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Original Research

Double blind randomized controlled trial for subjects undergoing surgery receiving surgical antimicrobial prophylaxis at tertiary hospital: the clinical pharmacist's interventions

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Abstract

Background: A surgical site infection (SSI) has significant clinical, humanistic and economic consequences. Surgical antimicrobials prophylaxis (SAP) is a reliable standard to prevent SSIs. **Objective:** The objective was to test that the clinical pharmacist's interventions may facilitate the implementation of SAP protocol and subsequent reduction of SSIs. **Methods:** This was double blinded randomized controlled interventional hospital-based-study at Khartoum State-Sudan. A total of 226 subjects underwent general surgeries at four surgical units. Subjects were randomized to interventions and controls in a (1:1) ratio where patient, assessors and physician were blinded. The surgical team has received structured educational and behavioral SAP protocol mini courses by way of directed lecturers, workshops, seminars and awareness campaigns delivered by the clinical pharmacist. The clinical pharmacist provided SAP protocol to the interventions group. The outcome measure was the primary reduction in SSIs. **Results:** There were (51.8%, 117/226) females, (61/113 interventions versus 56/113 controls), and (48.2%, 109/226) males (52 interventions and 57 controls). The overall rate of SSIs was assessed during 14 days post-operatively and was documented in (35.4%, 80/226). The difference in adherence to locally developed SAP protocol regarding the recommended antimicrobial was significant (P <0.001) between the interventions group (78, 69%) and the controls group (59, 52.2%). The clinical pharmacist's implementation of the SAP protocol revealed significant differences in SSIs with reduction in SSIs from 42.5% to 25.7% versus the controls group from 57.5% to 44.2% respectively, P = 0.001 between the interventions group and the controls group respectively. **Conclusion:** The clinical pharmacist's interventions were very effective in sustainable adherence to SAP protocol and subsequent reduction in SSIs within the interventions group.

Keywords: adherence; clinical pharmacist; randomized clinical trial; surgical antimicrobials prophylaxis (SAP); surgical site infections (SSIs)

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INTRODUCTION

The clinical outcomes of surgical site infections (SSIs) included: hospital acquired infection, poor scars, persistent pain, itching, restriction of movement, significant impact on emotional, mental and physical wellbeing, reduced patients' quality of life, increased length of hospital stay, increased direct/indirect costs of health care and increased morbidity and death.[1]

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Surgical site infections (SSIs) are a common post-operative complication, and are the third most commonly reported nosocomial infection. The use of surgical antimicrobials prophylaxis (SAP) protocol for surgical procedures is one of the measures deployed to prevent the development of SSIs.[2] The Center for Disease Control and Prevention (CDC), estimates that approximately 500,000 SSIs occur annually in the United States of America (USA). SSI is the second leading cause of hospital acquired infections,[2] and second most common nosocomial infection.[3] The use of SAP for surgical subjects is associated with medication errors in hospitals.[4] The CDC has established a surgical wound classification system (class I. clean; class II. clean/contaminated; class III. contaminated; and class IV. dirty) to proactively identify patients at risk of SSI.[5] A multicenter, national retrospective cohort study, reported that increasing duration of SAP was associated with higher odds of acute kidney injury (AKI) and Clostridium difficile infection and extending the duration of SAP has no additional SSI reduction.[6]

The Surgical Care Improvement Project (SCIP) includes standards that are nationally reported with the aim of improving patient outcomes after surgery.[7] The 4 elements of appropriate SAP protocol are timing, antimicrobial selection, dosing, and intraoperative re-dosing. Effective use of SAP also requires monitoring of and feedback on patterns of used programs. In order to improve SAP, it should be multidisciplinary and should aim to improve the use of antimicrobials, not simply to change physician practice patterns, and should have primary care physicians participate in the pre and postoperative care of patients, as they should be familiar with the SCIP recommendations.[8,9] A cross-sectional study conducted in Ethiopian hospital surgical wards revealed that the incidence rate of SSIs was 11.1%,[10] while it was 16.4% in Ugandan's study.[11]

The rationale of the current trial

The lack of existing SAP protocols is imposing enormous challenges for the management of SSIs in the local hospitals at Sudan. Further, there were no randomized trials in Sudan that addressed SAP protocols implementation, monitoring and follow-up. In addition to absence of the clinical pharmacist's interventions to improve the antimicrobial clinical practice and adherence to any existing SAP protocols. The rationale of the current study was to examine the clinical pharmacist's interventions on the use of SAP protocol and their effectiveness in minimizing the SSIs, and highlight any obstacles to their implementation.

OBJECTIVE

The objective of the current study was to test the hypothesis that the clinical pharmacist's interventions may facilitate the implementation of SAP protocol and subsequent reduction of SSIs.

Ethics approval

The current study was approved by the local hospital institute research review board (IRB) of the study hospital site in Khartoum State-Sudan [IRB082017].

METHODS

This was a double blinded randomized controlled interventional hospital-based-study. The study setting was general surgical units at a tertiary hospital in Khartoum State-Sudan. We have followed 226 subjects who underwent both clean and clean contaminated general surgery, namely: hernia repair, thyroidectomy, appendectomy and cholecystectomy at the hospital's four surgical units. We have provided enrolled subjects with information sheet about the trial and have taken informed consent from the consented subjects prior to randomization.

Inclusion and exclusion criteria

Subjects of both genders above 18 years and less than 65 years undergoing elective surgery were suitable for study inclusion. The following subjects were excluded: those with malignant disease, subjects undergoing long-term antimicrobial therapy, pregnant and lactating women and immune-compromised subjects. The current study data variables follow normal distribution. We have used 80% confidence level (80% actual mean falls within our confidence interval), 0.5 standard deviation (the expected variance), margin of error (confidence interval) of ± 5% (much higher or lower than the population mean to let our sample mean falls); and two tailed statistical significances.

