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The effect of topical povidone-iodine on the incidence of infection in surgical wounds

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SUMMARY

A randomized stratified clinical trial of topical povidone-iodine in 627 patients undergoing abdominal procedures demonstrated a reduction in postoperative wound sepsis in female patients, in patients receiving subcutaneous low dose heparin and during the first quarter of the trial when the infection rate in control subjects was high. Overall, there was no significant reduction in wound sepsis after administration of povidone-iodine due mainly to a high infection rate in povidone-iodine treated male appendix operations where, by chance, there was an increased incidence of contamination with Bacteroides fragilis.

Postoperative stay in those developing wound infection was significantly reduced in the povidone-iodine group. This is considered as indirect evidence for a decrease in severity of wound infection.

PREVIOUS trials have suggested that the antiseptic agent, povidone-iodine (a complex of iodine and the polymer polyvinyl pyrrolidone) may be valuable in prophylaxis of wound infection. Reported here are the results of a randomized stratified double-blind clinical trial of topical povidone-iodine conducted over a 12-month period at a new general hospital, Flinders Medical Centre.

Patients and methods

The study involved 647 patients undergoing abdominal procedures. Twenty patients were withdrawn because of early death or early reoperation. Wounds were stratified on the basis of expected bacterial contamination and obesity since these factors are known to influence wound infection. The three categories of expected bacterial contamination were (*a*), clean, (*b*), potentially infected, i.e. cases in whom the gastrointestinal or biliary tract was opened at operation, and (*c*), dirty, i.e. frank contamination by pus.

Stratification on the basis of thickness of abdominal fat was: normal <3 cm, obese $\geqslant 3$ cm fat. Within each group, after closure of the peritoneum, patients were randomly allocated to wound spraying with povidone-iodine solution (as 5 per cent Betadine (Napp) aerosol spray with 0·5 per cent available iodine) or no treatment (control) on the basis of computer-generated matched pairs. The surgeon was informed of the treatment allocation after closure of the peritoneum or the first layer of sutures in the abdominal wall.

Standard skin preparation with povidone-iodine was used throughout the trial, along with standard techniques of wound closure with absorbable sutures in peritoneum or muscle and monofilament nylon in the anterior rectus sheath or linea alba. The skin was closed with interrupted nylon sutures. Drains, when required, were brought out through a separate stab incision away from the operative wound.

A standard form was completed at the end of each operation and all wounds were inspected by an infection control sister who was unaware of the treatment given. A wound was considered to be infected if a purulent discharge (with or without bacteriological analysis) appeared at any time within 1 month of operation, or a serosanguinous discharge was positive on culture. The wound was also inspected for any evidence of skin sensitivity to povidone-iodine.

Microbiology

At operation, a swab tip was rolled along the fat and muscle of both sides of the wound prior to povidone-iodine treatment, if any. Postoperative wound discharges were cultured and any growth compared with the original operative culture result. Swabs were transported within 5 min to the laboratory for quantitative and qualitative aerobic and anaerobic cultures. Quantitation was according to the method of Rotheram (1) and anaerobic procedures were undertaken in an anaerobic chamber, using pre-reduced media.

Statistical methods

The SPSS set of subprograms (2) on a DEC-10 computer was used for contingency table analysis of the data. Where appropriate, raw χ^2, the χ^2 statistic with Yates' correction (χ_c^2), Fisher's exact test and the Mann–Whitney U test (3) were used to test the significance of observed differences in incidences. Additionally, Student's t test was used for the analysis of differences in means.

Results

There were 314 males and 313 females with a mean age of 43·4 years (range 6–92 years); 178 (28 per cent) were obese. Operations included appendicectomy (226), biliary tract procedures (166), colonic operations (41), gastroduodenal operations (63) and miscellaneous procedures (131).

Analysis indicated no significant bias in patient allocation to povidone-iodine or control groups in relation to category of operation, stratification subgroup, surgeon, patient age, length of incision, duration of operation, presence of a drain or administration of subcutaneous heparin. No patient showed any sensitivity to povidone-iodine.

Influence of povidone-iodine on wound infection rates

Sixty-eight patients (11 per cent) developed wound infection: 28 of 308 (9 per cent) in the povidone-iodine treatment patients and 40 of 319 (12 per cent) in the control group. Treatment with povidone-iodine was associated with a decreased infection rate in females (14 to 6 per cent), a finding most clearly seen in appendicectomy (15 to 6 per cent) and large bowel operations (64 to 9 per cent) (*Table I*). In contrast, there was an increase in sepsis in males undergoing appendicectomy (4 to 17 per cent). As there were apparent differences in infection rates as the trial proceeded, an analysis was performed for each 3-month segment. The use of povidone-iodine was associated with a significantly decreased infection rate in the first quarter (22 to 9 per cent). However, there was a significant decrease in infection rate as the trial progressed, with the rate in control patients falling from 12 to 9 and 8 per cent over the subsequent 3-month periods at a time when the infection rate in the povidone-iodine group remained about 9 per cent.

