ARTICLE IN PRESS

Journal of the Egyptian National Cancer Institute (2013) xxx, xxx–xxx

Cairo University

Journal of the Egyptian National Cancer Institute

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Original article

Comparing a combination of penicillin G and gentamicin to a combination of clindamycin and amikacin as prophylactic antibiotic regimens in prevention of clean contaminated wound infections in cancer surgery

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Received 30 September 2012; accepted 3 December 2012

KEYWORDS

Surgical site infection;
Prophylactic antibiotics

Abstract *Background and aim:* Appropriate antibiotic selection and timing of administration for prophylaxis are crucial to reduce the likelihood of surgical site infection (SSI) after a clean contaminated cancer surgery. Our aim is to compare the use of two prophylactic antibiotic (PA) regimens as regards efficacy, timing, and cost.

Patients and methods: Two hundred patients with gastric, bladder, or colorectal cancer were randomized to receive preoperative PA, group A received penicillin G sodium and gentamicin and group B received clindamycin and amikacin intravenously. The demographic data of patients were collected, and they were observed for wound infections.

Results: Infected wounds occurred in 19 patients with a rate of 9.5%. Highest incidence of SSI was among bladder cancer patients (14.2%); $p = 0.044$. The rate of SSI was 11% in group A, and 8% in group B, $p = 0.469$. The cost of PA administered in group A was significantly less than that of group B (21.96 ± 3.22 LE versus 117.05 ± 12.74 LE, respectively; $p < 0.001$). SSI tended to be

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Peer review under responsibility of The National Cancer Institute, Cairo University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jnci.2012.12.001

Please cite this article in press as: El-Mahallawy HA et al. Comparing a combination of penicillin G and gentamicin to a combination of clindamycin and amikacin as prophylactic antibiotic regimens in prevention of clean contaminated wound infections in cancer surgery, J Egyptian Nat Cancer Inst (2013), http://dx.doi.org/10.1016/j.jnci.2012.12.001

higher among those who had longer time for antibiotic and incision (⩾30 min) than those who had shorter time interval (<30 min), (13% vs. 6.5%, respectively).
Conclusion: Both penicillin + gentamicin and clindamycin + amikacin are safe and effective for the prevention of SSI in clean contaminated operative procedures. In a resource limited hospital, a regimen including penicillin + gentamicin is a cost-effective alternative for the more expensive and broader coverage of clindamycin + amikacin. Timing of PA is effective in preventing SSIs when administered 30 min before the start of surgery.

Introduction

Surgical Site Infection (SSI) is one of the most important post-operative complications. Despite the advances in infection control practice, SSIs still cause substantial morbidity and mortality rates among hospitalized patients and contribute to increased hospitalization and increased consumption of resources and costs [1]. SSIs are the third most common health care associated infections (HAI) accounting for approximately 38% of infections in the surgical patient population [2].

For clean-contaminated and contaminated operative procedures, antibiotic prophylaxis is recommended. Colorectal surgery is the most thoroughly studied type of procedure in this category. The most commonly encountered organism in clean-contaminated and contaminated SSIs is still *Staphylococcus aureus*, though other aerobic as well as anaerobic bacteria are also detected, as such, prophylaxis should be broader than that used for clean cases [3]. Antibiotic prophylaxis in colorectal surgery revealed that the most efficacious regimens include coverage against both aerobic and anaerobic organisms (such as a 2nd or 3rd generation cephalosporin, or gentamicin in combination with metronidazole) [4]. Wound infections after cancer surgery may result in severe consequences, significant psychological trauma and delay in receiving adjuvant chemotherapy or radiotherapy [5]. These consequences make any attempt to reduce infection rate an important goal. In a limited resource country, using a cost effective PA regimen to prevent SSIs could be of economic value. Therefore, the aim of this study was to compare the use of two prophylactic antibiotic regimens in surgery as regards: efficacy, optimal timing, and cost. Defining the risk factors affecting the occurrence of wound infections will be also attempted.

Patients and methods

Patient selection

Adult patients admitted to the National Cancer Institute (NCI), Cairo University, for a clean contaminated surgical procedure to be operated upon by radical cystectomy, gastrostomy and colectomy ± rectal surgery in a single surgical unit were included in the study. These were legible for randomization. The study was a prospective randomized study approved by the Ethics Committee Board of the NCI, and written consents were obtained before enrollment in the study.