80%-Z score= 1.282, $(1.282)^2$ X 0.5(0.5) / $(0.05)^2$, (1.643 X 0.25) / 0.0025 = 164. Therefore, we need 164 to detect a 20% difference in the development of SSIs (outcome variable is dichotomous) between the interventions group and the controls group. To detect a 20-point difference at a P value of <0.05, and a power of 80%, it was calculated that a total of 82 interventions group and 82 controls group were required. During the study a 20% over-recruitment was sought to allow for any drop-outs. Therefore, the sample size was inflated to 226 to account for any subject missed data, dropouts and/or withdrawals. We have prospectively randomized the eligible selected candidates who have fulfilled the inclusion criteria by concealment randomization technique into two closely matched groups (type of surgery, age, gender, and BMI), namely; an interventions group and controls group which involved 113 subjects each (all underwent one of the four-mentioned surgical procedures).

The current trial was powered based on a target of minimum 210 subjects to account for possible dropouts and missing data, randomized equally as interventions and controls groups. Post recruitment, subjects were randomized into two groups: interventions or controls groups in the ratio of 1:1 using published restricted randomization and validated procedure.[12,13] The participants and the surgical team educated with the protocol were both blinded to the assigned groups. In order to prevent selection bias, we have incorporated a concealment method by concealing the allocation sequence

(adequate generation of allocation sequence) from those assigning participants to the interventions group until the time of assignment (concealment of the allocation sequence) to further avoid researcher bias (assessor bias). We have adjusted for confounders by matching baseline group imbalances for age, Body Mass Index (BMI), surgery type, and comorbidities. Both interventions and controls groups were matched as closely as possible, for baseline characteristics. We have adjusted and controlled both groups for diabetes as it poses significant risk factor for SSI and might introduce considerable bias to the results. We have educated the surgical team against the risk of contamination and empower them provision of clear information about the purposes of the study (contamination due to health professionals with training managing both interventions and controls groups).

The role of the clinical pharmacist in the delivery of SAP protocol

The clinical pharmacist developed the SAP protocol in collaboration with the surgical team and provided surgical antimicrobial stewardship services (pursued of strict protocol) to the interventions group while the controls have received the traditional usual services without any support by the clinical pharmacist for the strict protocol [Figure 1]. The surgical team (assessors) had received the locally developed SAP protocol and were all blinded to the interventions and controls group assignment. We have set up a variety of different procedures to enable continued blinding of healthcare professionals. For instance, the surgical team who has received the SAP protocol were accompanied by the clinical pharmacist when they prescribe the antimicrobial to the interventions group to ensure strict adherence to the SAP protocol. The surgical team was blinded for the allocated interventions and controls groups but not for the SAP management. Subjects were also blinded for the group assignment. The study was commenced on a real-time basis and was implemented, monitored and sustained by the main investigators including the clinical pharmacist. The selected surgical team has received structured educational and behavioral SAP mini courses by way of directed lecturers, workshops, seminars and awareness campaigns delivered by the clinical pharmacist. The clinical pharmacist provided antimicrobial stewardship services to represented members of the surgical team (assigned and consented for the study) involved in the SAP protocol. Furthermore, the clinical pharmacist provided surgical antimicrobial stewardship services (adherence to the strict protocol) to the interventions group while the controls have received the traditional usual services without the pursued of adherence to the strict protocol. The clinical pharmacist ensured that the interventions group has received the developed protocol for SAP. The clinical pharmacist continued the care plan with the interventions group and further followed up the selected administered antibiotics timing, duration and doses was as per the developed protocol. The data collected and the main outcome (SSI) was reported by the blinded assessors from the surgical team (consented, educated, trained, and assigned by the study researchers). The clinical pharmacist was not involved in the collection neither in the reported clinical data for participants.

An example of the clinical pharmacist's SAP protocol (educational and behavioral interventions) detailing the delivered protocol to improve the uptake of the protocol, and the subsequent reduction in SSIs and improved subject's clinical outcomes was shown as an Appendix 1 and Appendix 2.

Operational definitions

SSIs: are wound site infections that develop within 30 days after surgery.

SAP: refers to the use of antibiotics for the prevention of SSIs and does not include preoperative decolonization or treatment of established infections.

Traditional care services: defined as usual care without further SAP protocol adherence, monitoring, and follow up of respective guidelines implementation for infection control including SSIs preventive measures.

Main outcome measure

The main outcome measure was the reduction in the SSIs within the interventions group (reported as differences in reducing SSIs between the interventions group and the controls group).

Statistical analysis

We have used Soft Package for Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) for data analysis. The Pearson Chi squared (Chiχ2) test was used to analyze the categorical variables. The difference between interventions and control groups (matched prior to randomization) for the SSI events was analyzed with a student t-test (data was normally distributed). A significant difference was considered at $P < 0.05$ (2-tailed test).

RESULTS

We followed 226 subjects (with no dropouts), who were operated for clean and clean contaminated surgeries (hernia repair, thyroidectomy, appendectomy, and cholecystectomy). The mean age of the population was 45.5 ±2.3 years, depicted as 47 ±2.4 and 47 ±3.3 for the interventions and controls groups, respectively. There were (51.5%, 117/226) females distributed as 61 interventions versus 56 controls, and (48.0%, 109/226) males distributed as 52 interventions group and 57 controls group. There was slight preponderance of the female gender, 54% in the controls group versus 49.6% in the interventions group. Furthermore, the two study groups reported predominance of normal weight (BMI: 18.5-25.0 kg/m2), depicted as 86.7% in interventions and 89.4% in controls, respectively. There were (30.1%, 68/226) subjects who were current smokers. Slightly over half of the study population was living in urban areas (54.9%, 124/226), as opposed to rural areas (102/226, 45.1%); [Table 1]. Patients who had diabetes were (18.6%, 42/226), hypertension (16.8%, 38/226), asthma (6.2%, 14/226), heart failure (3.5%, 8/226), acute coronary syndrome (2.2%, 5/226), and chronic kidney disease (CKD) (1.8%, 4/226).

