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Pharmacology Section

Original Article

Prophylactic Antibiotics and Wound Infection

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ABSTRACT

Introduction: Surgical site infections account for 14%-25% of all nosocomial infections. The main aims of this study were to audit the use of prophylactic antibiotic, to quantify the rate of post-operative wound infection, and to identify risk factors for its occurrence in general surgery.

Methodology: A cross-sectional study was conducted in the General Surgery Department in Khartoum Teaching Hospital–Sudan. All Adult patients (age $\geq$18 years) admitted during March 1st to 31st October 2010 were recruited. Multivariable logistic analysis was done to identify wound infection risk factors. Prescriptions were audited against predetermined criteria.

Results: A total of 540 patients were recruited; (females73.7% of total). The performed surgical procedures were 547. The rate of wound infection was 10.9%. Multivariable logistic analysis showed that; ASA score $\geq$ 3; (p= <0.001), wound class (p= 0.001), and laparoscopic surgical technique; (p= 0.002) were significantly associated with prevalence of wound infection. Surgical prophylaxis was unnecessarily given to 311 (97.5%) of 319 patients for whom it was not recommended. Prophylaxis was recommended for 221 patients; of them 218 (98.6 %) were given preoperative dose in the operating rooms. Evaluation of prescriptions for those patients showed that; spectrum of antibiotic was adequate for 160 (73.4%) patients, 143 (65.6%) were given accurate doses, only 4 (1.8%) had the first preoperative dose/s in proper time window, and for 186 (85.3%) of them prophylaxis was extended post-operatively. Only 36 (6.7%) prescriptions were found to be complying with the stated criteria.

Conclusion: The rate of wound infection was high and prophylactic antibiotics were irrationally used. Multiple interventions are needed to correct the situation.

Keywords: Prophylactic antibiotics, Wound infection, Sudan

INTRODUCTION

Surgical site infections (SSIs) account for 14%-25% of the total hospital acquired infections [1]. Despite advances in technology that have been made; wound infection is still a problem in the field of surgery [2]. The most important risk factors for infection are the general health of the patients and the level of bacterial contamination associated with the specific operative procedure [3].

Antibiotic prophylaxis as an intervention is effective in reducing the risk of wound infection for all types of surgery [4]. It is indicated for all clean–contaminated procedures [5]. The use of prophylaxis in clean procedures that do not involve insertion of implants is controversial because the associated risk is quite low [6].

Critical aspects of prophylaxis antibiotics administration are: giving an appropriate antibiotic, giving adequate dose, achieving proper timing before incision, and maintaining drug level throughout the operation [7]. There is no benefit from antibiotic prophylaxis after wound closure and most studies conducted to compare single–dose versus multiple–dose regimens revealed no benefit of the multiple doses [8]. Prolonged use of prophylactic antimicrobials has been associated with the emergence of resistant bacterial strains [9] and predisposing the patient to infection [10].

The main aims of this study were to audit the use of prophylactic antibiotic, to quantify the rate of post-operative wound infection, and to identify risk factors for its occurrence in general surgery.

MATERIAL AND METHODD

Setting and study design

A Prospective cross-sectional study was conducted in the General Surgery Department, Khartoum Teaching Hospital, Sudan.

Patients

All adult patients (age $\geq$18 years) admitted for elective clean and clean-contaminated procedures during March 1st to 31st October 2010 were recruited consecutively. Exclusion criteria were: use of antibiotic/s for non-prophylactic purpose 48 hours before surgery, principal diagnosis suggestive of a preoperative infectious disease, procedure involving the insertion of an implant, surgical procedure that did not involve incision, patient already recruited in the study and scheduled again for another surgery during the study period, patient refused to participate in the study, and patient that did not complete the follow up period.

Data collection

Data was collected by trained nurses using a pre-coded questionnaire; which was developed by the research team and tested among 25 patients for applicability. Demographic data was obtained directly from the patients, intra-operative data was collected on observational-base, and data on post-operatively prescribed antibiotics was extracted from the patient's hospital file. The recorded variables included: gender; age in year; dates of admission, surgery and discharge; body mass index; and presence of co-morbidities. The American Society of Anesthesiologists score (ASA score) [11]; type, name, category, and duration of operation; and wound class were also documented. A section in the questionnaire was designed to collect data on wound infection (occurrence, and clinical signs). For patients who received prophylactic antibiotic/s in the operating room, the following parameters were registered: antibiotic's generic name, timing of first preoperative dose, and dose strength. Antibiotic's generic names, doses, in addition to duration of prophylaxis were registered for patients who were given antibiotics post-operatively.