Wound infection rates differed significantly according to whether the operation was classified as clean, potentially infected or dirty (*Table II*). Povidone-iodine administration did not influence infection rates

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Table I: EFFECT OF POVIDONE-IODINE ON WOUND INFECTION RATES IN APPENDICECTOMY AND LARGE BOWEL SURGERY

Sex	Treatment group	Appendicectomy No.	%	Large bowel No.	%
Male	Povidone-iodine	11/64	17	2/11	18
	Control	2/54	4*	1/8	12
Female	Povidone-iodine	3/49	6	1/11	9
	Control	9/59	15	7/11	64**
Total	Povidone-iodine	14/113	12	3/22	14
	Control	11/113	10	8/19	42

* $\chi_c^2 = 4{\cdot}14$; $P < 0{\cdot}05$.
** Fisher's exact test = 4·91; $P < 0{\cdot}03$.

Table II: EFFECT OF POVIDONE-IODINE ON WOUND INFECTION RATES IN DIFFERENT CLASSIFICATIONS OF OPERATION

Treatment group	Classification of operation: Clean No.	%	Potentially infected No.	%	Dirty No.	%
Povidone-iodine	2/59	3	21/232	9	5/17	29
Control	6/63	10	25/232	11	9/24	38
Total*	8/122	7	46/464	10	14/41	34

* Significant differences in wound infection rates between (but not within) groups: $\chi^2 = 25{\cdot}76$; d.f. = 2; $P < 0{\cdot}0001$.

Table III: EFFECT OF POVIDONE-IODINE ON WOUND INFECTION RATES IN DIFFERENT CATEGORIES OF ANTIBIOTIC ADMINISTRATION

Treatment group	None No.	%	Antibiotics Postoperative No.	%		Perioperative No.	%
Povidone-iodine	15/195	8	2/42	5	*	11/71	16
Control	17/210	8	10/41	24	*	13/68	19
Total	32/405	8	12/83	14		24/139	17

* $\chi_c^2 = 4{\cdot}97$; $P < 0{\cdot}03$.

within these three categories. As previous analysis indicated significant differences between the sexes with regard to the effect of povidone-iodine on wound infection rates, this variable was considered within these strata. Povidone-iodine was protective in 'dirty' operations in females (7/15 to 0/7; $P < 0{\cdot}05$ by Fisher's exact test).

The stratification of patients on the basis of obesity appeared in retrospect to be unnecessary. There was no significant difference between the strata with respect to wound infection rates. Patients receiving prophylactic subcutaneous heparin injections were found to have a significantly decreased wound infection rate with povidone-iodine administration (5 per cent of 97 patients), when compared with controls (15 per cent of 109 patients).

Influence of antibiotics

There were 405 patients who did not receive antibiotics at any time (*Table III*) and 32 of these developed wound infections. Povidone-iodine administration did not influence the wound infection rate in these patients.

Eighty-three patients received antibiotics postoperatively only: the povidone-iodine group recorded a 5 per cent infection rate, and the controls a 24 per cent rate. However, where antibiotics were administered perioperatively, there was no difference in infection rates in the two groups. This latter category of patients included the severely ill patients with more advanced or established sepsis and hence a higher risk of wound infection. Twenty-four of the 68 wound infections occurred in this group; the pooled infection rate was 17 per cent (*Table III*). Closer analysis reveals that appropriately selected systemic antibiotics, e.g. clindamycin plus gentamicin, given before or at operation resulted in an infection rate of 12 per cent compared with 29 per cent where a single broad spectrum antibiotic (e.g. oral neomycin) was administered.

Influence of povidone-iodine on the severity of postoperative wound infection

Although no direct analysis of the severity of wound infection was made in this trial, one indirect measure may be the time of postoperative stay in hospital. For patients developing a wound infection, there was an average decrease in postoperative stay of 5·3 days per patient in those receiving povidone-iodine compared with controls (*Table IV*). This was statistically significant, representing a 28 per cent decrease in the mean postoperative stay of the untreated group with wound infections. In patients not developing a wound

