperative day.

References

1. Ellis H, Moran BJ, Thompson JN (1999) Adhesion related hospital readmissions after abdominal pelvic surgery: a retrospective cohort study. Lancet 353:1476–1480
2. Lower AM, Hawthorn RJS, Ellis H, O'Brien F, Buchan S, Crowe AM (2000) The impact of adhesions on hospital re-admission over ten years after 84889 open gynaecological operations: an assessment from the surgical ands clinical adhesions research study. BJOG 107:855–862
3. Di Zerega GS, Verco SJS, Young P, Kettel M, Kobak W, Martin D, Sanfilippo EM, Peers EM, Scimgeour A, Brown CB (2002) A randomised controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. Human Reprod 17:1031–1038
4. Wiseman DM, Trout JR, Diamond MP (1998) The rates of adhesion development and the effects of crystalloid solutions on adhesion development in pelvic surgery. Fertil Steril 70:702–711
5. Verco SJS, Peers EM, Brown CB, Rodgers KE, Roda N, di Zerega G (2000) Development of a novel glucose polymer solution (icodextrin) for adhesion prevention: pre-clinical studies. Hum Reprod 15:1764–1772
6. Basile C, De Padova F, Montanaro A, Giodano R (2003) The impact of relapsing sterile icodextrin-associated peritonitis on peritoneal dialysis outcome. J Nephrol 16:384–386
7. Gradden CW, Ahmed R, Bell GM (2001) Peritoneal dialysis: new developments and new problems. Diabet Med 18:360–363
8. Rodgers KE, Verco SJS, di Zerega GS (2003) Effects of intraperitoneal 4% icodextrin solution on the healing of bowel anastomoses and laparotomy incisions in rabbits. Colorectal Dis 5:324–330
9. Trout SW, Kemmann E (1996) Vulvar edema as a complication of laparoscopic surgery. J Am Assoc Gynecol Laparosc 4:81–83