Wound Infection Surveillance

Wound infection was detected by two methods: bedside and post-discharge surveillance. Bedside surveillance involved following the patient during hospital admission and started from the day after surgery until the patient was discharged. Post-discharge surveillance was conducted by telephoning the patient for up to four telephone calls (on day 7th, 14th, and 21th, and 28th day of the operation). A trained nurse administered to the patient structured questions about the presence of any sign /s of wound infection. Patients who returned to the hospital after reporting any sign/s of wound infection; confirmation of the diagnosis of wound infection was done in collaboration with the unit that performed the procedure. For patients who did not return back to the hospital, signs of wound infection were recorded as disclosed by the patient during the interview. Wound infection diagnosis was based on the criteria of the Centre of Disease Control [12].

Antibiotics Utilization Review

Antibiotics utilization review was done by assessing antimicrobial prescriptions against the guidelines published by the Scottish Intercollegiate Guidelines Network (SIGN)[13].The prescriptions' parameters were assessed against the following criteria.

- Indication for prophylaxis was categorized as recommended or not recommended based on SIGN recommendations.
- Choice of antibiotic which was categorized with respect to spectrum of coverage and bacteria most likely to be encountered at the specific surgical site (narrow / did not cover the range of bacteria anticipated, adequate / covered the bacteria anticipated, and broad or unnecessary combination / covered bacteria more than anticipated at the surgical site)[5].
- Time of administration of the first preoperative dose /s (too early / if given more than one hour before incision was made, proper / if given within 30-60 minutes before incision [14], late / if given between 0-29 minutes before incision, and too late / if given after incision was made).
- Accuracy of the first preoperative dose/s was/were based on dose/s used for surgical prophylaxis purposes in clinical trials for each antibiotic/s.
- Duration of prophylaxis (Appropriate / if given as one preoperative dose and inappropriate / if extended post-operatively), [13].

If more than one drug were prescribed for a single operation, all parameters for each drug were evaluated separately. If an antibiotic was given while it was not indicated, the parameters were not evaluated. Finally, a prescription was considered concordant if it satisfied the above mentioned criteria for all drugs prescribed. If there was any divergence from the above stated criteria for one or all drugs the prescription was considered as discordant. If data on a certain parameter of antibiotic prescription was lacking, this was classified as missing data on this parameter only. For patients who developed wound infection during admission only the antibiotic prescribed before onset of infection was registered. This was done in order to differentiate between prophylactic and treatment courses.

The study was approved by the National Health Research Ethics Committee, National Ministry of Health –Sudan.

Potential Predictors of Wound Infection

Potential predictors for wound infection included gender, patient's age in years, patient's body mass index, presence of other disease/s, diabetes, ASA score, type of surgical technique, and wound classification.

Data Analysis

Frequencies and proportions/percentages were used to describe categorical variables and means and standard deviations were used to describe continuous variables. To identify factors associated with occurrence of post-operative wound infection; the analysis aimed to develop a multivariable model to allow prediction of wound infection in the presence of potential predictors or covariates. Crude logistic regression analyses were performed as initial steps of qualifying covariates to be included in the multivariable logistic regression analyses. Covariates with p-values <= 0.25 were included to develop an initial reduced model. Multicollinearity among the covariates was assessed using variance inflation factors. Variables that tested insignificant (with p-values > 0.05) were then eliminated from this model and interactions were tested. Each variable was sequentially removed at a time and its significance was tested. Likelihood ratio of tests which were used to compare models and Hosmer and Lemeshow test was used to assess goodness of fit of the final model. All statistical tests were conducted by using Stata version 12.

RESULTS

Patients and Procedures Characteristics

One thousand and twenty three patients were scheduled for surgery, of them 682 were eligible (age ≥18 years). Of the included patients 540 (79.2%) successfully completed the follow up period. The patients lost for follow up were 137 (20.1%) and 5 (0.7%) died. Of the patients completed the follow up period; females were 398 (73.7%). Clean procedures were done for 373 (69.1%) patients. [Table/Fig-1] shows patients' demographic characteristics. The total numbers of the performed surgical procedures was 547. Multiple procedures done through the same incision were performed for 7 (1.3%) patients. Neck surgeries performed for 157 (42%) patients and open cholecystectomies for 98 (56.6%). [Table/Fig-2] shows the distribution of the performed clean and clean-contaminated procedures.

Rate of Wound Infection

Out of the total patients included in the study 59 (10.9%) had wound infection. The rate of post-operative wound infection was 8.9% and 15.4% for clean and clean-contaminated procedures respectively. The signs of wound infections were detected during hospital stay for 5(8.5%) patients. Wound infection was recognized during the post-discharge period for 54 (91.5%) patients; for 32 (59.3%) of them wound infection was confirmed by the surgical units that performed the procedures when they returned back to the hospital and 22 (40.7%) reported the signs of infection through telephone contacts.

