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Prevention of intraperitoneal adhesions: a comparison of noxythiolin and a new povidone-iodine/PVP solution

O. J. A. GILMORE AND CLARE REID*

SUMMARY

Peritoneal adhesions were induced in 250 female Wistar rats by the excision and closure of a right lower quadrant parietal peritoneal defect. After closure of the defect each rat was randomly allocated to one of five treatment groups: A, control with no instillate; B, control with Ringer solution; C, noxythiolin 0·5 per cent solution; D, noxythiolin 1 per cent solution; E povidone-iodine/PVP solution. Two millilitres of the appropriate solution were injected into the peritoneal cavity just before closure of a standard 4-cm midline incision. Assessment of adhesion formation was made at 1 week in ignorance of the treatment group. Noxythiolin 1 per cent was more effective than Ringer solution and noxythiolin 0·5 per cent in reducing the mean number of adhesions ($P<0·05$) but was inferior to povidone-iodine/PVP ($P<0·05$). Povidone-iodine/PVP solution significantly reduced the number of adhesions compared with the four other groups. In addition, it significantly reduced the mean length of attachment of each adhesion compared with the two control groups ($P<0·001$).

SINCE the advent of abdominal surgery one of the main aims of the surgeon has been to prevent intraperitoneal adhesions. All surgeons dislike finding adhesions when they explore a patient who has had a previous laparotomy. Ellis (1974) reported a 92 per cent incidence of adhesions in such patients. Abdominal surgery is now so common that the adhesions that it produces are the most frequent cause of small bowel obstruction (Ellis, 1974). Krook (1947) concluded from an extensive study that just under 1 per cent of patients who undergo gynaecological surgery develop intestinal obstruction caused by adhesions: this compares with a figure of 4 per cent for those who have an appendicectomy for a perforated appendix.

Ellis (1962, 1971, 1974) believes the aetiology of adhesions to be ischaemic, whereas Boys (1942) and Krook (1947) indicate infection. Experimental and clinical observations suggest that both are potent causes, but whether infection induces adhesions by means of ischaemia remains uncertain.

Noxythiolin (Noxyflex) is a widely used antiseptic and will significantly reduce adhesion formation in the rat (Gilmore and Reid, 1976). A polyvinylpyrrolidone (povidone/PVP) iodine solution containing 1 per cent PVP and 0·1 per cent available iodine failed to prevent adhesions in rats following colectomy (Gilmore, Rosin et al., 1978). However, 6–7 per cent PVP solutions have been effective in both animals (Kalligianis, 1961; Mazuji et al., 1964; Badowski and Daciewicz, 1971) and man (Oetell et al., 1954; Upplegger, 1956). Recently a newly formulated povidone-iodine/PVP solution containing 11 per cent PVP and 0·1 per cent available iodine has been found to reduce significantly peritoneal adhesion formation in the rat (Gilmore and Reid, 1978).

A safe and effective intraperitoneal antiseptic with anti-adhesive properties has enormous potential in both elective and emergency surgery. It was therefore decided to compare the efficacy of noxythiolin and povidone-iodine/PVP in preventing adhesions in a standard animal model (Gilmore and Reid, 1976).

Materials and methods

Povidone-iodine/PVP solution

A mixture of 10 g of dry PVP powder and 1 g of dry povidone-iodine (containing 0·9 g PVP and 0·1 g available iodine) was added to approximately 89 g of sterile water. In order to determine the available iodine content (0·1 per cent was required), the solution was titrated against sodium thiosulphate. More sterile water was added and further titrations performed until the povidone-iodine/PVP solution was demonstrated to contain 0·1 per cent available iodine.

Experimental model

A total of 250 female Wistar rats weighing 150–200 g was used. To avoid the chance deposition of starch granules in the peritoneal cavity all the operations were performed without gloves in clean, but not sterile, conditions.

Peritoneal adhesions were induced by the excision and closure of a standard-size peritoneal defect (Gilmore and Reid, 1976). Under ether anaesthesia, following shaving and skin disinfection, the abdomen of each rat was opened through a 4-cm vertical, midline incision.

An area of parietal peritoneum in the right lower quadrant was then grasped and lifted with a pair of Duval forceps measuring 1·4 cm along their grasping tip. The forceps were adjusted so that the flap of peritoneum reached a point 0·5 cm proximal to the teeth of the forceps. The peritoneum and underlying muscle were incised with a scalpel along all margins of the forceps which, when removed, left a clearly marked window of peritoneum measuring $1·0 \times 1·4$ cm. This window and the underlying muscle were then excised and the resultant defect closed with continuous atraumatic 3/0 black silk sutures.

