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Combined topical povidone–iodine and systemic antibiotics in postappendicectomy wound sepsis

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Three hundred and fifteen patients with appendicitis were randomized into two groups. One group received pre-operative systemic gentamicin and metronidazole while the other group received 1 per cent topical povidone–iodine solution in addition to the antibiotics. For early appendicitis including normal and acutely inflamed appendices, only one dose of antibiotics was used. The postoperative wound sepsis was very low in both groups of patients and there was no statistical difference between them. For late appendicitis including gangrenous and perforated appendices, the antibiotics were continued for 7 days. Eight out of 51 patients who had the topical agent developed wound sepsis compared with one out of 52 patients who received no topical agent. This difference is statistically significant ($P = 0.03$). *All wound infections presented within 2 weeks of operation and were deep. Povidone–iodine, 1 per cent, adversely affects the wound infection rate in late appendicitis and should not be used.*

Keywords: Postappendicectomy sepsis, prophylaxis, topical povidone–iodine, gentamicin, metronidazole

Although some surgeons have advocated a 'belt and braces' policy of systemic combined with local antimicrobial agents in gastrointestinal surgery[1] there have been few scientific evaluations of this combination[2]. In animal experiments in contaminated wounds, systemic and topical agents are more effective than either alone[3,4]. In late appendicitis, systemic clindamycin and gentamicin and topical povidone–iodine is more effective than topical povidone–iodine or no treatment[5]. Unfortunately no control group who received systemic antibiotics was included in this study and most surgeons would have used systemic antibiotics in such patients to reduce both the wound and the more dreaded intraperitoneal septic complications[6]. Thus, we still do not know whether there is any additional beneficial effect in combining topical and systemic antimicrobial agents. A small study on perforated appendicitis seemed to suggest that a combination of topical povidone–iodine and systemic antibiotics was not useful in humans[7]. However, the number of patients studied was small and the wound infection rate was high (around 50 per cent) in both groups. Also, the systemic antibiotics used were not stated and we do not know whether effective systemic antibiotics were used. We conducted a randomized, prospective trial to find out whether there was any additional beneficial effect in combining topical povidone–iodine and effective systemic antibiotics.

Patients and methods

All patients admitted to the Government Surgical Unit, Queen Mary Hospital, Hong Kong between September 1984 and May 1985 undergoing appendicectomy through a gridiron wound were included in this study. During this period, there were 14 patients who underwent appendicectomy but were not entered into this study: 8 patients had appendicectomy done through a laparotomy wound, 3 patients received other antibiotics before admission, 2 had incidental appendicectomy during an operation for another pathology and 1 had interval appendicectomy done 6 weeks after drainage of an appendicular abscess.

Informed consent was obtained and the patients were randomly allocated into two groups. One group received gentamicin and metronidazole while the other group received in addition to the systemic antibiotics 1 per cent topical povidone–iodine. The antibiotics were infused intravenously over half an hour just before surgery. The dose used was gentamicin 2 mg/kg and metronidazole 10 mg/kg. Appendicectomy was performed in the usual manner. A drain was used only in patients with an abscess and it was brought out through a separate incision some distance away from the main wound. Two culture swabs were taken from the appendicular fossa after the peritoneum was opened using the Culturette and the Anaerobic Culturette (manufactured by Marion Scientific Corporation, a Division of Marion Laboratories Inc., Kansas City, Missouri, USA). The swabs were sent to the laboratory as soon as possible. The time between specimen collection and inoculation never exceeded 1 h. All resected specimens were sent for histological section.

After closure of the peritoneum a sealed envelope containing the random code number which defined the treatment group was opened. When topical povidone–iodine was assigned, 10 ml 1 per cent povidone–iodine was poured onto the wound after careful removal of all clots. Usually the gridiron incisions were not big enough to hold the 10 ml of topical agent. The excess that overflowed was mopped off. The topical agent was left for 10 min and then the muscle layers were closed with polyglycolic acid sutures and the skin with nylon. In the group of patients assigned not to receive topical agents, the wound was closed after removal of all clots.