Prophylactic antibiotic regimen

Patients included in the present study were randomized into one of the two groups, group A or group B during the time period from March 2008 to September 2010. Group A included 100 patients who received IV penicillin G sodium (4,000,000 IU) and gentamicin 80 mg IV. An initial preoperative dose was given 20 min before the skin incision and another just before closure of the skin. In operative procedures lasting more than 2 h, an additional intra-operative dose is provided. Group B included 100 patients who received iv clindamycin 600 mg and amikacin 500 mg intravenously. An initial preoperative dose was given 20 min before the skin incision and another just before wound closure. In operative procedures lasting more than 2 h, an additional intra-operative dose is provided.

Evaluation of factors affecting SSI

A special case sheet was constructed for every patient to collect the demographic data, history, preoperative preparation, preoperative antibiotic received, and duration of operation, opened body cavity, spillage, post operative wound monitoring, late infection, and sub-diaphragmatic or pelvic collection. Routine laboratory investigations were performed during the preoperative period and included, complete blood picture, and fasting and post prandial blood sugar, and rigorous universal aseptic precautions were strictly fulfilled in the surgical theater. Before wound closure, surgical toilet was performed with sterile saline. Follow up of the wound was carried out until removal of stitches. Drains were observed for type and material of discharge. Catheters were also observed. In case of infection, the maintenance dose of antibiotic taken was continued with the same dosage and route till the infection subsided. SSI was defined according to the modified Centers for Disease Control and Prevention criteria. [6].

Statistical methods

Standard descriptive statistical methods were used to describe the patient data. Numeric data were summarized as mean ± standard deviation, categorical measurements and percentages. Pharmacoeconomic parameters were analyzed. The main end point was SSI. Comparison between two groups for numeric variables was done using the Mann–Whitney test, and the Kruskal–Wallis test for more than two groups. Comparison between categorical measurements was done using the Chi-square or Fisher exact tests, depending on sample size. Data were analyzed using Statistical Analysis Systems SPSS in statistical package version 12. All p-values were 2 sided and p-values <0.05 were considered significant.

Results

Patients' demographics

The present study is a randomized study comprising a consecutive sample of 200 patients recruited from a single unit in the Surgery Department of National Cancer Institute, Cairo, Egypt. The demographic data, type of operation, and rates of infection of patients randomized in groups A and B to receive different arms of prophylactic antibiotics are summarized in Table 1. The malignant disease, patients' clinical conditions, and surgical procedures undergone were comparable in both groups.

Rate and risk factors of SSI

Infected wounds occurred in 19 patients with a rate of 9.5%. The different risk factors of the groups A and B included in the study in relation to wound infection are shown in Table 2. The duration of operative procedure exceeded 2 h in 84% of the study group, (168/200) and was ⩽2 h in 32 (16%) cases. No adverse responses to the test antibiotics were observed.

Distribution of wound infection state in relation to time interval from antibiotic injection till incision is shown in Table 2. This relation was not statistically significant, though SSI tended to be lower in patients with time interval between PA and incision < 30 min.

Table 1 Demographic data, type of operation, and rates of infection of patients randomized in groups A and B to receive different arms of prophylactic antibiotics.

Parameter	Group A	Group B	Total	p Value
	N (%)	N (%)	N (%)	
Age				
⩽40	38 (38)	34 (34%)	72 (36)	0.96
> 40	62 (62)	66 (66%)	128(64)	
Sex				
Male	69 (69)	68(68)	137 (69)	0.88
Female	31(31)	32(32)	63(31)	
Smoking				
Yes	64(64)	56(56)	120(81)	0.25
No	36(36)	44(44)	80(40)	
Diabetes				
No	82(82)	80(80)	162 (81)	0.72
Yes	18(18)	20(20)	38 (19)	
Kidney function				
Normal	94(94)	94(94)	188(94)	1.00
Impaired	6(6)	6(6)	12(6)	
Liver function				
Normal	80(80)	88(88)	168(84)	0.12
Impaired	20(20)	12(12)	32(16)	
Site of cancer				
Bladder	60(60)	60(60)	120(60)	0.99
Stomach	7(7)	8(8)	15(7.5)	
Colon	20(20)	19(19)	39(19.5)	
Rectum	13(13)	13(13)	26(13)	
Surgery				
Radical Cystectomy	60(60)	60(60)	120(60)	0.99
Gastrectomy	7(7)	8(8)	15(7.5)	
Colectomy ± rectal surgery	33(33)	32(32)	55(27.5)	
Infected wounds				
Clean	89(89)	92 (92)	181(90.5)	0.47
Infected	11(11)	8 (8)	19(9.5)	

Table 2 Different risk factors in relation to wound infection in the 200 patients included in the study.