Table 1. Demographics and socio-demographics characteristics of the study population (interventions versus controls)

Parameter		Interventions group	Controls group	Total
		F, (%)	F, (%)	F, (%)
Age (years)	18- 29	26 (23.0)	35 (30.9)	61 (27.0)
	30-60	51 (45.1)	56 (49.6)	117 (51.8)
	<60	36 (31.9)	22 (19.5)	48 (21.2)
Gender	female	61 (54.0)	56 (49.6)	117 (51.7)
	male	52 (46.0)	57 (50.4)	109 (48.3)
BMI (Kg/m²)	>18.5	11 (9.7)	10 (8.8)	21 (9.3)
	18.5-25	98 (86.7)	101 (89.4)	199 (88.1)
	26-29	4 (3.5)	2 (1.8)	6 (2.6)
	<30	0 (0.0)	0 (0.0)	0 (0.0)
Residence	rural	51 (45.9)	51 (45.9)	102 (45.1)
	urban	62 (54.9)	62 (54.9)	124 (54.9)
Socio-economic Status	Low	77 (68.1)	68 (60.2)	145 (64.2)
	medium	36 (31.9)	45 (39.8)	81 (35.8)
Smoking status	Yes	27 (24.0)	41 (36.3)	68 (30.1)
	No	86 (76.1)	72 (63.7)	158 (69.9)
Alcohol consumption	Yes	2 (1.8)	4 (4.5)	6 (2.7)
	No	111 (98.2)	109 (96.5)	220 (97.3)
Comorbidities	Angina	3 (2.7)	2 (1.8)	5 (2.2)
	Asthma	8 (7.1)	6 (5.3)	14 (6.1)
	HF	4 (3.5)	4 (3.5)	8 (3.5)
	CKD	2 (1.8)	2 (1.8)	4 (1.8)
	Hypertension	18 (15.9)	20 (17.7)	38 (16.8)
	Diabetes	23 (20.4)	19 (16.8)	42 (18.6)
	subtotal	58 (51.5)	53 (46.9)	111 (49.1)
Total (at each subtotal column)		**(50.0) 113**	**(50.0) 113**	**(100.0) 226**

Key: F= frequency, (%) = percent; BMI: Body mass index; HF: heart failure; CKD; chronic kidney disease

A total of (5.3%, 12/226) have had previous operations and (30.5%, 69/226) were currently on chronic medication. The most frequently used medications were: anti-diabetics (18.6%, 42/226), angiotensin converting enzyme (ACE) inhibitors (11.5%, 26/226), aspirin (4.4%, 10/226), calcium channel blockers (4.0%, 9/226), corticosteroids (4.0%, 9/226), diuretics (2.7%, 6/226), β- (beta) blockers (2.2%, 5/226), and short acting beta agonist (1.8%, 4/226).

SAP adherence, selection and appropriateness

The adherence of general surgeons to the SAP protocol in major aspects of surgical prophylaxis was assessed by evaluating three major criteria; (type of antimicrobial selected, time and duration of its usage). The difference in the overall rate of adherence to the developed SAP protocol was significant between the interventions group (56.7%) and the controls group (43.6%) respectively (P < 0.001). Adherence to the three mentioned criteria was significant between the interventions group and the controls group. The difference in the adherence to the locally developed SAP protocol regarding the recommended antimicrobial (first generation cephalosporin [cefazolin]) and the SAP appropriateness was significant (P <0.001) between the interventions group (69.0%, 78/113) and the controls group (52.2%, 59/113). The SAP was prescribed at the time of anesthesia induction or at one hour before operation and was appropriately prescribed and administered to 77.0% of the interventions group versus 66.4% of the controls group (P <0.001). The recommended duration of SAP (single and multiple post-operative doses less than 24 hours) was reported in 62.8% interventions versus 44.2% controls (P <0.001); [Table 2].

The distribution of subjects according to the type of surgery involved: (35.4%, 80/226) hernia (interventions [34.5%, 39/113] versus controls [36.3%, 41/113]), (28.3%, 64/226) cholecystectomy (interventions [26.5%, 30/113] versus controls [30.1%, 34/113]), (26.5%, 60/226) appendectomy (interventions [29.2%, 33/113] versus controls [23.9%, 27/113]), and (9.7%, 22/226) thyroidectomy (interventions [4.9%, 11/113] versus controls [4.9%, 11/113]) [Table 3].

Table 2. The distribution of study groups based on adherence and non-adherence with surgical antimicrobial prophylaxis (SAP) selection, dosing time, and duration in interventions group and controls group

	Controls group F [%]	Interventions group F [%]	Total F [%]	*P* value
	Antimicrobial selection, F (%)			
Adhered to SAP protocol	78 (69.0)	59 (52.2)	137 (60.4)	< 0.0001
Not adhered to SAP protocol	35 (31.0)	54 (47.8)	89 (39.6)	
Total	(50.0) 113	(50.0) 113	(100.0) 226	
	Antimicrobial dosing timing, F (%)			
Adhered to SAP protocol	87 (77.0)	75 (66.4)	162 (71.7)	< 0.0001
Not adhered to SAP protocol	26 (23.0)	38 (33.6)	64 (28.3)	
Total	(50.0) 113	(50.0) 113	(100.0) 226	
	Antimicrobial duration of use F, (%)			
Adhered to SAP protocol	71 (62.8)	46 (44.2)	117 (51.8)	< 0.0001
Not adhered to SAP protocol	42 (37.2)	67 (55.8)	109 (48.2)	
Total	(50.0) 113	(50.0) 113	(100.0) 226	

Key: F: Frequency; **P*-value: < 0.05 significant; (%): percent; SAP: surgical antimicrobial prophylaxis

Timing and duration of SAP

The adherence to the dosing time of SAP was appropriate in (77.0%, 87/113) of the interventions group versus (66.4%, 75/113) of the controls group with significant difference (P <0.001). The adherence to SAP administration at the time of induction of anesthesia was reported in (54.9%, 62/113) of the interventions group versus (39.8%, 45/113) of the controls group (P <0.001). Furthermore, adherence to the administration of preoperative SAP (<24 hours) was reported in (26.5%, 30/113) of the interventions group versus (22.1%, 25/113) of the controls group. SAP was not prescribed at the recommended time (> 24 hours) in 23.0% interventions versus 33.6% controls respectively. The adherence to the recommended duration of SAP used was exhibited in (62.8%, 71/113) of the interventions versus (44.2%, 46/113) in the controls (P <0.001).

