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Proper Timing for Administration of Prophylactic Intravenous Antibiotics for Elective Surgical Procedures

Ala Odah[1*], Hussein Alhusban[1], Abdullah Abu Kaff[1], Feras Alkhawaldeh[1], Sa'ad Alwraikat[1], Saed Alshoufeen[1]

[1]Department of General Surgery, the Royal Medical Services, Amman, Jordan

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***Corresponding author:** Ala Odah
Department of General Surgery, the Royal Medical Services, Amman, Jordan

Abstract **Original Research Article**

***Background*:** Preoperative antibiotic prophylaxis is administering antibiotics before performing surgery to help decrease the risk of postoperative infections. The antibiotic selected should only cover the likely pathogens. It should be given at the correct time. The timing of antibiotic administration may vary, but the goal of administering preoperative systemic prophylactic antibiotics is to have the concentration in the tissues at its highest at the start and during surgery. The literature supports at least 30 minutes, but no greater than 60 minutes before the skin incision is made to the optimal timing for the preoperative administration of most commonly used antibiotics. ***Aims and Objectives*:** To obtain precise information on the optimal time window for surgical antimicrobial prophylaxis (SAP). ***Methodology*:** A retrospective observational study design was used to investigate the effect of timing of SAP on the risk of surgical site infection (SSI) from September 2021 until September 2022. Patients with Inguinal hernia who performed elective inguinal hernia repair were eligible for enrollment in the study. The risk of SSI was compared between patients, categorized by the time interval between SAB administration and incision, and adjusted for confounding through Univariate Analysis logistic regression. Hakeem data base was used to collect the required data. This study was performed in King Hussein Medical Center (KHMC) at the Royal Medical Services in Amman/Jordan. ***Results*:** Data included in the current study was collected for the period between September 2021 until September 2022, in which 500 patients were randomly assigned into two arms; Patients in arm A received the in a time window of 60 to 30 minutes before the scheduled incision while Patients in arm B received the antibiotics in time window of less than 30 minutes to 0 minutes before the scheduled incision. In 52% of the procedures, SAP was administered within 60 minutes before incision Inpatient and outpatient follow-up rate was 100% (500/500 with an overall SSI rate of 9.2% (46 of 500). Early administration (Arm B) of SAP did significantly reduce the risk of SSI compared to late administration (Arm A) [odds ratio: 0.7; 95% confidence interval (0.32-1.21)].; P value =0.02). ***Conclusions*:** The present results support that narrowing of the time window for the administration of SAP to 0–30-minute window would decrease the risk of SSI incidence.

Keywords: Antibiotic prophylaxis, infection prevention, perioperative care, surgical site infection, wound infection.

INTRODUCTION

One of the most frequent causes of nosocomial infections, responsible of about 30 to 35% of all nosocomial infections globally, is surgical site infection (SSI) [1]. The Centre for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC)] precisely defined SSI as "postoperative infection occurring within 30 days of a surgical procedure (or within one year for permanent implants)" [2]. As stated by the estimations of the World Health Organization (WHO) in 2011, the rate of SSI in developed countries ranges from 1.2 to 5.2%, whereas that in developing countries is 10.8% [3]. The incidence of SSIs leads to a significant rise in the clinical and financial load of surgical interventions. The direct costs incurred by the patient's prolonged hospital stay, diagnostic procedures, and therapy increase the economic burden of surgery [4]. Additionally, certain patients might necessitate a second surgery after developing an SSI, which would incur significant additional expenses. Preventive interventions necessitate a comprehensive strategy that focuses on pre-, intra-, and postoperative care and involves all medical care professionals because there are many factors that can increase the chance of SSI incidence. Infection at the surgical site is caused by a variety of factors. The primary patient-related (endogenous risk factors) and procedure-related (external risk factors) factors that affect the risk of SSI have been identified in

several investigations [5]. Operating room quality also has a significant impact on the frequency of surgical wound infections. An operating room that is safe and healthy is one where all pollution sources and little environmental changes are strictly controlled. Only thorough planning, upkeep, regular inspections, and staff that have received the appropriate ongoing training will be able to accomplish this [6]. Numerous global scientific societies have produced recommendations on healthcare-associated infections, including SSI, concerning surveillance techniques, intervention to actively prevent SSI, and methods to monitor the implementation of such strategies [7].