Parameter	Clean N = 181	Infected N = 19	Total	p-Value
	N (%)	N (%)	N (%)	
Age (years)	42.62 (7.79)*	53.68 (10.23)*		$p < 0.001$
Sex				
Male	123(90.0)	14(10.0)	137(68.5)	$p = 0.609$
Female	58(92.0)	5 (8.0)	63(31.5)	
Smoking				
No	111(92.5)	9(7.5)	120(60.0)	$p = 0.237$
Yes	70(87.5)	10 (12.5)	80(40.0)	
Diabetes				
No	154(95.5)	8(4.9)	162(81.0)	$p < 0.001$
Yes	27(71.1)	11(28.9)	38 (19.0)	
Site of cancer				
Bladder	103(85.8)	17(14.2)	120(60.0)	$p = 0.044$
Stomach	14(93.3)	1(6.7)	15(7.5)	
Colon	38(97.4)	1(2.6)	39(19.5)	
Rectum	26(100)	0(0.0)	26(13.0)	
Duration of surgery (hours)	3.24 ± 0.74*	3.74 ± 0.45*		$p < 0.001$
Time interval Antibiotic–incision				
< 30 min	101(93.5)	7(6.5)	108(54)	$p = 0.115$
⩾30 min	80(80)	12(13)	92(46)	

* Values are in mean ± standard deviation.

Causative organisms

Table 3 summarizes the organisms isolated from wounds of cases with SSI in groups A and B. No significant difference was reported between the results of both groups.

Costs

Fig. 1 illustrates the cost of the prophylactic antibiotic regimens used in groups A and B. The direct cost related to the prophylaxis of SSI was 21.96 ± 3.22 LE in Group A and was 117.05 ± 12.74 LE in Group B. The difference between the costs of both groups was statistically significant ($p < 0.001$).

Discussion

Prevention of SSI is an important component of surgical care improvement. Appropriate antibiotic selection and timing of administration for prophylaxis are crucial to reduce the likelihood of SSI after a clean contaminated cancer surgery [7]. Timing the administration of PA within 1 h of incision, using

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Table 3 Illustrates the organisms isolated from wounds of cases with SSI in group A and B.

Causative organism	Group A (N = 11)		Group B (N = 8)		Total (N = 19	
	N	%	N	%	N	%
Gram negative	3	27.3	2	25.0	5	26.3
Staphylococcus aureus	5 (3 MRSA)*	45.5	3	37.3	8	42.1
Streptococci	3	27.3	3	37.5	6	31.6

* Methicillin resistant *Staphylococcus aureus*.

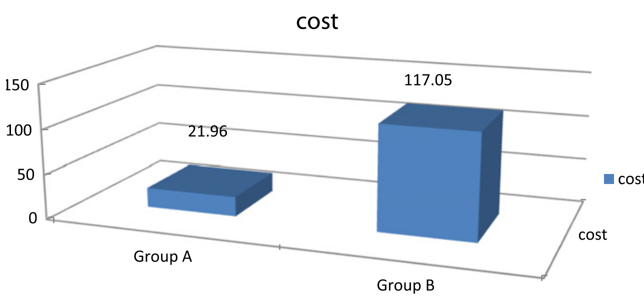

Figure 1 Cost of administered prophylactic antibiotic in both groups of the study (the cost of prophylactic antibiotics administered to patients in group A was significantly less than that of group B. The cost in group A was 21.96 ± 3.22 LE compared with 117.05 ± 12.74 LE in group B, $p < 0.001$).

improved regimens and discontinuing PA within 24 h are necessary elements for achieving surgical care improvement [8]. The present study comprised 200 patients undergoing a clean contaminated operation randomized into Group A receiving iv penicillin G sodium (4,000,000 IU) and gentamicin 80 mg, and Group B receiving iv clindamycin phosphate (600 mg) and amikacin 500 mg.