The details of the SAP dosage regimen, revealed that a single pre-operative dose was administered to (34.5%, 39/113) of subjects in the interventions group versus (21.2%, 24/113) in the controls group (P < 0.001), post-operative multiple doses within 24 hours was administered to (32.7%, 37/113) in the interventions group versus (23.0%, 26/113) in the controls group (P 0.001). Post-operative multiple doses that have exceeded the recommended doses (>24 hours) were administered to (41.6%, 47/113) in the intervention group versus (55.8%, 63/113) in the controls group (P >0.001) [Table 3]. While (18.6%, 21/113) in the interventions group and (38%, 43/113) in the controls group, have received an extended post-operative SAP doses in addition to oral antimicrobial doses (P 0.001) respectively.

Surgical site infections (SSIs)

The overall rate of SSIs was assessed during 14 days post-operatively and was documented in (35.4%, 80/226) of the study group across the different conducted procedures. The implementation of the SAP local protocol in the general surgical procedures has shown significant reduction in development of SSIs between the interventions group and the controls group from 42.5% to 25.7% versus the controls group from 57.5% to 44.2% [P = 0.001] respectively. However, the SSIs has reduced significantly in the interventions group compared to the controls group (P 0.001). The association between SSIs and the type of surgery was presented in [Table 4]. The risk of infection according to type of surgery 14 days postoperatively didn't reveal significant differences, but showed decrease among interventions group when compared to the controls group in thyroidectomy, appendectomy, cholecystectomy and hernia (13.6% versus 18.2%, 10% versus 21.7%, 17.2% versus 26.6% and 12.5 versus 20.0) respectively. In the current study the distribution of SSI according to type of surgery revealed more frequent infection among subjects of cholecystectomy, hernia and appendectomy (35%, 32.5%; and 23.8%) respectively.

Risk of SSI according to the type, timing, and duration of SAP

The current study did not indicate any significant associations between the risk of postoperative SSIs according to the type of surgery within 14 days (thyroidectomy, appendectomy, cholecystectomy and hernia). The risk of infection according to type of surgery 14 days postoperatively didn't reveal significant differences, but showed decrease among interventions group when compared to the controls group in thyroidectomy, appendectomy, cholecystectomy and hernia (13.6% versus 18.2%, 10% versus 21.7%, 17.2% versus 26.6% and 12.5 versus 20.0) respectively.

However, the risk of SSI in the study population according to the type of SAP has revealed significant differences between

Table 3. The distribution of the type of surgery, regimen, and the duration of surgical antimicrobial prophylaxis (SAP) in interventions group and controls group

Type of surgery	**Type of regimen and duration of SAP**	**Both groups F (%)**	
		Interventions group	**Controls group**
Hernia	Single pre-operative dose	17 (43.6)	9 (22.0)
	Multiple post-operative < 24 hours	12 (30.8)	12 (29.3)
	Multiple post-operative doses > 24 hours + Extended oral antimicrobial	10 (25.6)	20 (48.7)
	Subtotal at columns	39 (48.8)	41 (51.2)
		80 (35.4)	
Thyroidectomy	Single pre-operative dose	5 (22.7)	5 (22.7)
	Multiple post-operative < 24 hours	3 (13.6)	2 (9.1)
	Multiple post-operative doses > 24 hours plus Extended oral antibiotic	3 (13.6)	4 (18.2)
	Subtotal at columns	11 (50.0)	11 (50.0)
		22 (9.7)	
	P value	0.049	
Appendectomy	Single pre-operative dose	9 (15.0)	5 (8.3)
	Multiple post-operative < 24 hours	14 (23.3)	6 (10.0)
	Multiple post-operative doses > 24 hours plus Extended oral antimicrobial	10 (16.7)	16 (26.7)
	Subtotal at columns	33 (55.0)	27 (45.0)
		60 (26.5)	
Cholecystectomy	Single pre-operative dose	8 (12.5)	5 (7.8)
	Multiple post-operative < 24 hours	8 (12.5)	6 (9.4)
	Multiple post-operative doses > 24 hours plus Extended oral antimicrobial	14 (21.9)	23 (35.9)
	Subtotal at columns	30 (46.9)	34 (53.1)
		64 (28.3)	
	Subtotal	113 (50.0%)	113 (50.0%)
Total	**Total**	**226 (100.0)**	

Key: F: Frequency; (%): percent; SAP: surgical antimicrobial prophylaxis

Table 4. The distribution of the type of surgery, regimen, duration of surgical antimicrobial prophylaxis (SAP), and surgical site infection (SSI)

Type of surgery	**Type of regimen and duration of SAP**	**SSIs in both groups F[%]**	
		Interventions group	**Controls group**
Hernia	Single pre-operative dose	2 [7.7]	3 [11.5]
	Multiple post-operative < 24 hours	4 [15.4]	4 [18.2]
	Multiple post-operative doses > 24 hours plus Extended oral antimicrobial	5 [19.2]	8 [30.8]
	Subtotal at columns	11 [42.3]	15 [57.7]
		26 [32.5]	
	P value	< 0.001*	
Thyroidectomy	Single pre-operative dose	1 [14.3]	2 [28.6]
	Multiple post-operative < 24 hours	0 [00.0]	0 [00.0]
	Multiple post-operative doses > 24 hours plus Extended oral antibiotic	2 [28.6]	2 [28.6]
	Subtotal at columns	3 [42.8]	4 [57.1]
		7 [8.7]	
	P value	0.049	

