



Post-surgical antibiotic prophylaxis: Impact of pharmacist's educational intervention on appropriate use of antibiotics

Saba Zia Butt^a, Mobasher Ahmad^a, Hamid Saeed^{a,b,*}, Zikria Saleem^{b,c,d}, Zaida Javaid^e

^a Section of Biomedical Sciences, University College of Pharmacy, University of the Punjab, Allama Iqbal Campus, 54000, Lahore, Pakistan

^b Section of Clinical Pharmacy, University College of Pharmacy, University of the Punjab, Allama Iqbal Campus, 54000, Lahore, Pakistan

^c School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 Gelugor, Penang, Malaysia

^d Rashid Latif College of Pharmacy, 54000, Lahore, Pakistan

^e Punjab Institute of Cardiology, Jail Road, Lahore, Pakistan

ARTICLE INFO

Article history:

Received 24 December 2018

Received in revised form 13 May 2019

Accepted 23 May 2019

Keywords:

Surgery
Pharmacist interventions
Antibiotics
Rational use
Prophylaxis
Cost analysis

ABSTRACT

Background: Guidelines assisted appropriate use of prophylactic antibiotics can lower the prevalence of surgical site infections (SSIs). The present study was conducted to evaluate the impact and cost-benefit value of pharmacist's educational intervention for antibiotic use in post-surgical prophylaxis.

Methods: A prospective quasi experimental study was conducted by enrolling 450 patients from tertiary care hospital of Lahore, Pakistan, 225 patients in each, control and intervention, arm using non-random convenient sampling. The study parameters included antibiotic indication, choice, dose, frequency, duration and associated costs. This study is registered with Chinese Clinical Trial Registry # ChiCTR-OON-17013246.

Results and conclusion: After educational intervention, in post-intervention arm, total compliance in terms of correct antibiotic choice, dose, frequency and duration increased from 1.3% to 12.4%. The rate of inappropriate antibiotic choice did not change significantly. After intervention only metronidazole utilization decreased (16%) significantly ($p = 0.011$). Significant reductions were observed in mean duration of antibiotic prophylaxis (17%, $p = 0.003$), average number of prescribed antibiotics (9.1%, $p = 0.014$) and average antibiotic cost (25.7%, $p = 0.03$), with reduction in mean hospitalization cost ($p = 0.003$) and length of stay ($p = 0.023$). Educational intervention was significantly associated (OR; 2.4, $p = 0.005$) with appropriate antibiotic prophylaxis. The benefit of pharmacist intervention, mean antibiotic cost savings to mean cost of pharmacist time, was 4.8:1. Thus, the educational intervention resulted in significant reductions in the duration and average number of antibiotic use having considerable effect on therapy and hospitalization cost.

© 2019 The Authors. Published by Elsevier Limited on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Antibiotics are often used exuberantly among post-operative patients in many clinical situations – an irrational practice which is still common in many countries [1,2]. Recently, it is estimated that the global antibiotic consumption, expressed in defined daily doses (DDDs), increased from 21.1 to 34.8 billion DDDs – an increase of 65% from 2000 to 2015 [3]. This increase in global antibiotic

consumption was primarily driven by increased consumption in low middle income countries (LMICs), including Pakistan. In this context, between 2000 and 2015, the highest surge in antibiotic consumption was observed among LIMCs, i.e. 103% in India, 79% in China and 65% in Pakistan [3].

In Pakistan, guidelines regarding the post-surgical antibiotic prophylaxis are almost non-existent. In most of the hospitals and the clinics, conventional antibiotic therapy is given for 7–10 days to post-surgical patients [4]. Moreover in Pakistan, surgeons probably speculate that prolong antibiotic use would lower the incidence of post-operative infections, including wound space and organ infection [4]. Two observational studies from Islamabad, Pakistan have clearly demonstrated that the surgical site infection (SSI) rates were 8.3% and 6.5% in patients undergoing emergency surgery and patients undergoing elective surgeries, respectively

* Corresponding author at: Punjab University College of Pharmacy, University of the Punjab, Lahore, Pakistan.

E-mail addresses: sabaziabutt@gmail.com (S.Z. Butt), ahmadmobasher@hotmail.com (M. Ahmad), hamid.pharmacy@pu.edu.pk (H. Saeed), xikria@gmail.com (Z. Saleem), zeepharm@yahoo.com (Z. Javaid).

[5,6] – much higher in comparison to those observed in the developed world [6,7]. As a common practice, surgeons neither act in accordance with the short term courses of antibiotic prophylaxis before surgery nor they avoid the use of broad-spectrum antibiotics unnecessarily [8,9]. This leads to human sufferings along with substantial economic fritters [10]. Inappropriate prescriptions, including antibiotic choice, dose, frequency and duration aimed at unnecessary prophylaxis can increase the risk of adverse drug reactions, which may lead to the emergence of resistant organisms, un-necessary therapy cost and waste of health care resources [11,12].