Table IV: INFLUENCE OF POVIDONE-IODINE ON MEAN POSTOPERATIVE HOSPITAL STAY IN PATIENTS WITH WOUND INFECTION

Operation	Mean postoperative hospital stay (d) Povidone-iodine group	Control group	Net decrease in povidone-iodine group
Appendicectomy	10·8 (7)*	17·3 (3)	6·5
Biliary tract	18·0 (2)	23·8 (5)	5·8
Gastroduodenal + small bowel	17·5 (2)	15·3 (7)	−2·2
Large bowel	14·7 (3)	23·9 (8)	9·2
Other	23·0 (1)	21·7 (3)	−1·3
Total†			5·3‡

* Number of patients is given in parentheses.
† The net decrease in mean postoperative hospital stay for all patients receiving povidone-iodine and developing a wound infection in hospital is a theoretical overall figure. The data for each category of operation contribute to it in proportion to the number of povidone-iodine treated patients in that category.
‡ Net decrease in postoperative stay with povidone-iodine for 280 patients not developing wound infection = 0·2 days (not significant). For the 15 patients with infection in the povidone-iodine group, this represents a 28 per cent decrease in mean postoperative stay when compared to the patients in the control group with infection (Mann–Whitney U test: $P < 0{\cdot}015$).

infection, there was no difference in postoperative stay in the two groups.

Microbiology

When bacteria of any type were isolated from the wound swab, 12 per cent of wounds became infected. If no bacteria were isolated, the wound infection rate was 3 per cent.

Pus or serosanguinous discharge was cultured from 45 of the 68 patients who developed a wound infection. *Bacteroides fragilis* group was cultured from 86 (14 per cent) of 601 wound swabs and appeared in 36 per cent of 45 wound infections analysed. Twenty-five of the 86 patients (29 per cent) with a positive wound swab culture for bacteroides subsequently developed a wound infection. The relatively high isolation rate of anaerobes (14 per cent) from operative wound swabs is attributed to the rapid processing of fresh material from the operating theatre rather than relying on some form of transport medium.

Analysis of wound bacteriology at operation from males and females indicated a significantly higher isolation rate of the *Bacteroides fragilis* group in male appendicectomy wounds allocated to povidone-iodine (29 per cent) compared with those in the control groups (14 per cent). No other significant differences were noted in any other category of operation for either sex for 17 species or families of bacteria.

The use of povidone-iodine had no significant influence on the spectrum of bacterial isolates found at sepsis. A detailed analysis of bacteriological findings including quantitative bacteriology at operation and at sepsis will be reported elsewhere (McDonald et al., in preparation).

Discussion

There was a markedly decreased infection rate in povidone-iodine treated females in the present series (14 per cent in the control group, 6 per cent in the treated). This finding is accounted for largely by the appendicectomy and colectomy subgroups, but the trend is apparent in all categories of operation. A similar effect in females was found by Gilmore and Sanderson (4). A perplexing finding was the apparent enhancement of sepsis by povidone-iodine treatment of males undergoing appendicectomy (4 per cent in the control group to 17 per cent in the treated). A probable explanation was revealed by analysis of bacteroides isolates from appendicectomy wounds where the *Bacteroides fragilis* group was present in 29 per cent of male appendicectomy wounds subsequently treated with povidone-iodine, whereas it was found in only 14 per cent of control male appendicectomy wounds. This finding means that, by chance, in spite of care in trial design, there was significant bias in the allocation of povidone-iodine treatment to more heavily contaminated male appendicectomy wounds. No such bias was found after analysis of bacterial isolates in female appendicectomy wounds or other category of operation. Thus, the decreased infection rate in treated females is probably due to povidone-iodine administration whereas the enhanced infection rate in treated male appendicectomy patients may be related to a chance increase in incidence of contamination with the *Bacteroides fragilis* group.

If for the above reason the male appendicectomy patients (treated and control) are excluded from the study, the overall infection rate becomes 7 per cent in the povidone-iodine group and 14 per cent in the controls ($\chi_c^2 = 6{\cdot}42$; $P < 0{\cdot}025$).

The stratification of wounds into clean, potentially infected and dirty categories proved to be useful in practice and its validity was confirmed since the wound infection rate was significantly different between the categories (*Table II*). Povidone-iodine, however, did not influence the infection rate within any of the three categories overall, except that it appeared to protect females in the dirty category. When planning the trial, it was predicted that povidone-iodine would reduce wound infection in the potentially infected group, i.e. the group with the expected modest inoculum of micro-organisms. However, this postulate was not supported by the observations.

Povidone-iodine did appear to protect patients receiving prophylactic subcutaneous heparin since there was a significant reduction in infection rate in these patients. This effect may indicate that povidone-iodine

'sterilizes' small wound haematomas or prevents the enhancement of anaerobic infections by blood and haemoglobin as has been demonstrated experimentally in mice by Hill (5).