Appendectomy	Single pre-operative dose	3 [27.3]	3 [27.3]
	Multiple post-operative < 24 hours	1 [9.1]	1 [9.1]
	Multiple post-operative doses > 24 hours plus Extended oral antimicrobial	5 [45.4]	6 [54.5]
	Subtotal at columns	9 [47.4]	10 [52.6]
		19 [23.8]	
	P value	0.047	
Cholecystectomy	Single pre-operative dose	3 [10.7]	3 [10.7]
	Multiple post-operative < 24 hours	2 [7.1]	3 [10.7]
	Multiple post-operative doses > 24 hours plus Extended oral antimicrobial	6 [21.5]	11 [39.3]
	Subtotal at columns	11 [39.3]	17 [60.7]
		28 [35.0]	
	P value	< 0.001*	
	Subtotal	34 [42.5]	46 [57.5]
	P value	< 0.001*	
Total		**80 [100.0]**	

Key: F: Frequency; *P*-value*: < 0.05 significant; (%): percent; SAP: surgical antimicrobial prophylaxis, SSIs: surgical site infections

the interventions group compared to the controls group in hernia, thyroidectomy, appendectomy, and cholecystectomy (P <0.001). [Table 4].

The risk of SSI distribution according to SAP timing reported a lower rate among those who received antimicrobials within one hour or less before operation (27.3%), followed by those who received antimicrobials at the time of anesthesia induction (32.7%) and further delay in taking antimicrobials (>1 hour). The latter has reported a higher rate of infection (46.9%). However, multiple post-operative doses of SAP for less than 24 hours were administered to 39 (75.70%) subjects without post-operative infection and to 13 (25.0%) of those who developed post-operative infection.

Length of hospital stay

Regarding the duration of length of hospital stay in the interventions and controls group, (82.3%, 93/113) and (81.4%, 92/113) stayed for one day; while 18 (15.9%) and 20 (17.9%) stayed for two days, respectively. Further, staying for 2-4 days was reported in (19.5%, 22/113) in the interventions group versus (26.5%, 30/113) of the controls group. However, hospital length of stay for more than 4 days was reported as (1.7%, 2/113) in the interventions group versus (3.5%, 4/113) in the controls group (P <0.001) respectively.

DISCUSSIONS

SSI is a major contributor to serious post-operative complications with increased mortality; this risk can be reduced by sustained adherence to SAP. The main findings of the current study indicated that the implementation of the developed protocol of ASP by the surgical team including the clinical pharmacist, has improved the clinical outcomes of the interventions group in terms of reduced SSI in general surgical units. However, our study population has shown a very high rate of SSIs compared to previous local and regional studies.

Adherence to the local SAP protocol

Adherence to the type of selected antimicrobial (cephalosporin), timing (one hour before operation) and duration (single and multiple post-operative doses less than 24 hours) were revealed to be more in the intervention group of subjects. The improvement on the above-mentioned SAP criteria was consistent with that reported in numerous studies.[14-18]

The adherence to international guidelines for SAP was reported in many studies to be far from optimum, such as in Jordan.[19] Another was reported in Iran and Nicaragua, where rates of complete adherence to SAP practice guidelines were 0.3% and 7%, respectively.[20,21] This was far less than that reported in developed countries such as the Netherlands, France and the USA, where the overall adherence was achieved at 26%, 28% and 40-50% respectively.[22-24] The interventions group who have received a single pre-operative dose and the extended post-operative doses with addition to oral antimicrobial doses have revealed superior results as opposed to post-operative multiple doses. This was clearly shown with improved SAP adherence and improved clinical outcome, in the interventions group. Similar findings were reported in some studies.[25,26] Adherence to SAP selection, dosing and duration was significantly higher in the interventions group with a lower occurrence of SSI. The study in Palestine has shown poor adherence to the three assessed criteria, with a high rate of broad spectrum antimicrobial use; long duration and inappropriate time of first dose.[27]

Surgical site infection (SSI)

Our study reported high SSIs. However, the implementation of the SAP local protocol has improved with the interventions group with the subsequent reduction in SSIs consistent with some studies.[28-30] SSIs were very common among subjects in the current study; it was reported with a rate of 35.4% among

the different procedures conducted. SAP revealed a positively significant effect in reducing SSIs in the interventions group from 42.5% to 25.7% versus the controls group from 57.5% to 44.2% respectively, P = 0.001.

This significant difference is most probably impacted by adherence to guidelines, which was higher than rates of SSIs reported in two Sudanese studies conducted by Ahmed and colleagues; (12.7% and 8.0%) respectively.[28,31] Another interventional study conducted by van Kasteren and colleagues in the Netherland has reported a much lower rate of SSI. They showed that, the overall SSI rates before and after intervention were 5.4% (95% CI: 4.3-6.5); and 4.6% (95% CI: 3.6-5.4) respectively.[32]

Type of surgery

The current study did not indicate any significant associations between the risk of postoperative SSIs according to the type of surgery within 14 days (thyroidectomy, appendectomy, cholecystectomy and hernia). This was consistent with that reported in a previous Sudanese study.[31] The risk of infection according to type of surgery 14 days postoperatively didn't reveal significant differences, but showed decrease among interventions group when compared to the controls group in thyroidectomy, appendectomy, cholecystectomy and hernia (13.6% versus 18.2%, 10% versus 21.7%, 17.2% versus 26.6% and 12.5 versus 20.0) respectively. The study by Ahmed and colleagues in Sudan reported that SSIs among listed operations revealed that thyroidectomy had the lowest rate at 3.7% while hernia repair had the highest rate.[31] In the current study the distribution of SSI according to type of surgery revealed more frequent infection among subjects of cholecystectomy, hernia and appendectomy (35%, 32.5%; and 23.8%) respectively.