If the appendix was normal or acutely inflamed, no further antibiotic was given. If the appendix was gangrenous, perforated or there was an abscess, the antibiotics were continued intravenously at 8 h intervals for 7 days. Serum peak and trough levels of gentamicin and serum creatinine were determined routinely on days 1, 3 and 6. The gentamicin dose was adjusted to give a peak level of 5–10 μg/ml. Although a considerable discrepancy in the diagnosis made by surgeons and pathologists on the degree of appendicitis was found in a previous study[8], for practical purposes the antibiotic regimen used in this study followed the surgeons' operative findings because the histopathological reports were not available for 2–3 days.

The patients were routinely examined before being discharged from the hospital and during follow-up visits at 2 and 6 weeks after the operation. All patients with suspected wound or intraperitoneal sepsis were inspected by one independent assessor who had no idea whether topical agents had been used. All patients were contacted by telephone when they failed to attend the outpatients' clinic. Aerobic and anaerobic cultures were taken from patients with wound infection. The criteria of Ljungqvist based upon the clinical appearance of the wound combined with the results of culture were used to determine whether the wounds were infected or clean[9]. Wounds with purulent discharge and wounds with serous discharge which gave positive bacteriological cultures were classified as infected. Wounds with serous discharge after the patients had returned home and in whom cultures could not be taken were also included in the infected group.

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Results

Three hundred and fifteen patients were included in this study; 156 received systemic antibiotics alone while 159 received systemic antibiotics and 1 per cent topical povidone–iodine. The two groups of patients were comparable in every respect (*Table 1*).

For early appendicitis, the infection rates were very low and there was no statistically significant difference between the two groups (*Table 2*). For late appendicitis, statistically more wound infection occurred in the group of patients who received both systemic and topical agents (*Table 2*) (Fisher's exact probability test, $P = 0{\cdot}03$).

All patients with wound infection presented within the first 2 weeks of operation and all the wound infections were deep. There was no superficial wound infection in this series of patients (*Table 3*). Only one patient who received systemic antibiotics alone had suspected intraperitoneal sepsis and he responded to another course of antibiotics. Seven out of 12 patients developed wound infection in the hospital. Two patients were readmitted with fever while the other three patients were found to have wound infection on follow-up in the outpatients' clinic.

The duration of hospital stay and the duration of pyrexia was similar in the two groups.

Table 1 *Comparability of the groups*

	Systemic agents	Systemic + local agent
Age (years)		
>60	14	16
17 59	107	111
<16	35	32
Degree of appendicitis		
Early (normal, acutely inflamed)	104	108
Late (gangrenous, perforated)	52	51
Peritoneal effusion		
Nil	63	69
Serous	56	50
Purulent	37	40
Culture from fossa of appendix		
Positive	50	56
Negative	106	103
Obesity	11	9

Table 2 *Wound infection in relation to degree of appendicitis*

Degree of appendicitis	Systemic agents		Systemic + local agent	
	n	Infected	*n*	Infected
Early	104	2	108	1
Normal	10		12	
Acutely inflamed	94	2	96	1
Late	52	1	51	8
Gangrenous	18		16	2
Perforated	27	1	30	4
Abscess	7		5	2

Table 3 *Time of presentation of wound infection*

Degree of appendicitis	Time (days)	Systemic agents	Systemic + local agent
Early (normal, acutely inflamed)	<7	2	1
	8 14		
	>15		
Late (gangrenous, perforated, abscess)	<7		3
	8 14	1	5
	>15	-	-

Routinely, aerobic and anaerobic cultures were taken from the appendicular fossa during the operation. Positive cultures were obtained in 106 patients (33·7 per cent) and pure growth of bacteria occurred in 51 patients (16·2 per cent). A positive culture increased the risk of postappendicectomy sepsis. When a mixed growth of aerobes and anaerobes was isolated, the subsequent sepsis rates were 7·1 per cent for patients who received systemic antibiotics alone and 20·1 per cent for patients who received both systemic antibiotics and topical povidone–iodine. The corresponding figures fell to 4·2 and 7·4 per cent respectively when the isolates were pure aerobes or anaerobes, and they further fell to 0 and 1 per cent respectively when no organism was isolated. The commonest organisms isolated in the peritoneal culture were *Escherichia coli* and *Bacteroides fragilis*. All the organisms were sensitive to the systemic antibiotics used. For the 12 patients with wound infection, wound culture yielded more than one aerobe in 6 patients, a single aerobe in 4 patients, mixed aerobe and anaerobe in 1 patient and no growth of organism in 1 patient. For the patient with anaerobe isolated, the culture was *Peptostreptococcus* species resistant to metronidazole. The commonest aerobes isolated were *Escherichia coli*, *Proteus mirabilis* and *Klebsiella* and they were all sensitive to gentamicin.