Several management stratagems have been employed to control this multifaceted problem of inappropriate prophylactic antibiotic usage. In this regard, pharmacist, being a key member in the antibiotic management team could play a significant role in controlling inappropriate use of antibiotics [13,14]. Furthermore, studies have also shown that the pharmacist directed drug utilization evaluation (DUE) strategy can promote rational use of antibiotic prophylaxis in hospital settings [14] with significant reduction in antibiotic costs [13]. A study from Brazil has demonstrated that the pharmacist interventions were efficient enough to correct the prescription errors, and is well placed to participate in health education to promote rational use of antibiotics at the hospital [15]. In the United States, the provision of antibiotic prophylaxis managed by a pharmacist was associated with significant improvements in clinical and economic outcomes [16]. In European hospitals pharmacist advice on prescribing resulted in lower median levels of antibiotic consumption [17]. In respiratory wards of a Chinese hospital, in a small scale randomized controlled trial, the pharmacist intervention resulted in optimized utilization of antibiotics with reduction in the length of hospitalization & healthcare costs [18].

There are only a few published research papers on the pattern of antibiotic use in hospitals of Pakistan [2,19,20] including irrational use [4,21]. We are also aware that there have been initiatives to improve antibiotic use by implementing National Action Plan of Pakistan on antimicrobial resistance (AMR) [22]. To date, there are no published reports from Pakistan regarding the role of a pharmacist in optimizing and promoting the rational use of antibiotics in post-surgical antibiotic prophylaxis. Thus, the objective of this study, the first of its kind, was to evaluate the role of a pharmacist in administering educational intervention to the health care providers of a tertiary care hospitals on the appropriate use of antibiotics in post-surgical patients and its impact on economic outcomes.

Study objective

To evaluate the impact and cost-effective value of pharmacist's educational intervention on the use of antibiotics in post-surgical prophylaxis.

Materials and methods

Ethical approval

The study was approved by the Ethical Committee on Human Research, Punjab University College of Pharmacy, University of the Punjab, Lahore, Pakistan, ref #.HEC/PUCP/1931 and Institutional Review Board (IRB), ref# 5777/HR/GTTH, of the hospital. Moreover, the study is registered with the Chinese Clinical Trial Registry, reference registration # ChiCTR-OON-17013246.

Study design

A prospective quasi experimental study design was used by enrolling 450 patients undergoing different surgical procedures in general, orthopedic and gynecological wards from a tertiary care

hospital of Lahore. Non-random convenient sampling was done to enroll subjects with no blinding. The study was divided into two phases i.e. pre & post-intervention. Pre-intervention phase was merely an observational phase from August 22, 2016 to November 21, 2016. After the pre-intervention phase, two educational and training sessions were conducted for doctors and nurses to brief and discuss the standard treatment guidelines regarding the use of antibiotics for surgical prophylaxis. In the post-intervention phase, from December 06, 2016 to March 05, 2017, pharmacist re-evaluated the utilization of post-surgery antibiotic prophylaxis and estimated the costs.

Study population

Patients with clean/clean contaminated surgeries from three different surgery wards, general, orthopedic and gynecology were recruited in the study. A total of 225 subjects were included in each arm as per inclusion and inclusion criteria – 125 from Orthopedic surgery, 50 from Gynecology and 50 General surgery. In the pre-intervention phase, data of 225 patients were collected. However, to minimize bias, after the educational intervention, a similar number of patients, age and gender-matched, were enrolled in the post-intervention arms from similar wards.

Inclusion criteria

Inpatients with clean and clean-contaminated procedures, surgical antibiotic prophylaxis, without systemic disease and willing to participate in the study were included in the study.

Exclusion criteria

All inpatients, who underwent invasive procedure at least thirty days prior to the surgery, known allergies to antibiotics, have been using any antibiotic within fourteen days before the procedure and were not willing to participate were excluded from the study.

Intervention

The standard criteria for antibiotic prophylaxis in surgical procedures was established according to clinical practice guidelines for antimicrobial prophylaxis in surgery published in 2013 by American Society of Health-System Pharmacist [23], (Table S1). Results obtained in the pre-intervention arm were shared and discussed with surgeons, surgery residents, postgraduate fellows and nurses in ward meetings. After general ward meetings, in each ward, the general and specific problems related to the appropriate use of antibiotic prophylaxis were discussed regarding post-surgical antibiotic prophylaxis with concerned personals & committees. The principle of post-surgery prophylaxis & precautionary measures need to be taken were discussed and reviewed with the concerned surgeons to reduce the probability of SSIs. The educational training continued for 10–15 days. In the second phase, i.e. post-intervention, data was arbitrated identically as was done in the first phase. Data obtained from both the phases were compared to ascertain the effectiveness of pharmacist educational interventions.

Data collection

Data of 450 patients were recorded for both phases (pre/post-intervention) using data collection form as per study objectives. A precise MS Excel sheet (ver. 2016; MS Corporation, Washington, US) was prepared to record basic data (age, gender, weight, employment status, area of residence, date of admission, date of surgery, date of discharge, length of hospital stay, diagnosis, antibiotic allergy, postoperative infections), surgical procedures (surgery type, surgical wound class, surgery name, implant use,

use of intra-operative antibiotic dose & surgery duration), antibiotic usage (generics, dose, route, number of doses, duration, antibiotic replacement, antibiotic combination & conversion) & costs (total hospitalization cost and cost of antibacterial agent). A cost-benefit analysis was done by comparing the cost and resources employed in pharmacist educational intervention to doctors and nurses to the benefits from intervention in terms of mean antibiotic cost reduction.