Risk of SSI according to the type and the time of SAP

The current study revealed a significant association between the risk of SSI and the type and time of SAP, which was similar to reported studies.[33,34] The risk of SSI distribution according to SAP timing was reported a lower rate among those who received SAP within one hour or less before operation, with multiple post-operative doses of SAP for less than 24 hours and with extended post-operative SAP doses, similar to an earlier reported study.[35]

Our finding was consistent with the study of Ahmed and colleagues in Sudan, who has reported that regardless of type of surgery, subjects who received multiple doses of antimicrobials for more than 24 hours reported higher risk of SSI (14.0%), while those who adhered to the recommended regimen reported less rate of SSI (single dose pre-operatively SSI [1.6%], multiple doses < 2 hours postoperatively SSI [9.6%]).[31]

Non-adherence to the recommended duration of antimicrobial use was found very common in the two groups. However, surgeons in the controls group reported significantly more frequent prescriptions of multiple post-operative doses post 24 hours (21.2% versus 18.6% respectively) or extended postoperative dose (38% versus 18.6%). Expecting nosocomial infection seems to impact doctors and act as an obstacle against their adherence to the guidelines, and this is most probably influenced by the general status of hospitals in Sudan and the high risk of non-sterile environment. The study in Palestine has observed adherence to duration antimicrobials in three hospitals with reported rates of (36.6%, 27.4%; and 31.5%).[27] The Turkish study also found that prolonged antimicrobial prophylaxis was used in 56.9%.[36] The Jordanian reported 99.1% adherence.[19] USA studies where protocols are usually followed showed high compliance (92.6%) in antimicrobial selection.[8,37]

Our study results were in line with the published guidelines of the American Society for Hospital Pharmacists (ASHP), which reported that antimicrobial administration should be discontinued within 24 hours after the end of surgery, to prevent emergence of resistance.[38] Long hospital stays are considered in studies as one of the main risks of developing nosocomial infections.[39,40] However, our study did not show significant differences between controls and interventions, which can be attributed to the type of surgery. Unlike many studies with different surgery types, they have reported that hospital-acquired infections (HAIs) are associated with length of stay in the hospital.[41-43] In our current study staying for 2-4 days was significantly higher in the controls group.

The implementation of the SAP protocol has shown a reduced overall rate of SSIs in the interventions group assessed during 14 days post-operatively, which was similar to one study.[28] Therefore, we support sustained effective dissemination of SAP protocols with effective implementation, monitoring, follow-up, quality indicators and reporting. In this respect, the current study lends support to many studies.[28,31,43,44]

The study limitations

The main limitation of the current study may be the relative small size of the study population and the single center trial despite the use of sample size power and restricted randomization to reduce such bias. However, the study findings may serve as a foundation for larger studies in the future.

CONCLUSION

The clinical pharmacist's interventions have proved to be very effective in sustainable adherence to SAP protocol and in reducing SSIs within the interventions group of subjects. The highly informed surgical team via behavioral and educational interventions and with continued pursuit of SAP protocol successfully facilitated its implementation. Incorporation of clinical pharmacist in surgical team would have enormous benefits to the clinical outcomes in terms of the reduction of SSIs, and length of hospital stay, and subsequent improved clinical outcomes. Future research should be directed to multicenter trials for more generalizability of the effect of the SAP interventions in similar populations.

IMPACT ON CLINICAL PRACTICE

The clinical pharmacist interventions and sustained follow up of the surgical antimicrobial prophylaxis (SAP) protocol

has provided successful improved clinical outcomes for the intervention group of subjects. This represents valuable documentation of the clinical pharmacist's interventions in the SAP and antimicrobial stewardship program (ASP).

The sustained improvement in adherence to the implemented SAP protocol for the three major criteria provided strong evidence for the effectiveness of the behavioral and educational interventions deployed by the clinical pharmacist.

Deployment of the clinical pharmacist in surgical units enhances the implementation and sustainability of SAP protocol and increases the opportunities of a successful ASP.

The achieved reduction in surgical site infections has reflected the possible emulation of the clinical pharmacist's interventions by other healthcare facilities.

What is already known on this subject?

Adherence to surgical antimicrobial prophylaxis protocol has been shown to improve the clinical outcomes.

What is new in the current study?

The clinical pharmacist interventions and sustained follow up of the SAP protocol facilitates the development of antibiotics steward program.

Behavioral and educational interventions deployed by the clinical pharmacist have a profound impact on the implementation of SAP protocol.

Deployment of the clinical pharmacist in surgical units enhances a implementation and sustainability of SAP protocol and increases the opportunities of successful antimicrobial stewardship program.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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ETHICS APPROVAL STATEMENT

The current study was approved by the local hospital institute research review board (IRB) of the study hospital site in Khartoum State-Sudan.

COMPETING INTEREST

All authors declare no competing interest.

AUTHORS' CONTRIBUTIONS

We declare that A A Elnour, IYK, A ElK, H Elkheir, A OMA, K Al-Kubaissi, G Nahar, S F Alrwili, D A Alshelaly, A Saleh, L khulif and A A Alrashedi; had complete access to the study data that support the publication. All authors have contributed to the whole study design, statistical work, results interpretation and manuscript writing and proof read.

ABBREVIATIONS

ACE	angiotensin converting enzyme
AKI	Acute kidney injury
ASHP	American Society for Hospital Pharmacists
ASP	Antimicrobial stewardship program
β-blockers	Beta blockers
BMI	Body Mass Index
CDC	Center for Disease Control
Chiχ2	Chi squared
CKD	Chronic kidney disease
HAIs	Hospital-acquired infections
IRB	Institute research review board
SAP	Surgical antimicrobials prophylaxis
SCIP	Surgical Care Improvement Project
SPSS	Soft Package for Social Sciences
SSI	Surgical site infection
USA	United States

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Appendix 1. Clinical pharmacist's SAP protocol (educational and behavioral interventions)

Permeable

An example of the clinical pharmacist's SAP protocol (educational and behavioral interventions) detailing the mini course delivered to achieve the improved in the uptake of the protocol and the subsequent reduction in SSIs and improved subject's clinical outcomes (Appendix 1).

The below mini-course was conducted in hospital targeting the most commonly performed surgical procedures in the general surgery.