Wound Infection Risk Factors

Univariate logistic regression analysis found three variables to be significantly associated with the prevalence of wound infection; ASA score (p= 0.001), laparoscopic technique (p= 0.029), and wound classification (p=0.017). Multivariable logistic analysis concluded that; ASA score ≥ 3; {adjusted OR=4.4, 95% CI (2.2-8.8), p = <0.001}, wound class {adjusted OR =5.5; 95% CI (2.0-14.8); p= 0.001}, laparoscopic surgical technique; {adjusted OR= 4.8 95% CI (1.7-13.3); p= 0.002} were significantly associated with prevalence of wound infection. [Table/Fig-3] shows the risk factors for wound infection.

Use of Antibiotics for Prophylaxis

Prophylactic antibiotic was administered for 529 (98%) patients in the operating rooms, of them 503 (95%) were given cefuroxime, 23(4.3%) had ceftriaxone, 2 (0.4%) received co-amoxiclav, and 2(0.4%) administered ceftizoxime. Metronidazole was given alone or combined with others antibiotics for 15 (2.8%) patients.

Based on the stated criteria, antibiotic prophylaxis was not recommended for 319 (59.1%) patients but it was unnecessarily given for 311 (97.5%) of them. However; for 221 (40.9%) patients it was recommended; of these 218 (98.6 %) were given the first preoperative dose in the operating rooms.

Background characteristics	(n)	Percentage
Gender		
Male	142	26.3
Female	398	73.7
Age (years)		
<30	117	21.7
30 to <40	127	23.5
40 to <50	134	24.8
>=50	162	30.0
Body mass index (Kg/m²)		
<20	79	14.6
20 to <25	245	45.4
25 to <30	156	28.9
>=30	60	11.1
Co-morbidity		
Yes	90	16.7
No	450	83.3
Diabetes		
Yes	36	6.7
No	504	93.3
ASA score		
1	390	72.2
2	92	17.0
3+	58 (10.8%)	
Surgical Technique		
Conventional	520	96.3
Laparoscopic	20	3.7
Wound classification		
Clean	373	69.1
Clean contaminated	167	30.9
Duration of operation in hours		
<1	216	40.0
≥1	324	60.0
Total	540	100

[Table/Fig-1]: Patients and Procedures characteristics

Clean	(n)	%	Clean- contaminated	(n)	%
Neck surgery	157	42.0	Open Cholecystectomy	98	56.6
Mastectomy	97	25.9	Laparoscopic Cholecystectomy	20	11.6
Hernia repair	74	19.8	Laprotomy	18	10.4
Thoracic surgery	9	2.4	Appendectomy	10	5.8
Vascular surgery	8	2.1	Gastric surgery	8	4.6
Hydrocelectomy	6	1.6	Splenectomy	7	4.0
Varicocelectomy	4	1.1	Colon surgery	5	3.0
Others	19	5.1	Small bowel surgery	4	2.3
			Oesophageal surgery	3	1.7
Total	374	100	Total	173	100

[Table/Fig-2]: The performed clean and clean-contaminated surgical procedures

Out of the patients for whom prophylaxis was recommended and given; the spectrum of antibiotic/s given was/were adequate for 160 (73.4%) patients. Accurate doses were given for 143 (65.6%) patients. The first preoperative dose/s was/were given in the proper time window for only 4 (1.8%) patients. Prophylaxis duration was extended for 186 (85.3%) patients. [Table/Fig-4] shows the evaluation of prescription's parameters against the predetermined criteria. Overall; only 36 (6.7%) were found to be concordant with all stated criteria.

	Univariable analysis		Multivariable analysis	
Covariates	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Gender		0.423		
Male	1.0			
Female	1.3 (0.7-2.5)			
Age (years)		0.401		
<30	1.0			
30 to <40	1.3 (0.6-3.1)			
40 to <50	1.1 (0.4-2.5)			
>=50	1.8 (0.8-3.9)			
Body mass index (kg/ m2)		0.075		
<20	1.0			
20 to <25	0.6 (0.3-1.4)			
25 to <30	1.3 (0.6-2.9)			
>=30	1.6 (0.6-4.1)			
Co-morbidity		0.257		
Yes	1.0			
No	0.7 (0.3-1.3)			
Diabetes		0.282		
Yes	1.0			
No	0.6 (0.2-1.5)			
ASA score		0.001		
1	1.0		1.0	
2	1.7 (0.8-3.4)		1.7 (0.8-3.5)	0.151
3+	3.9 (2.0-7.8)		4.4 (2.2.8.8)	<0.001
Technique		0.029		
Conventional	1.0		1.0	
Laparoscopic	1.9 (1.1-3.2)		4.8 (1.7-13.3)	0.002
Classification		0.017		
Clean	1.0		1.0	
Clean contaminated	3.8 (1.4-10.2)		5.5 (2.0-14.8)	0.001