Data appraisalment

Inappropriate use of antibiotic prophylaxis was determined after comparing with standard protocols [23] as per evaluation criteria in Table S1. Antibiotic costs were estimated taking into account the actual prices of administered antibiotics, calculated discretely & then summed up to find out the overall cost. There was only one source to obtain all the prescription drugs, i.e. hospital pharmacy, while multiple brands of the same generic in different prescriptions was cogitated while analyzing costs. Average antibiotic cost reduction in phase-II was estimated by calculating the difference in average antibiotic costs of both arms. Overall adherence with standards guidelines was ascribed as the summation of “indicated & administered (appropriate choice, dose, and duration)” & “neither indicated nor administered” (Table S2).

Primary outcome

Improved rationality in antibiotic selection, dose, frequency, and duration.

Secondary outcome

Average reduction in antibiotic and hospitalization costs along with the cost to benefit ratio – reduction in the antibiotic cost of all the cases to pharmacist average time cost.

Data analysis

Data were analyzed using SPSS 24.0 (Inc. Chicago, Illinois US). Descriptive statistics were performed to estimate the frequencies of all socio-demographic and clinical variables. Student's t-test was used to compare the length of hospitalization, antibiotic cost, hospitalization cost, duration of antibiotic used and the number of antibiotics used. For categorical variables, chi-square statistics were used & stated in terms of frequencies/percentages. Cost-benefit ratio was estimated by dividing antibiotic cost reduction for all the cases by pharmacist's average time cost. An alpha value of equal or less than 0.05 was considered statistically significant.

Results

Baseline patient's characteristics

The characteristics of surgical procedures and patients in pre and post-intervention arms are summarized in Table 1. Data suggested that the patient's mean age was similar in both the arms and most of the patients fall within age brackets of 18–36 years (Table 1). No differences in frequency distribution were observed between pre and post-intervention arms for variables, such as gender ($p=0.637$), type of surgery ($p=0.99$), surgical wound class ($p=0.923$) and with regards to the use of an implant (Table 1). Most of the patients were un-employed (*pre-I*; 61.3%, *post-I*; 63.6%) and were hailing from urban areas (*pre-I*; 60%, *post-I*; 62.2%). As for the surgical procedures, internal fixation was the most frequently used surgical procedure in both pre and post-intervention arms followed by cesarean section and cholecystectomy (Table 1).

Table 1

Patient's basic and clinical characteristics in pre and post-intervention arms.

Parameters	Pre-intervention <i>n</i> = 225 (%)	Post intervention <i>n</i> = 225 (%)	<i>p</i> - Value
Gender			
Male	113 (50.2%)	107 (47.6%)	0.572
Female	112 (49.8%)	118 (52.4%)	
Age			
18–36 yrs	111 (49.3%)	112 (49.8%)	0.532
37–60 yrs	77 (34.2%)	68 (30.2%)	
>60 yrs	37 (16.4%)	45 (20%)	
Age (Mean ± SD)	42.23 ± 18.92	42.47 ± 18.45	
Employment status			
Employed	87 (38.7%)	82 (36.4%)	0.626
Un-employed	138 (61.3%)	143 (63.6%)	
Area of residence			
Urban	135 (60%)	140 (62.2%)	0.63
Rural	90 (40%)	85 (37.8%)	
Type of surgery			
Orthopedic surgery	125 (55.6%)	125 (55.6%)	0.99
General surgery	50 (22.2%)	50 (22.2%)	
Gynecological	50 (22.2%)	50 (22.2%)	
Surgical wound class			
Clean	138 (61.3%)	140 (62.2%)	0.923
Clean contaminated	87 (38.7%)	85 (37.8%)	
Surgical procedure			
Cholecystectomy	27 (12%)	23 (10.2%)	
Appendectomy	10 (4.4%)	11 (4.9%)	
Hernia procedure	12 (5.3%)	15 (6.7%)	
Thyroidectomy	1 (0.4%)	1 (0.40%)	
Cesarean section	40 (17.8%)	40 (17.8%)	
Hysterectomy	10 (4.4%)	10 (4.4%)	0.624
Arthroscopy	18 (8.0%)	18 (8.0%)	
Internal fixation	84 (37.4%)	89 (39.6%)	
THR	10 (4.4%)	9 (4.0%)	
TKR	13 (5.8%)	9 (4.0%)	
Implant used	108 (48%)	115 (51.1%)	0.572

Pharmacist's interventions & frequency of prophylactic antibiotic usage

As shown in Table 2, in both the arms, other β -lactams (*pre-I*; 63.5%, *post-I*; 52.8%) and other antibiotics (*pre-I*; 63.5%, *post-I*; 52.8%) were the most frequently used antibiotic classes, with almost equal usage of cefoperazone/sulbactam (*pre-I*; 52.9%, *post-I*; 49.3%) and amikacin (*pre-I*; 46.2%, *post-I*; 42.2%) (Table 2). After the intervention, in other- β -lactams and others category, significant reductions were observed only in the utilization of co-amoxiclav (*pre-I*; 10.2%, *post-I*; 3.1%) and metronidazole (*pre-I*; 26.2%, *post-I*; 16%) (Table 2). While cefazoline (*pre-I*; 63.5%, *post-I*; 52.8%), the first generation cephalosporin, exhibited increased utilization in the post-intervention arm (Table 2).