Surgical Antimicrobial Prophylaxis

Surgical antimicrobial prophylaxis effectively lowers the rate of SSI and hospital length of stay while reducing the load of microorganisms at the surgical site. It has been demonstrated that using antibiotics reduces SSI by 39%. Antibiotics must be given before to surgery in order to successfully prevent SSIs. Preoperative management of active wound infections is excluded from this. The SAP rules across nations and institutions show minor variations. Several guidelines generally recommended that in surgical interventions associated with a high risk of infection; antibiotic prophylaxis should be used (e.g.; Clean-contaminated or contaminated operations) [8]. Only procedures involving prosthetic implantation are supported by the need for SAP due to the risk of serious complications if the prosthesis becomes infected after surgery. The use of SAP before all gastrointestinal, oropharyngeal, and gynecological procedures is widely implemented based on evidence from observational and randomized controlled trials (RCT). In the absence of high rates of resistant bacteria, current recommendations suggest that a single dose of a first- or second-generation cephalosporin is sufficient for the best SSI prevention [9]. The benefits of SAP must be weighed against its costs and potential drawbacks because, in clean procedures, the infection's morbidity is typically modest. Updated guidelines should be followed for the most efficient antibiotic prophylaxis of SSIs. First, the antibiotics that are being recommended should be capable of killing the bacteria that is most likely to infect the surgical site. Regarding gastrointestinal surgery, in clean procedures, the most common pathogens are those included in the skin flora, mainly Staphylococcus aureus and Staphylococcus epidermidis, whereas in clean-contaminated procedures, most of the cases are due to enteric Gram- negative rods, mainly Escherichia coli, Proteus spp., Klebsiella spp., enterococci and, in some cases, anaerobes, mainly Bacteroides and Clostridia. However, the predominance of certain species can change depending on the procedure, the time, and the location of the study [10]. Cefazolin, Cefuroxime, Cefoxitin, and Cefotetan are the most suggested and often used medications for SSI prophylaxis after gastrointestinal surgery given the likely aetiology of SSIs [11]. Additionally, it's important to give antibiotics at a dosage and timing that will result in adequate serum and tissue concentrations that will kill bacteria for the duration of the intervention. It has been determined that 30 minutes prior to the surgical incision is the best time to administer preoperative dosages, while other guidelines recommend a time window of 30-60 minutes before incision. These suggestions, however, are not supported by thorough assessments of the available evidence or systematic reviews of the literature or meta-analyses [12]. The majority of these observational studies favours administration of SAP just before incision most of the time. The American Society of Health-System Pharmacists, the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, the Royal College of Physicians of Ireland, and Health Protection Scotland are just a few professional organizations or national authorities that have recently released guidelines that suggest administration no later than 60 minutes before an incision. According to some recommendations, SAP should be delivered within the last 30 minutes prior to incision, with the exception of vancomycin and fluoroquinolones [13]. The largest prospective cohort trial on cefuroxime (a second-generation cephalosporin) to date was one of several observational studies that revealed treatment close to the incision time may be too late for the best SSI prevention [14]. In this study, the goal was to identify the ideal window for SAP during elective inguinal hernia repair, one of the most frequently done procedures by general surgeons. The main outcome of concern was the SSI incidence following the administration of antibiotic prophylaxis at various times following the initial incision in elective inguinal hernia repair. The results revealed that early administration of cefuroxime did not significantly lower the risk of SSI compared with late administration before incision.

The aim of our study is to obtain precise information on the optimal time window for surgical antimicrobial prophylaxis (SAP). The results of this study will address areas that have not been sufficiently covered in Jordan in the past, if not completely fill the knowledge gap. By revealing the ideal window for surgical antimicrobial prophylaxis in patients having procedures in Jordan, the study's findings will add to the body of knowledge in this field.

METHODS

Study Design and Site

A retrospective observational study design was used to investigate the effect of timing of SAP on the risk of SSI. The risk of SSI was compared between patients, categorized by the time interval between SAP administration and incision, and adjusted for confounding through Univariate Analysis logistic regression. The study was carried out from September 2021 until September 2022 in King Hussein Medical Center (KHMC) at the Royal Medical Services in Amman/Jordan.

Study Population

All patients who underwent elective inguinal hernia repair and received SAP during the study period constituted the study population.