Prior to the development of the SAP protocol we have identifies the following:

lack of adherence to existing SAP guidelines

deficit in communications and documentation of relevant data.

diminished SAP prescribing skills

absence of mandates on roles, tasks, safety, infection control and accountability

Objectives of the mini-course

Gain knowledge of decision-making for SAP prescribing from multiple perspectives across a range of surgical specialties.

The selected surgical team has received structured educational and behavioral SAP mini courses by way of directed lecturers, workshops, seminars and awareness campaigns delivered by the clinical pharmacist. Furthermore, we have conducted 10 focus group discussions (each included 5 surgeons) with selected surgical team involved with SAP at the hospital.

Hospital Surgical Antimicrobial Prophylaxis (SAP) Protocol		
Division/Dept./Section: Surgical department **Section:** General surgery **Subject** Surgical Antimicrobial Prophylaxis (SAP) in general surgicalprocedures	**Ref. No : xxxxxxxxxxx**	
	Issue Date:	
	Next Revision Date :	
	Version : 00001	**Page 1 of 6**

Prepared By		Reviewed By	Dr …..- consultant general surgeon /HOD	
APPROVALS				
Name	**Designation**			**Signature**
	Hospital director			

INTRODUCTION

Antibiotic prophylaxis in surgical procedure is mainly given to prevent patient from post-operative infections.

Surgical Site Infections (SSIs) are most common type of post-operative infection in surgery patient.[1]

Occurrence of these post-operative infections is influenced by many factors like type of surgical procedure, preoperative preparation of patient, elective/emergency, and type of wound, hospital premises and wound care given to patient, thus if there are these many influencing factors, then there is much more care healthcare providers must take before selecting SAP for a particular patient for reduction in overall risk of development of SSI's.[2]

SAP can be illustrated by different protocols carried out simultaneously for a particular patient of surgery; include selection of appropriate antimicrobial agent, selection of right dose for that particular patient, selection of right dosing time for that particular agent, selection of right route of administration, selection of second dose and time of that dose, if needed and post-operative duration of that prophylaxis in that particular patient and to carry out these steps in appropriate way, there has to be complete compliance with SAP guidelines.[3]

Guidelines for any hospital setting should be prepared with keeping some factors in mind like available facilities, expertise available and practicality in implementation, implementation of these local protocols can help to decrease variations in SAP administration amongst different providers in utilization of resource.[4]

Role of clinical pharmacist

Role of clinical pharmacist Implementation of SAP guidelines is a work of great responsibility, and inclusion of clinical pharmacist in this area holds the key to success of these guidelines by implementing them to patient level.

Implementation of SAP guidelines includes understanding both needs of patient and medical practitioner; clinical pharmacist with proper interprofessional corresponding command can maneuver situations evolving during communicating about implementation issues with other healthcare professionals and can play an important role in implementing decisions.[5]

Clinical pharmacy practice in hospitals leading to an effective strategy to improve medication use, clinical services provided by practicing pharmacists include consultation about adjustment of dosage, antibiotic prescribing recommendations, pharmacokinetic evaluations and drug information and this study of United States in 2013 states growth of role played by pharmacists in rationale medication prescribing.

Development of antibiotic prophylaxis guidelines for local settings on international recommendations with providing clinical pharmacist a key position in monitoring and intervention of antimicrobial prophylaxis may improve present prescribing practice.[6]

Clinical pharmacists can attend surgical department rounds. the goals are improved understanding of patient's history, progress, clinical details, to provide the information on clinical aspects of patient's therapy and to improve discharge planning.

The Pharmacists can also help in decision making to select the quality low cost medicine; optimize the quality of patient care and clinical outcomes; ensure medicine selection as per formulary and local guidelines.[7]

Patient counseling can be considered as the most important clinical pharmacists from the patient's point of view. the Clinical Pharmacists may provide the information about current clinical condition/proceedings of the patient and educate him about the safe and appropriate use of medicines, thereby enhancing his therapeutic outcomes.

A Clinical Pharmacist may provide information on ongoing care to the patient to ensure continuity of supply of drugs, continuity of medication concordance aids, communication of special problems, appropriate monitoring of the dosages and for minimal disruption.[8]

GENERAL

These policies apply to all elective operations in the clean, clean- contaminated or contaminated categories

Antibiotic therapy for emergency operations with contaminated or dirty wounds is standard therapy rather than prophylaxis

Definition

Prophylactic antibiotic: The use ofantibiotics before, during, or after adiagnostic, therapeutic, or surgical procedure to prevent infectious complications

Therapeutic antibiotic: This term is used to describe antimicrobial therapy prescribed to clear infection by an organism or to clear an organism that is colonizing a patient but is not causing infection

Class definition

Clean	Operations in which no inflammation isencountered and the respiratory,alimentary or genitourinary tracts are not entered. There is no break in aseptic operating theatre technique.
Clean-contaminated	Operations in which the respiratory,
	alimentary or genitourinary tracts are
	entered but without significant spillage
contaminated	Operations where acute inflammation (without pus) is encountered, or where there is visible contamination of thewound. Examples include grossspillage from a hollow viscus during the operation or compound/open injuries operated on within four hours
Dirty	Operations in the presence of pus, where there is a previously perforated hollow viscus, or compound/open injuries more than four hours old.

Policy

Preoperative intravenous (IV) antibiotic administration should occur up to 60 minutes before surgical incision; **however, 15 to** 30 minutes before surgical incision is optimal.

Antibiotic selection may need to be modified according to patient risk factors.

Dosage adjustment may be necessary in patients with BMI >30.

A single dose of antibiotic(s) is sufficient for the majority of procedures.

Postoperative doses of IV antibiotics of up to 24 hours are only required in defined circumstances (prolonged surgery MORE than 4 hrs, major blood loss >1500 ml or intra- operative contamination)

Urinary or intravascular catheters or indwelling surgical drains that remain in situ are not a justification to extend the duration of antibiotic prophylaxis.