Pharmacist's intervention and appropriateness of prophylactic antibiotics

When appropriateness of prophylactic antibiotic use was examined, as per the defined criteria, most of the antibiotics were administered where indicated (*pre-I*; 99.6%, *post-I*; 99.1%). As for antibiotic choices, only 11.6% choices were appropriate in pre-intervention arms which increased to 28% after pharmacist's intervention – an increase of 142% (Table 3). Likewise, after the intervention, there was 152% increase incorrect choice and dose, 142% increase with regards to correct choice, dose and frequency, and 833% increase incorrect choice, dose, frequency and duration, i.e. from 1.3% to 12.4% (Table 3).

Post-intervention; antibiotic and hospitalization costs & durations

As shown in Table 4, after pharmacist's intervention, significant reductions (17%) were observed in average duration of antibi-

Table 2
Antibiotics used for prophylaxis in pre and post-intervention arm.

Antibiotics	Pre-intervention n = 225 (%)	Post intervention n = 225 (%)	p-Value
First generation cephalosporin	41 (18.2%)	68 (30.0%)	
Cefazoline	34 (15.1%)	53 (23.6%)	0.031*
Cephadrine	7 (3.1%)	15 (6.7%)	0.124
Second generation cephalosporin	27 (12%)	19 (8.4%)	
Cefuroxime	27 (12%)	19 (8.4%)	0.276
Third generation cephalosporin	44 (19.5%)	34 (15.1%)	
Ceftriaxones	23 (10.2%)	16 (7.1%)	0.315
Cefixime	21 (9.3%)	15 (6.7%)	0.385
Ceftazidime	0 (0%)	3 (1.3%)	0.248
Other β -lactams	143 (63.5%)	119 (52.8%)	
Cefoperazone/sulbactam	119 (52.9%)	111 (49.3%)	0.509
Co-amoxiclav	23 (10.2%)	7 (3.1%)	0.004*
Piperacillin/tazobactam	1 (0.4%)	1 (0.4%)	1.0
Others	225 (100%)	185 (82.2%)	
Amikacin	104 (46.2%)	95 (42.2%)	0.448
Metronidazole	59 (26.2%)	36 (16%)	0.011*
Ciprofloxacin	42 (18.7%)	36 (16%)	0.534
Moxifloxacin	3 (1.3%)	7 (3.1%)	0.338
Vancomycin	17 (7.6%)	11 (4.9%)	0.329

* ≤ 0.05 , ** < 0.001 .**Table 3**
Impact of pharmacist's intervention on the appropriateness of antibiotic prophylaxis.

Parameters	Pre-intervention n = 225 (%)	Post intervention n = 225 (%)	p-Value
Not administered but indicated	0 (0%)	0 (0%)	–
Not indicated not administered	1 (0.4%)	2 (0.9%)	–
Indicated and administered	224 (99.6%)	223 (99.1%)	–
Correct choice			
Yes	26 (11.6%)	63 (28%)	0.0005**
No	199 (88.4%)	162 (72%)	
Correct choice & dose			
Yes	25 (11.1%)	63 (28%)	0.0005**
No	200 (88.9%)	162 (72%)	
Correct choice, dose & frequency			
Yes	24 (10.7%)	61 (27%)	0.0005**
No	201 (89.3%)	164 (73%)	
Correct choice, dose, frequency & duration			
Yes	3 (1.3%)	28 (12.4%)	0.0005**
No	222 (98.7%)	197 (87.6%)	

* ≤ 0.05 , ** < 0.001 .**Table 4**
Impact of pharmacist's intervention on antibiotic usage and associated costs.