All abdominal incisions were closed in two layers. The musculoperitoneal layer was closed with continuous 2/0 chromic catgut and the skin was sutured with continuous 2/0 black silk.

A card was drawn allocating each rat to one of five treatment groups: group A, control, no intraperitoneal instillate; group B, control, 2 ml of Ringer solution; group C, 2 ml noxythiolin 0·5 per cent solution; group D, 2 ml noxythiolin 1·0 per cent solution; group E, 2 ml povidone-iodine/PVP solution. All solutions were injected into the peritoneal cavity just before the insertion and tying of the final musculoperitoneal suture.

Assessment of adhesion formation

All rats were killed at 1 week and an autopsy examination of the abdomen performed in ignorance of the treatment group. A reversed 'C' incision was made along the left side of the abdomen, as the peritoneal defect was on the right. In every rat the following details were recorded: number of adhesions present; length of attachment of each adhesion, measured in millimetres with a ruler; the site of origin of each adhesion and the site of adherence.

Statistical methods

The mean number of adhesions per rat was calculated for each treatment group. These means were then compared using the technique of analysis of variance, since five groups were involved (Armitage, 1973). Distribution curves were drawn for

* Department of Surgery, St Bartholomew's Hospital, London ECIA 7BE.

Table I: TOTAL AND MEAN NUMBER OF ADHESIONS RELATED TO TREATMENT

Group	No. of adhesions*	Mean no. adhesions per rat
A	78	1·58
B	92	1·84
C	93	1·88
D	75	1·50
E	59	1·16

* Data for 50 rats.
Standard error of differences in means = 0·016.
E *v.* D, $P<0·05$; E *v.* C, $P<0·001$; E *v.* B, $P<0·001$; E *v.* A, $P<0·001$.
D *v.* C, $P<0·05$; D *v.* B, $P<0·05$; D *v.* A, n.s.

Table II: TOTAL AND MEAN LENGTH OF ATTACHMENT OF ADHESIONS RELATED TO TREATMENT

Group	Length of adhesions* (mm)	Mean length of adhesions per rat (mm)
A	664	8·57
B	736	8·80
C	615	7·30
D	568	6·32
E	345	4·91

* Data for 50 rats.
Standard error of differences in means = 0·819.
E *v.* D, n.s.; E *v.* C, $P<0·01$; E *v.* B, $P<0·001$; E *v.* A, $P<0·001$.
D *v.* C, n.s.; D *v.* B, $P<0·01$; *D v.* A, $P<0·01$.

each treatment group to check that the data were normally distributed. An overall F test of the treatment effects was carried out before comparison of individual pairs of means by an unpaired Student's t test (Armitage, 1973). This gave protection against spurious significant differences arising from the simultaneous comparison of several means.

The average length of adhesions was calculated for each rat. The means for each treatment group were again compared by analysis of variance.

Results

The peroperative intraperitoneal instillation of povidone-iodine/PVP solution gave a statistically significant reduction in the number of adhesions formed in treated rats, compared with all four other groups (*Table I*). Treatment with the povidone-iodine/PVP solution not only resulted in fewer adhesions, but the mean length of attachment of each adhesion was significantly shorter than for either of the two control groups or for group C (*Table II*).

The rats treated with noxythiolin 1 per cent had significantly fewer adhesions ($P<0·05$) compared with groups B and C (*Table I*). The mean length of attachment of each of these adhesions was significantly shorter than that of those occurring in either of the control groups ($P<0·01$) (*Table II*).

Of the 250 rats in the study, 229 developed adhesions. Of the 21 who had no adhesions, 12 were in group E (povidone-iodine/PVP solution) and 8 in group D (noxythiolin 1 per cent). The intraperitoneal instillation of Ringer solution or noxythiolin 0·5 per cent had no effect on the incidence of adhesion formation (*Tables I, II*).

The mean total length of attachment of adhesions per rat (as opposed to the mean length of each adhesion) varied according to the treatment group. Rats in group A had an average 13·3 mm of adhesions, those in group B 14·7 mm, group C 12·3 mm, group D 11·4 mm and group E 6·9 mm.