Inclusion and Exclusion Criteria

Inpatients aged 18 years or older underwent elective inguinal hernia repair with an indication for SAP according to clinical standards are eligible for this study. The exclusion criteria were patients with:

1. Recurrent hernia.
2. Immuno-suppressive disease (Malignancy).
3. Kidney Dialysis.

Ethical Considerations

The protocol of this study was approved by the ethics committee in the Royal Medical Services.

Data Collection

Data were collected from Hakeem Data base. Relevant data were retrieved from the patient's files. We collected socio-demographic data, clinical data, and data regarding the SAP.

Antibiotics Administration

SAP was administered by the anaesthesia team to all patients in a standardised manner via single-shot, intravenous infusion of (1 gm Cefazolin, 1 gm Cefoxitin, or 1.5 g of cefuroxime) in 100 ml of a 0·9% sodium chloride solution over 2-5 minutes.

Sample Size

During the study period, 603 patients received elective inguinal hernia repair; however, 103 individuals were disqualified based on the exclusion criteria. Two arms of patients were used (A and B). Patients who got SAP in the anesthesia room, as opposed to the operating room itself (arm A), (arm B). Patients in arm A got the SAP between arrival the anesthesia room and moving to the operating room, or between 60 and 30 minutes prior to the planned incision. Between their arrival in the operating theatre and the time of incision for patients in arm B, which corresponds to the time period of less than 30 minutes to 0 minutes before the scheduled incision, ideally as near to the scheduled incision.

Study Endpoints

The primary endpoint of this study is the occurrence of any SSI within 30 days after surgery. SSI are defined as incisional (either superficial or deep) infection or organ-space infection according to CDC criteria [15].

Statistical Analysis

Descriptive analyses were performed using SPSS version 24.0. A *P*-value < 0.05 was considered statistically significant. Descriptive analysis (Frequencies, percentages, mean, and standard deviation) were obtained to illustrate the study variables. In order to analyze the difference in SSI occurrence between the two-timing groups, logistic regression models have been used to exposure differences between variables.

RESULTS

Between September 2021 and September 2022, 603 patients underwent elective inguinal hernia repair in the designated operating rooms. Finally, 500 eligible patients were included in the analysis. Of these, 240 patients (48%) received SAP between 30 and 0 minutes before incision, 260 (52%) between 60 and 30 minutes before incision. Patient characteristics are described in Table 1. All regimens provided adequate coverage and antibiotics requiring longer infusion time (eg, vancomycin) were not used). Patients who received SAP 60 to 30 minutes before incision were slightly older and had more comorbidities than those receiving SAP 30–0 minutes before incision.

Table 1: Patient Characteristics and General Demography

Variable	Total	60–30 min Before Incision (%)	30–0 min Before Incision (%)
	500	**260 (52%)**	**240 (48%)**
Age in years (%)			
18–41	146 (29.2)	88 (60.2)	58 (39.8)
41–52	115 (23)	70 (60.9)	45 (39.1)
52–61	118 (23.6)	45 (39.2)	73 (61.8)
61–70	121 (24.2)	67 (55.3)	54 (44.7)
Male (%)	289 (57.8)	181 (62.6)	108 (37.4)
BMI (%)			
Underweight (0–18.5)	15 (3.0)	6 (4.0)	9 (2.4)
Normal weight (18.5–25.0)	134 (26.8)	60 (23.0)	74 (30.8)
Overweight (>25.0)	351 (70.2)	177 (68.0)	174 (72.5)
Smoking (%)	310 (60.2)	178 (68.4)	132 (55.0)
Diabetes (%)	186 (37.2)	95 (36.5)	91 (37.9)
Cardiovascular disease (%)	144 (28.8)	82 (31.5)	62 (25.8)
Pulmonary disease (%)	232 (46.6)	152 (58.4)	80 (33.3)

Antibiotic prophylaxis agent			
Cefazolin	288 (57.6)	145 (55.7)	143 (59.5)
Cefoxitin	122 (24.4)	71 (27.3)	51 (21.2)
Cefuroxime	62 (12.4)	38 (14.6)	24 (10)
Others*	28 (5.6)	17 (6.5)	11 (4.5)
SSI			
SSI, superficial, deep, organ-space (%) [§]	46 (9.2)	23 (50)	23 (50)
Superficial (%)	9 (19.5)	6 (26)	3 (13)
Deep (%)	13 (28.2)	9 (39.1)	4 (17.4)
Organ-Space (%)	24 (52.3)	16 (69.5)	8 (34.7)
Length of stay [mean (SD)]	8.1 (3.1)	9.3 (3.4)	6.8 (2.3)

*Including: (combinations of) gentamicin, flucloxacillin, metronidazole, ceftriaxone, cefuroxime, cefotaxime, cefazolin
§According to the Center for Disease Control and Prevention definition of surgical site infection.