Parameter	Pre-intervention n = 225 (%)	Post intervention n = 225 (%)	p-Value
Antibiotic cost and usage			
Duration of antibiotic usage			
12–60 h	128 (57.1%)	150 (67%)	0.032*
>60 h	96 (42.9%)	74 (33%)	
Average duration of antibiotic use (Hours)	66.01 \pm 41.015	55.20 \pm 36.214	0.003*
% decrease	0	17%	
Average number of antibiotics 0–2 > 2	150 (66.7%) 75 (33.3%)	174 (77.1%) 51 (22.9%)	0.014*
Average number of antibiotic use	2.09 \pm 0.902	1.86 \pm 0.859	0.006*
% decrease	0	9.1%	
Cost of antibiotic use			
1–1500 PKR	115 (51.1%)	139 (61.8%)	0.023*
>1500 PKR	110 (48.9%)	86 (38.2%)	
Average antibiotic cost (PKR)	2463.17 \pm 3546.42	1829.56 \pm 2567.32	0.03*
% decrease	0	25.7%	
Hospitalization cost and stay			
Cost of hospitalization			
1–15 K	152 (67.6%)	186 (82.7%)	0.0001**
>15 K	73 (32.4%)	39 (17.3%)	
Average hospitalization cost (PKR)	19230.9 \pm 20075.8	12541 \pm 6463.18	0.003*
% decrease	0	34.8%	
Length of hospitalization			
1–5 days	164 (72.9%)	183 (81.3%)	0.033*
>5 days	61 (27.1%)	42 (18.7%)	
Average length of hospital stay	5.4 \pm 4.814	4.50 \pm 3.398	0.023*
% decrease	0	16.6%	

* ≤ 0.05 , ** < 0.001 .

Table 5
Cost benefit analysis of pharmacist intervention.

Pharmacist time & working costs	
Monthly salary	\$432 (50,000PKR)
Daily salary	\$ 14.4
Hourly salary	\$ 1.8
Pharmacist intervention time each intervention session of 4 h to doctors and nurses including time spent on preparation + arrangements	4 × 2 sessions = 8 h
Educational session arrangement cost (tea + stationary + printed material); 1 seminar = \$ 143	2 × \$ 143 = \$ 286
Total cost of pharmacist intervention	\$ 1.8 × 8 = \$ 14.4 \$ 286 + 14.4 = \$ 300
Mean cost of pharmacist intervention	\$ 300 ÷ 225 cases = \$ 1.3
Mean antibiotic cost reduction (pre-I – post-I = mean antibiotic cost reduction)	\$ 6.35
Cost benefit ratio	
Means antibiotic cost reduction for 225 cases: mean pharmacist time cost	4.8:1

otic usage, i.e. from 66.01 ± 41.01 h to 55.20 ± 36.21 h ($p=0.003$) (Table 4). Likewise, in post-intervention arm, there was 9.1% reduction in average number of antibiotic use (*pre-I*; 2.09 ± 0.90 , *post-I*; 1.86 ± 0.85 , $p=0.006$) and 25.7% reduction in average antibiotic cost (*pre-I*; 2463.17 ± 3546.42 , *post-I*; 1829.56 ± 2567.32 , $p=0.03$), respectively (Table 4).

In post-intervention arm, significant reductions of 34.8% and 16.6% were observed in average hospitalization cost (*pre-I*; 19230.9 ± 20075.8 , *post-I*; 12541 ± 6463.18 , $p=0.003$) and stay (*pre-I*; 5.4 ± 4.81 , *post-I*; 4.50 ± 3.39 , $p=0.023$), respectively (Table 4). After intervention, more patients were paying ≤ 15 K (PKR) in hospitalization costs (*pre-I*; 67.6%, *post-I*; 82.7%) with resultant decline in number of patients paying > 15 K in terms of hospitalization cost (*pre-I*; 32.4%, *post-I*; 17.3%) (Table 4).

Cost-benefit analysis

For cost-benefit analysis, pharmacist monthly salary in a hospital setting in Pakistan is around 50,000 PK Rs, was disbanded into monthly and hourly salary in US dollars (Table 5). Pharmacist time in hours for education sessions with doctors and nurses along with cost incurred in arranging the session was calculated by estimating the time of each session, i.e. 4 h – for 2 sessions 8 h in total, plus cost of arrangements – stationary, printed material and refreshment (tea), i.e. \$ 143 each. Thus, by adding the cost of time spent on education, \$ 14.4, and cost of logistics for two sessions, \$ 286, total costs of educational intervention to doctors and nurses stand at \$ 300 (Table 5). Thus, from the total cost of pharmacist intervention, the mean cost was estimated by dividing the total cost with a total number of cases, $300 \div 225$, yielding an average human cost of \$1.3 (Table 5). Thus, using means antibiotic cost reduction of all the cases and mean pharmacist cost resulted in the benefit to cost ratio of approximately 4.8:1 (Table 5).

Discussion

In the present study, we found that irrational practices were quite frequent regarding prophylactic antibiotic use in pre-intervention arm, such as the selection of inappropriate broad spectrum and costly antibiotics; gratuitously high doses of antibiotics; superfluous antibiotic combinations of the cephalosporin with aminoglycosides, fluoroquinolones & other β -lactam antibiotics etc., along with frequent antibiotic replacements without any reason – that adds to the total cost resulting from unnecessary therapy and hospitalization. While the educational intervention has a significant impact on the appropriateness of prophylactic antibiotic use in post-surgical procedures, particularly the antibiotic dose, frequency and duration that resulted in significant reductions in average cost of antibiotic use and of hospitalization.