Of the 200 patients undergoing resection of an abdominal malignant disease in the current study, including bladder, gastric and colorectal cancer, SSI was demonstrated in 19 cases with a rate of 9.5%. The highest incidence of wound infection was among bladder cancer cases (14.2%); with a p value of 0.044. An individual subjected to a major operation is expected to carry a 2% risk of SSI. This rate is substantially higher if the individual undergoes cancer surgery, with a current rate of 5–30% for SSIs in colorectal operations [9]. The rate of SSI was 12.6% in a series of 605 patients undergoing colorectal procedures with anastomosis [7]. The rates of SSI after elective colorectal cancer remain high in spite of following the appropriate preventive measures; ranging from 11% to 26% [10]. Radical cystectomy was associated with a total rate of SSI of 18% [11]. Different rates of infection following cancer surgery could possibly be related to the operative setting, whether it is a general hospital or a specialized cancer center. Another factor might be the epidemiological characteristics of cancer distribution among different populations.

In the present study, SSIs were significantly higher in diabetics than non-diabetics, (28.9% vs. 4.9%, respectively, $p < 0.001$), in older patients (53 ± 10.23 years vs. 42.62 ± 7.79 years, respectively, $p < 0.001$), and in prolonged surgical procedures (3.74 ± 0.45 h vs. 3.24 ± 0.74 h respectively, $p < 0.001$). Risk factors for SSI including disease acuity, SENIC score, patient characteristics such as age, and length of stay were reported to contribute to inpatient morbidity and expense [12]. Duration of surgery was an independent significant risk factor for development of SSI in a randomized study in 275 patients undergoing elective surgery for colon cancer [13].

As regards the PA regimen used in the present study, there was no difference in the incidence of wound infection among the patients in group A who received iv penicillin + gentamicin, and in group B who received iv clindamycin + amikacin 500 mg (11% vs. 8%, respectively), $p = 0.469$. However, the cost of PA administered in group A was significantly less than that of group B (21.96 ± 3.22 LE versus 117.05 ± 12.74 LE, respectively; $p < 0.001$). This indicates that the scope of prophylaxis covered by penicillin + gentamicin is more or less similar to that covered by the more expensive antibiotics clindamycin + amikacin.

Practically, regimen of PA used could vary among surgeons. Some prefer combined administration of two antibiotics (poly-antimicrobial regimen), whereas some prefer administration of a single antibiotic or monotherapy [14]. Internationally, cephalosporins are the preferred group of drugs but several different regimens have been studied in an attempt to reduce SSI. Generally, a single shot administration of 1.5 g of cefuroxime (plus 500 mg of metronidazole in colorectal surgery) is one of the preferred regimens of PA in surgical procedures with an overall SSI rate of 4.7% [15]. The decision on recommendations for PA has to take many aspects into consideration, like tissue penetration, mechanism of antibacterial action, and half life in vivo. Other considerations of importance are impact on bacterial resistance in the hospital and the community, side effects, especially allergic reactions [12].

Nowadays, antibiotic prophylaxis administered 1 h before skin incision is a well established procedure for reducing SSI. Still, the relation between timing of administration and incidence of SSI is not well defined. In the present study, the incidence of wound infection was higher among those who had longer time between antibiotic and incision (⩾30 min) than those who had shorter time interval (<30 min), (13% vs. 6.5%, respectively). No statistical significance was calculated, perhaps due to low numbers of infected patients. Similarly, Ho et al, found that early administration of the initial prophylaxis dose in patients undergoing surgical procedures mostly for cancer, was associated with higher rates of SSI [7]. In agreement with our findings, it was recently concluded that PA is most effective in preventing post-surgical infections when administered before the start of surgery, as near the time of incision. [16]. In a prospective study on 3836 surgical procedures, the administration of PA 59–30 min prior to incision was more effective in reducing SSI than during the last half hour with a p-value <0.001 [15]. The difference between the former study and our findings could be due to cancer surgery

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taking longer time and thus requires a different timing than general surgical procedures.

Based on the findings of the present study, it could be advised in case of clean contaminated surgical wounds that surgeons adopt prophylactic antibiotics with induction of anesthesia, within 30 min interval from antibiotic injection till incision. Considering the disadvantaged economic status of our country, penicillin G + gentamicin iv constitute an option for prophylactic antibiotics in cancer surgery as it was as efficient as clindamycin + amikacin, in addition to having the advantage of lesser costs. Postoperative wound infection was more encountered in older age and diabetic patients and with prolonged duration of operation. Incidence of wound infection is dependent on the anatomical site of surgery, the highest being associated with mainly bladder. Thus, more expensive regimens could be used in patients with more risk to develop SSI, while cheaper penicillin G + gentamicin combination could be used in less risky cases.

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