During the 30 days of follow up, 46 (9.2%) SSIs were diagnosed, of which 9 (19.5%) were superficial and 13 (28.2%) were deep. After adjustment for confounding in the univariate logistic regression model, there was conclusive evidence of a difference in SSI risk comparing SAP administration 60–30 to 30–0 minutes before incision (30-60 min OR=1.53) listed in Table 2.

Table 2: Association between Timing of SAP and SSI

Timing	**SSI/Total (%)**	**OR**	**95% CI**	***P***
		Univariate Analysis		
60-30 min before incision	23/260(8.8)	1.53	0.97-1.92	0.02
30-0 min before incision	23/240(9.5)	1.11	1.21-2.69	

*Variables included in the model: BMI, diabetes, cardiovascular disease, procedure duration, transfusion, blood loss.
CI indicates confidence interval; OR, odds ratio; *P*, *P*-value; SSI, surgical site infection.

DISCUSSION

To the best of our knowledge, this study is the first which investigate the impact of variuos SAP timings on the incidence of SSI in the RMS. It was found that giving SAP early (between 0 and 30 minutes before the incision) significantly reduces the risk of SSI compared to giving it late (between 30 and 60 minutes before the incision) ([odds ratio: 0.7; 95% confidence interval (0.32-1.21)]).; P value =0.02) and the only study to evaluate timing as a continuous variable. The results of our study are consistent with those of a large prospective observational cohort study on cefuroxime that looked at the incidence of SSI by the time of SAP in a series of 3836 consecutive general surgical procedures [16]. When SAP was provided more than 30 minutes before to incision, the risks of SSI were almost two times higher than they were within the reference range of 0 to 30 minutes prior to incision, according to multivariable logistic regression analysis (adjusted odds ratio = 195; 95% confidence interval, 14 to 28; *p* 0.001). The lowest prevalence of SSI was observed when the antibiotics were given between 10 and 30 minutes before to surgery, even though SAP was applied to the majority of patients between 32 and 0 minutes before incision.

According to the evidence now available, for a procedure to be effective, sufficient tissue concentrations of SAP must be present at the time of incision and during the entire surgical procedure until closure. Guidelines provide recommendations in keeping with this idea [17, 18], however there is still debate regarding the exact SAP timing that works best [19-21]. A systematic analysis on the time of SAP administration reported conflicting findings during the final 60 minutes before to incision, but recommended that SAP be delivered within 120 minutes of incision [22]. Some of the included studies support the administration of SAP within 30 minutes of incision, whereas others support administration of SAP in a time window exceeds 30 minutes prior to incision or show no benefit at all [23-25]. The drugs utilized, the use of intraoperative redosing, the use of postoperative antibiotics, and variances in half-life and infusion time are all different in these studies. There was no difference in SSI risk between early administration of SAP in the anesthetic room and later administration in the operating room, according to a recent randomized controlled trial. However, the uncertainty persisted because to the overlap in scheduling between the 2 groups [26].

LIMITATIONS

The first of this study's limitations concerns how generalizable the results are. The study was conducted in a central referral facility in Amman, Jordan, and its findings might not be generalizable to a different patient population, such as one with a significantly greater prevalence of infection or antibiotic resistance. Second, one month of follow-up after an elective inguinal hernia operation is insufficient to detect all SSI. Last but not least, our study was constrained by a small sample size.

CONCLUSION

The findings of this study suggest that limiting the SAP administration window to a 0 to 30-minute window would reduce the chance of SSI occurrence. As a result, the antibiotic would be present in sufficient tissue concentrations throughout the procedure. This demands administration before incision. Additional evidence demonstrates the link between greater SSI rates and low tissue concentrations of antibiotics at the time of wound closure.

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