[Table/Fig-3]: Risk Factors for Wound Infection

Parameter	Frequency (n)	Percentage
Choice of antibiotic:		
Narrow	31	14.2
Adequate	160	73.4
Broad	27	12.4
Dose		
Accurate	143	65.6
Sub-dose	72	33.0
Missing	3	1.4
Timing		
Proper	4	1.8
Late	183	84.0
Too late	29	13.3
Missing	2	0.9
Duration of prophylaxis:		
Single dose	32	14.7
Extended duration	186	85.3
Total	218	100

[Table/Fig-4]: Evaluation of the prescription's parameters

DISCUSSION

The audit of antibiotics prescribed for surgical prophylaxis in the current study revealed misuse of these agents. The indiscriminate use of antibiotics was observed in its administration for nearly all clean surgeries. In clean surgical interventions like breast cancer surgeries; antibiotic prophylaxis should be considered [13]. However; for other clean neck surgeries and hernia repair it is not recommended due to the low incidence of wound infection [15]. In

Brazil Fonseca and Contemnor reported that 26% of patients were unnecessarily given antibiotics for surgical prophylaxis [16].

For surgical prophylactic purposes international guidelines advocate the use of narrow spectrum antibiotic, namely Cefazolin [5,14]. Cefazolin is generally viewed as the first choice in clean operations and it provides adequate coverage for many clean-contaminated operations as well. However, for distal intestinal tract operations, second generation cephalosporins with anaerobic coverage are recommended [14]. The results of the present study showed that the majority of patients were given cefuroxime as prophylactic agent. Cefuroxime is less active against *staphylococci* compared to first generation cephalosporin [17]. This point is of utmost importance as *staphylococci* are the main organisms responsible for post-operative infections after elective surgery [18].

In the current study only 2% of the patients were given the first pre-operative dose/s in the proper time window period. Inappropriate timing of administration of first preoperative doses in the determined time window was mainly attributed to the unawareness of the responsible staff with the optimization of this parameter and the role it has in infection prevention. Weber et al., reported that when cefuroxime was used as prophylactic antibiotic; administration during 59-30 minutes before incision was associated with low rate of infection than administration during the last half hour [19].

For the majority of patients the duration of prophylaxis was extended post-operatively. In general, single-dose prophylaxis or prophylaxis ending within 24 hours after operation is recommended by some guidelines [8, 20]. However; SIGN recommended the use of a single dose of antibiotic with a long half-life. Prolongation of antibiotic prophylaxis for more than 24 hours was found to be an independent risk factor for the development of SSI [21]. In addition; administration of broad spectrum antibiotics suppresses the normal flora of patients and makes it easier for susceptible patients to be colonized or infected by drug-resistant organisms in the hospital [22].

The second objective of this study was to quantify the rate of post-operative wound infection in elective clean and clean-contaminated procedures. The overall rate of post-operative wound infection was found to be 10.9%. It was 8.9% and 15.4% post clean and clean-contaminated procedures respectively. In both wound classes the rate was high when compared with those quoted in the literature; as it was less than 3% [23] for the former and <10% for the latter [24]. In contrast Soleto et al*.,* reported infection rate of 6.9% and 13.7% for clean and clean-contaminated procedures respectively [25].

Logistic regression analysis identified ASA score $\pm$ 3 and wound class as important independent predictors of wound infection. In another study; both risk factors were also found to be significantly associated with SSI [26].

The increased rate of wound infection reported in this study may be attributed to the high number of surgical interventions performed each day which may affect appropriate patient assessment and preoperative preparation. The excessive use of broad spectrum antibiotics and improper optimization of the timing of the first preoperative prophylactic dose may also be contributory factors.

LIMITATION

This study had some limitations; some patients may fail to identify minor signs of wound infection when interviewed through telephone contact. In some cases the post-operatively prescribed antibiotics may not be documented in patients' hospital files or discharge cards so this information may not be available for registration. The time window period 30-60 minute before surgical incision was considered proper for all prophylactic agents despite the difference in pharmacodynamic and pharmacokinetics characteristics of the administered antibiotics.

CONCLUSION

Low compliance with international norms in the use of antibiotics for surgical prophylaxis and a high rate of post-operative wound infection were documented in this study.

RECOMMENDATIONS

The results call for multiple interventions to correct the situation. The urgent action to be taken is the activation of the infection control committee in the hospital and the formulation of antimicrobial subcommittee to develop guidelines and to audit the use of anti-microbials in surgery.

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