Intervention; pharmacist as the stewards of antibiotics rational use

In developing countries like Pakistan, the surgeons tend to use the broad spectrum antibiotics indiscriminately for a longer period of time, probably due to fear of infection, malnutrition, overcrowding and poor hygienic conditions of the hospitals – which might add to irrational prescription of antibiotics and patient's morbidity [24]. Considering these apprehensions in mind, surgeons in Pakistan tend to change not only the duration of antibiotic use but also the choice of antibiotics for postoperative period that resulted in unnecessary economic distress on the patient and the health system along with the emergence of anti-microbial resistance [25,26].

The benefits of educational intervention in post-surgical antibiotic prophylaxis have been documented previously [27,28]. In our study, except for the antibiotic selection, pharmacist intervention significantly improved the dose, frequency, and duration of antibiotic usage. In post-intervention arm, there was significant reductions in the average duration of antibiotic use, average days of antibiotic utilization, average number of antibiotic used and average antibiotic cost. Similar to our findings, Mannien et al., demonstrated that optimized antibiotic policies governed by pharmacist resulted in a 35% reduction in prophylactic antibiotic use and a 25% reduction in cost [28]. Studies have also shown that the most common mistake by surgeons is the extended use of prophylactic antibiotics, which not only adds to the unnecessary cost but also the emergence of bacterial resistance [29,30]. Additionally, even studies from the developed countries did not demonstrate complete compliance with antibiotic prophylaxis guidelines, e.g., a study from France reported compliance of 41% with surgical prophylaxis guidelines, while another study from Australia demonstrated compliance of 17% with surgical prophylaxis guidelines [29,31]. We observed that total compliance, i.e. drug choice, dose, frequency, and duration, improved from 1.3% in pre-intervention arm to 12.4% in post-intervention arm, demonstrating a significant increase. Similar to our findings, the impact of educational intervention has been shown to remarkably improve the rate of appropriate surgical prophylaxis from 54% to 100% via educational intervention [32]. Thus, the qualified pharmacist with technical skills, at every level of health care dispensation, is pivotal for implementing rationality in evidence based medicine use, especially antibiotics. Moreover, as practiced in developed world, where pharmacist and physician collaborative efforts are appreciated and ensured to control the flow of medicines to the patients, the antibiotics are handled with great care and with much less influence of prescriber's behavior towards pharmacist integrated clinical practice [33]. Similarly, interventions by a clinical pharmacist can be instrumental in promoting quality use of medicine by publishing evidence based standard protocols and contemporary therapeutic information, educational sessions on prescribing and diagnosis,

public awareness messages on mass media and periodic reviews on antibiotic prescription patterns.

Study scope: multi-faceted health policy

In Pakistan, most of the clinical settings lack proper prophylactic guidelines on antibiotic use in post-surgical procedures and antibiotics are usually administered for 7–10 days, which results in increase cost for the patient, increase workload of hospital staff and emergence of antibiotic resistance [4]. Pakistan lacks national antibiotic policy or infection control policy. Probably, a few institutions may have partial policies but unless majority institutions have such policies in place, any impact at country level will be minimal. Thus, guidelines for any clinical setting should be formulated keeping several factors in mind, such as available facilities and expertise, impediments in its implementation, apt utilization of skilled human resource, e.g., clinical pharmacist. Nevertheless, it is encouraging that Pakistan in line with World Health Resolution in May 2015 has also triggered efforts to tackle the challenges of antimicrobial resistance (AMR) [22,34]. Thus, there is an urgent need that Pakistan should initiate a national action plan for implementation of consensus policies in various health care settings across Pakistan. The chief components of this plan should include, realistic evidence base antibiotic policy, comprehensive infection control policy, apt regulation regarding over the counter (OTC) antibiotics, microbiology culture reporting, establishment of national antimicrobial resistance network, ensure capacity building through targeted trainings and antimicrobial stewardship program in all hospitals.

Challenges and recommendations

However, challenges faced by Pakistan in combating ever growing utilization of antibiotics are many. In Pakistan, the technical demands, such as barrier premises, laminar flow in the theatre, separate changing room in the theatre and minimal traffic are still not among the ideal operational settings, which might hamper the preventive efforts. Furthermore, due to lack of standardized sterilization protocols and to become successful in private practice attracting maximum clients, the use of un-necessary antibiotics in surgical procedures is quite a common practice in order to avoid any chance of complications, particularly infection that might affect surgeon's ratings [35]. However, despite all these impediments, our data suggested that the benefits of intervention in terms of ratio of mean antibiotic cost reduction to cost of pharmacist's intervention time is approximately 4.8:1. Nevertheless, we observed and believed that the chances of benefits from pharmacist's educational intervention would be manifold if doctor-nurse-pharmacist collaborative loop develop in Pakistan to ensure a team effort in improving patient treatment outcomes by rationalizing therapy choices and their use. Clinical pharmacist having comprehensive knowledge about the formulation and disease is best suited for implementing treatment guidelines and overcoming all the factors not under the influence of a prescriber, such as assuring rational dose and duration along with therapy compliance, thereby pharmacist can promote therapy reconciliation by acting as a bridge between the prescriber and a patient.