For the patients who received a full course of antibiotics, gentamicin had to be adjusted in about 23 per cent of patients. Nephrotoxicity (defined as an increase in creatinine of $\geqslant 35\,\mu$mol/l if the initial value was less than $265\,\mu$mol/l or $\geqslant 80\,\mu$mol/l if the initial value was $\geqslant 265\,\mu$mol/l)[10] was detected in about 3 per cent of these patients. The nephrotoxic effect was not detected in any patient who received a single pre-operative dose of antibiotics.

Discussion

The incidence of postappendicectomy wound sepsis increases as appendicitis progresses[11 13] and it is more than 50 per cent in perforated cases when antimicrobial agents are not used[12,14]. Postappendicectomy sepsis can be reduced significantly with appropriate use of systemic antibiotics and gentamicin and metronidazole is a good combination in *in vitro*[15] and *in vivo* studies[16]. Even with systemic antibiotics, there are few antibiotic regimes that can reduce the incidence of postoperative sepsis in perforated appendicitis to less than 25 per cent and there are even fewer regimes that can reduce it to less than 10 per cent[17]. The combined use of systemic and topical antimicrobial agents was shown to result in a significantly lower wound infection rate in animals than either alone[3,4] but there have been few scientific evaluations of the combination in humans[2].

Topical antiseptics have the advantages of having a wider spectrum of activity and faster action against bacteria than most antibiotics and they do not induce antibiotic resistant bacterial strains or antibiotic hypersensitivity. Many topical antiseptics have been used[18] and topical povidone–iodine appeared to be most effective though such effectiveness is not consistent. While it is effective in some studies on appendicitis [7,11,19], it is ineffective in others[5,20 22]. Such inconsistency is also shown in studies on abdominal operations [21,23 27] and elective non-abdominal operations[28,29]. Topical povidone–iodine has been used as dry powder aerosol spray (Disadine DP with 5 per cent available iodine)[5,12,19,22,23,25 27,29], solution spray (Betadine with 0·5 per cent available iodine[20,21]) and wound irrigation solutions (as 10 per cent povidone–iodine solution with 1 per cent available iodine[24,28]). Clinical studies on povidone–iodine lack uniformity in their methods of application, concentration and total amounts used and so it is not surprising that the results lack uniformity. In most studies, the concentrations of povidone–iodine used were too high (5 to 10 per cent)[5,11,19–29]. Five to ten per cent solutions of povidone–iodine were shown locally to inhibit leucocyte migration, fibroblastic activity and wound cellularity[7] and they have paradoxically lower 'free iodine'[30] and thus less antimicrobial

activity[31] than more dilute solutions ranging from 5 to 0·1 per cent. The serum levels of iodine should be low with the amounts of povidone iodine used in appendicitis. High serum iodine has been shown to inhibit lymphocytic blastogenesis[32] and to cause acid and electrolyte disturbances[33]. Thus, when povidone iodine is used, a more dilute form should be chosen. From the data available, 1 per cent povidone iodine solution (with 0·1 per cent available iodine) appears to be a good topical agent[7]. A powder form in 1 per cent concentration is not available and theoretically powder may stay in the wound longer than solution and in this respect it may be better.

Viljanto has shown that 5 per cent solution of povidone iodine caused a statistically significant increase in wound infection in acute appendicitis irrespective of the state of appendix[7]. Our results show that with effective systemic antibiotics, 1 per cent topical povidone iodine causes more wound infection in late appendicitis and it is of no additional benefit in early appendicitis. Recently, 1 per cent povidone iodine was shown to be cytotoxic. It adversely affected wound healing in rats[34] and it caused a decrease in local perfusion on the microcirculation in the wounds in rabbits to about half in the first minute[35]. These toxic effects of the topical agent on the wounds possibly explain the observed increase in wound sepsis in this study. Based on these data, povidone iodine solution even as dilute as 1 per cent should not be used clinically.

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