Two-thirds of the patients did not receive antibiotics at any time during the period of study. Their overall infection rate was 8 per cent in each treatment group, but they accounted for only 32 of the 68 wound infections observed. Thus, the remaining 36 infections occurred in the 222 patients who received antibiotics, either postoperatively or perioperatively. The combination of postoperative antibiotics and povidone-iodine resulted in a 5 per cent wound infection rate, while postoperative antibiotics alone were associated with a 24 per cent infection rate: this apparent interaction between povidone-iodine and postoperative antibiotics is unexplained. The infection rate in those receiving perioperative antibiotics was relatively high (17 per cent overall) with no significant difference between povidone-iodine treated and control groups. However, within this category, which included the toxic and severely ill patients, the use of fully effective systemic antibiotics was associated with a much lower wound infection rate (12 per cent) than with partially effective oral antibiotics (29 per cent). This suggests that the addition of topical povidone-iodine does not increase the protection afforded by appropriate parenteral antibiotics.

Analysis for each 3-month segment of the trial showed a high infection rate in control patients in the first quarter (22 per cent) and indeed povidone-iodine administration was associated with a decreased infection rate at this time. However, control infection rates fell to the order of 10 per cent over the latter 3 segments of the trial and it is suggested that this reduction may have been influenced by the more definitive use of perioperative antibiotics in the at-risk groups due to the unacceptably high infection rate in the early part of the study. Thus, any effect of wound antisepsis may have been masked.

Analysis of data of patients who developed wound infection revealed that postoperative stay was on average 5·3 days less in those pretreated with povidone-iodine. This is considered as indirect evidence for a decrease in severity of wound infection in the treated group, and it can be argued that the accumulated saving in the patient-days in hospital has an economic benefit. The necessity for careful follow-up of patients in wound infection trials is illustrated by the observation that 23 of the 68 patients developed their wound infection after leaving hospital. It was found that growth of an organism from the operation wound swab was a useful discriminant in predicting subsequent wound infection. Anaerobic flora was prominent and its importance in gastrointestinal sepsis is well recognized (6, 7).

The present study has failed to demonstrate an overall reduction in postoperative wound sepsis with topical povidone-iodine spray, although a significant reduction in sepsis was found in certain subgroups: female patients, patients receiving subcutaneous low dose heparin and during the first 3 months of the trial when the overall infection rate was high. It is also probable that the severity of wound infection was less in the povidone-iodine treated patients, since the total postoperative stay of patients with wound infection was significantly reduced. In addition, if the overall figures are adjusted to take account of bias in allocation of *Bacteroides fragilis*-contaminated male appendicectomy patients to treatment or control groups a significant reduction in postoperative sepsis with povidone-iodine treatment is observed.

Several trials have failed to demonstrate the efficacy of topical povidone-iodine (8–11). However, Gilmore and Sanderson (4), using a dry powder aerosol preparation, reported an infection rate of 8·6 per cent in treated versus 24 per cent in control patients in a study involving 144 abdominal operations. Similarly, Sindelar and Mason (12), using a 10 per cent povidone-iodine solution containing 1 per cent available iodine, i.e. double the strength used in the present series, reported a wound infection rate of 2·9 per cent in the treated group compared with 15·1 per cent in the control patients whose wounds were irrigated with saline. The latter series involved 500 general surgical procedures. Thus, it is possible that the dose, physical properties or technique of application of the topical agent together with patient-related and surgeon-related variables may explain the above contrasting reports.

In conclusion, although the overall effect was marginal, topical povidone-iodine did appear to reduce the incidence of wound sepsis in certain subgroups. Most recent evidence indicates that systemic administration of short courses of antibiotics fully effective against aerobic and anaerobic bacteria is the preferred method of prophylaxis of wound sepsis. However, topical povidone-iodine, which is cheap, non-toxic and free of the problems of induced bacterial resistance, offers the surgeon an additional measure which may have a place in reducing the bacterial population of the surgical wound.

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reason should tell you that this is not the case, and that if you persevere you can certainly do better.

For those who do not know how to start revising, I suggest that you start to rewrite the text and somehow to say it differently. Hunt for synonyms; try alternative constructions; eliminate an adjective here, a preposition there; convert a passive voice to an active; eliminate a whole sentence; and see if any of these changes makes any difference. Weigh the result carefully, and compare the old and the new. As you reflect, perhaps some still different mode of expression will pop into your mind and seem clearly superior. As you gain some critical sense, you will suddenly become aware that your own writing is showing the same faults to which you have become sensitized in the writings of others. The more you ask yourself 'How can I say this in a different way?' the more quickly will you develop sensitivity and skill in evaluation.

LESTER S. KING

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