Moreover, it is also imperative to establish a professional committee for antibiotic stewardship with members from various specialties including infectious disease area and microbiology. This might have a better impact on the willingness of the surgeons to accept guidelines guided utilization of antibiotics recommended or conversed by a committee of experts rather than just by a pharmacist. Additionally, antibiotic prophylaxis is not recommended for most clean surgeries in patients without additional postoperative infection risk factors. For clean-contaminated and clean

surgeries with risk of infection, a single dose of first generation cephalosporin is recommended. Regardless of the presence of indwelling catheters or drains, postoperative duration of antibiotic prophylaxis should be limited to less than 24 h. It is equally important that the training and educational programs should be in place for pharmacy and medical students with integration of AMR education and research in their professional curriculum, since we have already demonstrated rampant use of antibiotics by health professionals during their student lives [36]

Limitations

One of the major limitations of this study was non-availability of hospital standard guidelines for the use of prophylactic antibiotics in post-surgical procedures, since antibiotics were utilized as per surgeon's own experiences. Thus international guidelines were utilized to examine the rationality and same standards were conversed to surgeons during the interventional seminars and discussions. Similarly, due to non-existence of surgeon-patient-pharmacist loop, pharmacist acceptance is minimal in the health care system, and doctors seldom appreciate any intervention by a pharmacist, thus making it quite cumbersome to initiate such interventions convincing to the surgeons and having positive impact on patient's outcomes.

Conclusion

Thus, in conclusion our data suggested that pharmacist educational intervention contributed significantly in controlling inappropriate use of prophylactic antibiotic in post-surgical procedures. Data clearly demonstrated that there was considerable improvement in antibiotic dose, frequency and duration. Similarly, significant reduction was observed in average antibiotic cost, duration, hospitalization cost, in addition to overall benefits to cost ratio of 4.8:1. Thus, an effective communication and cooperation between clinical pharmacist and a surgeon could play an important role in promoting rationale use of prophylactic antibiotics along with minimum financial burden even in countries like Pakistan where pharmacist are still providing conventional services.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Approved from Punjab University College of Pharmacy, University of the Punjab, Lahore, Pakistan, ref #.HEC/PUCP/1931 and Institutional Review Board (IRB), ref# 5777/HR/GTTH, of the hospital.

Acknowledgements

We are thankful to all the surgeons, nurses & anesthetists for participating in the present study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jiph.2019.05.015>.