Throughout the study, all the adhesions seen were either adherent to the peritoneal defect or to the midline abdominal wound. Rats treated with povidone-iodine/PVP solution had fewer adhesions to both sites. Seventy-one rats (28·4 per cent) in the study developed adhesions to the midline laparotomy scar. The incidence of adhesions to this site varied from 14 per cent in the povidone-iodine/PVP group to 46 per cent in the noxythiolin 0·5 per cent group.

The commonest structure found at autopsy to be adherent to either the peritoneal defect or the midline scar was the ovarian complex. The ovary in the rat lies at the end of a long Fallopian tube which has attached to it an abundant broad ligament or mesentery. The entire complex is mobile. The greater omentum was the next most frequently involved with adhesions. Both the broad ligament (mesentery of the Fallopian tube) and the greater omentum are vascular structures and at autopsy new blood vessels were sometimes noted passing from these structures into the closed peritoneal defect or midline scar.

Discussion

This study shows that intraperitoneal instillation of the newly formulated povidone-iodine/PVP solution (PVP 11 per cent, available iodine 0·1 per cent) at operation results in a highly significant reduction in both the number ($P<0·001$) and the mean length of attachment ($P<0·001$) of adhesions forming in treated rats compared with untreated controls. The fact that povidone-iodine (PVP 1 per cent, available iodine 0·1 per cent) had no effect on the development of adhesions in rats following colectomy (Gilmore, Rosin et al., 1978) suggests that the anti-adhesive effect of the new formulation is due to the increased PVP content.

As might be expected from our previous study (Gilmore and Reid, 1976), noxythiolin 1 per cent significantly reduced the number of adhesions in treated rats compared with rats given Ringer solution ($P<0·05$) and also reduced the mean length of adhesions formed ($P<0·01$). Rats treated with noxythiolin 1 per cent, however, had significantly more adhesions ($P<0·05$) than those treated with povidone-iodine/PVP. The fact that noxythiolin 0·5 per cent was ineffective suggests that the anti-adhesive property of this antiseptic is related to its concentration.

It has been clearly demonstrated that it is not simply the presence of fluid in the peritoneal cavity which prevents adhesions forming. There was no significant difference in the number of adhesions between groups A, B or C, yet only rats in the latter two groups received intraperitoneal fluid.

It is difficult to relate the anatomy of the adhesions formed in this study to man. However, it is interesting to note that the greater omentum was frequently involved with adhesions and that 28·4 per cent of the laparotomy incisions had adhesions. How effective the new povidone-iodine/PVP solution would be in preventing intestinal obstruction due to adhesions in man remains a point of conjecture, since its use did not completely eliminate their formation in rats.

There are three possible reasons for the anti-adhesive effect of noxythiolin. O'Meara showed it to have anticoagulant properties, thus preventing fibrin deposition (Garratt, 1969). Its topical cytotoxic

effect (Jamieson, 1972; Desai and Jamieson, 1973) may prevent fibroblast proliferation, while as an antiseptic it removes septic foci, a potent cause of adhesions (Jackson, 1958; Muller and Rademaker, 1973).

It has been suggested that PVP solutions prevent adhesions by acting as visceral lubricants (Badowski and Daciewicz, 1971). Kalligianis (1961) claimed that PVP had anticoagulant properties, which is possible since it is a polymer of high molecular weight. Experimental work from Japan (Goto et al., 1973) indicates that such polymers also affect cell division by slowing mitosis and causing contact inhibition, thus cells lose their agglutinability. This seems the most likely explanation of the anti-adhesive effect of povidone-iodine/PVP solution. But again, as with noxythioloin, the solution's antiseptic properties probably also played a part.

We have shown in the rat that treatment with a newly formulated povidone-iodine/PVP solution is significantly more effective in reducing the number of peritoneal adhesions forming than is treatment with Ringer solution and noxythiolin 0·5 per cent and 1·0 per cent. A standard povidone-iodine has been shown to reduce significantly the mortality of mice and rats with peritonitis (Gilmore, Reid et al., 1978). It seems unlikely that the newly formulated mixture used in the present study loses its antiseptic properties when the additional PVP is added, since the chemical reaction between PVP and iodine is taken to completion when they are combined initially (Siggia, 1957).

This new solution with its antibacterial and anti-adhesive properties would appear to have considerable potential in all operations involving mesothelial surfaces.

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