Surgery that requires antibiotic prophylaxis is:

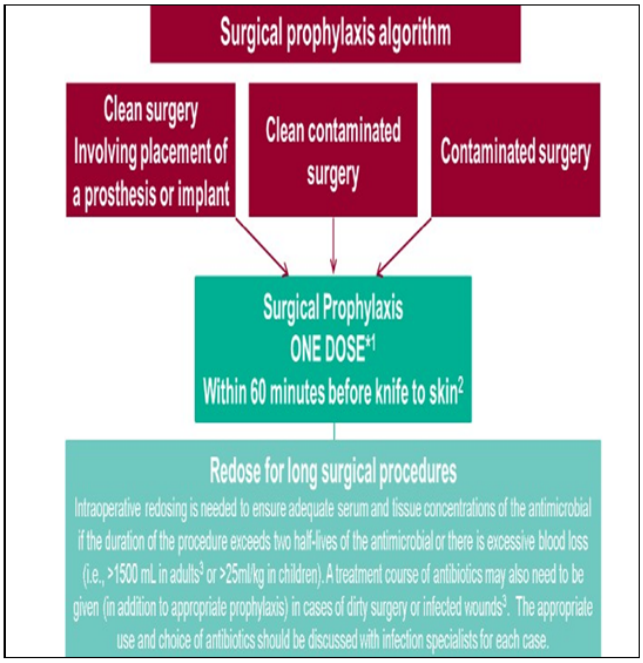
Clean surgery involving the placementof a prosthesis or implant

Clean-contaminated surgery

Contaminated surgery

Surgery on a dirty or infected wound.

Flow diagram



Medication

The antibiotics selected for prophylaxismust cover the expected pathogens for that operative site.

Narrow spectrum, less expensive antibiotics should be the first choice forprophylaxis during surgery eg: cefuroxime 1.5 gram.

Benefits and risks of antibiotic prophylaxis

The final decision regarding the benefits and risks of prophylaxis for an individual patient willshould be decided by a senior specialist depending on:

the patient's risk of SSI

the potential severity of the consequences of SSI

the consequences of prophylaxis for thatpatient (for example, increased risk of Clostridium difficile infection).

Appendix (1) Specific surgical sites

Head and neck surgery

(clean, benign) Antibiotic prophylaxis is not recommended

(clean, malignant) Antibiotic prophylaxis should be considered

(contaminated/clean-contaminated) Antibiotic prophylaxis is recommended

Breast cancer surgery

Antibiotic prophylaxis should be Considered

Stomach and duodenal surgery

Antibioticprophylaxis is recommended

Small intestine surgery

Antibioticprophylaxis is recommended

Bile duct surgery

Antibiotic prophylaxis is recommended

Pancreatic surgery

Antibiotic prophylaxis is recommended

Liver surgery

Antibiotic prophylaxis is recommended

Gall bladder surgery

(open) Antibiotic prophylaxis is recommended

(laparoscopic) Antibiotic prophylaxis can be omitted, Antibiotic prophylaxis should be considered in high risk patients

Hernia repair-groin

(inguinal/femoral without mesh) Antibiotic prophylaxis is not recommended

Hernia repair-groin

(inguinal/femoral withmesh) Antibiotic prophylaxis is recommended

Splenectomy

Antibiotic prophylaxis is not recommended. Antibiotic prophylaxis should be considered in high risk patients High risk: immunosuppression

Appendectomy

Antibiotic prophylaxis is highly recommended

Colorectal surgery

Antibiotic prophylaxis is highly recommended

Cutaneous and Superficial Soft Tissue Procedures

Prophylaxis is not recommended

Appendix (2) suggested antibiotic

Type of Surgery	Primary Regimen	Alternative Regimen
Head and neck	(Cefuroximeor Cefazolin) ± Metronidazole	Clindamycin + Gentamicin or Tobramycin
Gastro- duodenal oesophageal	Cefuroxime or Cefazolin / or Ceftriaxone	Vancomycin + gentamicin
Colorectal /appendectomy	(Cefuroxime or Cefazolin) + Metronidazole Or Cefoxitin as single drug	Clindamycin + (Gentamicin or Cipro)
Small intestinalsurgery	(Cefuroxime or Cefazolin) + Metronidazole Or Cefoxitin as single drug	
Biliary Tract	Cefuroxime or Cefazolin	Metronidazole +(Levofloxacin or cipro)
Breast surgery,herniorrhaphy	Cefuroxime or Cefazolin	Ampicillin- sulbactam/ Clindamycin/ Vancomycin

Appendix (3) Dosing and re-dosing of antimicrobial agents

Antimicrobial	RecommendedDose	Re- dosing (hours)
Cefazolin	2 grams	4
Clindamycin	900 mg	6
Vancomycin	< 80 kg = 1 gram	12
Ampicillin-sulbactam	3 grams	2
Aztreonam	2 grams	4
Cefotetan	2 grams	6
Cefoxitin	2 grams	2
Ceftriaxone	2 grams	N/A
Cefuroxime	1.5 grams	4
Ciprofloxacin	400 mg	8
Ertapenem	1 gram	N/A
Gentamicin	5 mg/kg (singledose)	N/A
Levofloxacin	500 mg	N/A
Metronidazole	500 mg	12

Appendix (4) Post-operative dosing (if needed)

Antimicrobial	Recommended Dose
Cefazolin	2 grams q8h up to 2 doses
Clindamycin	900 mg q8h up to 2 doses
Vancomycin	1 grams q12h up to 1 dose
Ampicillin-sulbactam	3 grams q6h up to 3 doses
Aztreonam	2 grams q8h up to 2 doses
Cefotetan	2 grams q12h up to 1 dose
Cefoxitin	2 grams q6h up to 3 doses
Ceftriaxone	No post-op doses needed (q24h hour dosing)
Cefuroxime	1.5 grams q8h up to 2 doses
Ciprofloxacin	400 mg q12h up to 1 dose
Gentamicin	No post-op doses needed (q24h hour dosing)
Levofloxacin	No post-op doses needed (q24h hour dosing)
Metronidazole	500 mg q8h up to 2 doses

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