References

- [1] Choi WS, Song JY, Hwang JH, Kim NS, Cheong HJ. Appropriateness of antibiotic prophylaxis for major surgery in Korea. *Infect Control Hosp Epidemiol* 2007;28(08):997–1002.
- [2] Saleem Z, Hassali MA, Versporten A, Godman B, Hashmi FK, Goossens H, et al. A multicenter point prevalence survey of antibiotic use in Punjab, Pakistan: findings and implications. *Expert Rev Anti Infect Ther* 2019;17(4):285–93.
- [3] Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci* 2018;201717295.
- [4] Nausheen S, Hammad R, Khan A. Rational use of antibiotics—a quality improvement initiative in hospital setting. *J Pak Med Assoc* 2013;63(1):60.
- [5] Malik AZ, Qasim A. Surgical Site Infections after Elective Surgery in Pakistan: SURGIPAK Study. *J Rawalpindi Med Coll* : 2015;19(3):209–14.
- [6] Malik ZI, Nawaz T, Abdullah MT, Waqar SH, Zahid MA. Surgical site infections in general surgical wards at a tertiary care hospital. *Pak J Med Res* 2013;52(4).
- [7] Saleem Z, Hassali MA, Godman B, Hashmi FK, Saleem F. A multicenter point prevalence survey of health care-associated infections in Pakistan: findings and implications. *Am J Infect Control* 2019;47(4):421–4.
- [8] Fonseca SN, Kunzle SR, Junqueira MJ, Nascimento RT, de Andrade JJ, Levin AS. Implementing 1-dose antibiotic prophylaxis for prevention of surgical site infection. *Arch Surg* 2006;141(11):1109–13.
- [9] Van der Sandt N, Schellack N, Mabope L. Prescribing practices of antibiotic prophylaxis used for surgical procedures in paediatric patients at Dr. George Mukhari Academic Hospital (DGMHA) and a Private Hospital. Sefako Makgatho Health Sciences University; 2016.
- [10] Prokuski L. Prophylactic antibiotics in orthopaedic surgery. *J Am Acad Orthop Surg* 2008;16(5):283–93.
- [11] Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006;42(Suppl. 2):S82–9.
- [12] Marquet K, Liesenborg A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Crit Care* 2015;19(1):63.
- [13] Zhang HX, Li X, Huo HQ, Liang P, Zhang JP, Ge WH. Pharmacist interventions for prophylactic antibiotic use in urological inpatients undergoing clean or clean-contaminated operations in a Chinese hospital. *PloS One* 2014;9(2):e88971.
- [14] Shi QP, Ding F, Liu Y, Sang R, Zhu JX, Shi PL, et al. Pharmacists promote rational use of antibiotic prophylaxis in Type I incision operations via application of drug use evaluation. *Int J Clin Pharmacol Ther* 2013;51(9):704–10.
- [15] Magedanz L, Silliprandi EM, Dos Santos RP. Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: a quasi-experimental study. *Int J Clin Pharm* 2012;34(2):290–4.
- [16] Bond C, Raehl CL. Clinical and economic outcomes of pharmacist-managed antimicrobial prophylaxis in surgical patients. *Am J Health Syst Pharm* 2017;64(18).
- [17] Dunn K, O'Reilly A, Silke B, Rogers T, Bergin C. Implementing a pharmacist-led sequential antimicrobial therapy strategy: a controlled before-and-after study. *Int J Clin Pharm* 2011;33(2):208–14.
- [18] Shen J, Sun Q, Zhou X, Wei Y, Qi Y, Zhu J, et al. Pharmacist interventions on antibiotic use in inpatients with respiratory tract infections in a Chinese hospital. *Int J Clin Pharm* 2011;33(6):929–33.
- [19] Khan MS, Ahmed Z, Jehan S, Fasseh-uz-Zaman, Khan S, Zaman S, et al. Common trend of antibiotics usage in a tertiary care hospital of Peshawar, Pakistan. *J Ayub Med Coll Abbottabad* 2010;22(1):118–20.
- [20] Atif M, Azeem M, Saqib A, Scahill S. Investigation of antimicrobial use at a tertiary care hospital in Southern Punjab, Pakistan using WHO methodology. *Antimicrob Resist Infect Control* 2017;6(1):41.
- [21] Tasawer Baig M, et al. Irrational antibiotic prescribing practice among children in critical care of tertiary hospitals. *Pak J Pharm Sci* 2017;30.
- [22] Saleem Z, Hassali MA, Hashmi FK. Pakistan's national action plan for antimicrobial resistance: translating ideas into reality. *Lancet Infect Dis* 2018;18(10):1066–7.
- [23] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J health-syst Pharm* 2013;70(3):195–283.
- [24] Riaz H, Malik F, Raza A, Hameed A, Ahmed SK, Shah PA, et al. Assessment of antibiotic prescribing behavior of consultants of different localities of Pakistan. *Afr J Pharm Pharmacol* 2011;5(5):596–601.
- [25] Rosenberg AD, Wambold D, Kraemer L, Begley-keyes M, Zuckerman SL, Singh N, et al. Ensuring appropriate timing of antimicrobial prophylaxis. *J Bone Jt Surg* 2008;90(2):226–32.
- [26] Cartmill C, Lingard L, Regehr G, Espin S, Bohnen J, Baker R, et al. Timing of surgical antibiotic prophylaxis administration: Complexities of analysis. *BMC Med Res Methodol* 2009;9(1):43.
- [27] Van Kasteren ME, Mannien J, Kullberg BJ, de Boer AS, Nagelkerke NJ, Ridderhof M, et al. Quality improvement of surgical prophylaxis in Dutch hospitals: evaluation of a multi-site intervention by time series analysis. *J Antimicrob Chemother* 2005;56(6):1094–102.
- [28] Mannien J, van Kasteren ME, Nagelkerke NJ, Gyssens IC, Kullberg BJ, Wille JC, et al. Effect of optimized antibiotic prophylaxis on the incidence of surgical site infection. *Infect Control Hosp Epidemiol* 2006;27(12):1340–6.
- [29] Ozkurt Z, Kadanali A, Ertek M, Erol S, Parlak M. Antibiotic use in surgical prophylaxis. *J Ankem* 2005;19:111–4.
- [30] Gyssens IC, Geerligs IE, Dony JM, van der Vilet JA, van Kampen A, van den Broek PJ. Optimising antimicrobial drug use in surgery: an intervention study in a Dutch university hospital. *J Antimicrob Chemother* 1996;38(6):1001–12.
- [31] Lallemand S, Thouverez M, Bailly P, Bertrand X, Talon D. Non-observance of guidelines for surgical antimicrobial prophylaxis and surgical-site infections. *Pharm World Sci* 2002;24(3):95–9.
- [32] Prado MA, Lima MP, Gomes Ida R, Bergsten-Mendes G, et al. The implementation of a surgical antibiotic prophylaxis program: the pivotal contribution of the hospital pharmacy. *Am J Infect control* 2002;30(1):49–56.
- [33] DeMik DE, Weg MWV, Lundt ES, Coffey CS, Ardey G, Carter BL. Using theory to predict implementation of a physician?pharmacist collaborative intervention within a practice-based research network. *Res Social Adm Pharm* 2013;9(6):719–30.
- [34] Pakistan, M.o.N.H.S.R.C.G.o. National Action Plan of Pakistan on Antimicrobial Resistance 2017.
- [35] Yousuf M, Hussain M. Need and duration of antibiotic therapy in clean and clean contaminated operations. *J Pak Med Assoc* 2002;52(7):284–7.
- [36] Saleem Z, Saeed H, Ahmad M, Yousaf M, Hassan HB, Javed A, et al. Antibiotic self-prescribing trends, experiences and attitudes in upper respiratory tract infection among pharmacy and non-pharmacy students: a study from Lahore. *PLoS One* 2016;11(2):e0149929.