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Original Article

A comparative study between a single-dose and 24-hour multiple-dose antibiotic prophylaxis for elective hysterectomy

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Abstract
Introduction: Surgical site infections (SSIs) are a major health issue in surgical specialties in terms of health care costs and patients' clinical outcomes. At the level of the patient, prolonged hospital stays or readmissions for SSIs, can affect the patient's quality of life. At the level of the health care system, it exhausts the hospital's resources and increases the burden on the medical staff due to the need for continuous wound care, microbiological cultures, laboratory tests and medications. In this study, we assessed the effectiveness of two antibiotic prophylaxis regimens for the prevention of SSIs in patients undergoing elective hysterectomy surgeries.
Methodology: A retrospective cohort, analyzing 141 patients, was conducted between November 2016 and January 2019 at a university hospital. We compared the efficacy of a single dose *vs.* 24-hour multiple doses of Cefazolin in patients who underwent elective hysterectomy for benign or malignant indications. The secondary objective was to identify potential risk factors associated with SSIs.
Results: There was no statistically significant difference between both groups ($p = 0.872$). Obesity and a laparotomy surgical approach are risk factors to the development of SSIs ($p = 0.001$ and 0.014, respectively). Other potential risk factors include the duration of hospital stay, the duration of the surgery and the amount of blood loss.
Conclusions: Although the rate of SSIs is not significantly different between both groups, risk stratification can be done after screening patients and the prophylactic regimen must be tailored for each patient in a cost-effective manner and using a multidisciplinary approach.

Key words: Antibiotics; cefazolin; hysterectomy; prophylaxis; surgical; site infections.

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Introduction

The rate of surgical site infections (SSIs) has recently increased with a significant number of patients being readmitted due to SSIs following hysterectomies [1]. This increased rate affects the patient's quality of life and leads to prolonged hospital stay and increased health-care costs [2]. Although SSIs are among the most preventable hospital-acquired infections, they still represent a significant burden in terms of patients' morbidity and mortality as well as further costs to health systems and service payers [3]. Thus, SSIs have been one of the most frequently investigated nosocomial infections, in low and middle-income countries, by medical professionals, health care authorities, the media as well as the public who may attribute SSIs to poor quality of care [4-7].

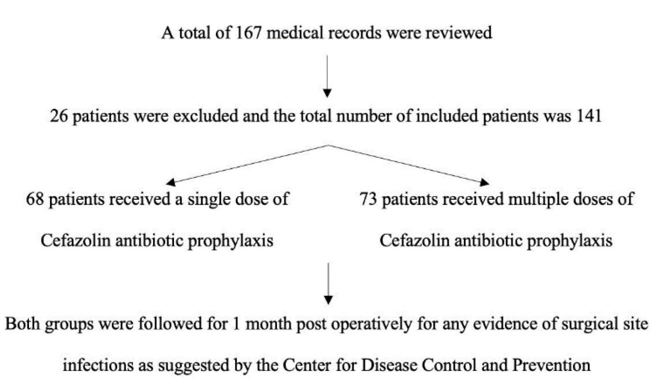
SSIs are potential complications to any surgical procedure and they represent 14%-16% of all hospital-acquired infections, with a frequency as high as 20% for intra-abdominal surgeries and up to 10% in gynecological surgeries [8,9].

Apart from two publications from Saudi Arabia, there is no published data on the rate of SSIs from any of the Arabian gulf countries [10,11]. A five-year analysis of SSIs related to orthopedic surgeries, in King Fahad University Hospital in Alkhobar, estimated a rate of 2.55% [10]. Another study from King Abdul-Aziz Medical City in Riyadh, showed that the rates of SSIs were 0.88% for herniorrhaphy surgeries and 0.48% for cholecystectomies in the period between 1999 and 2001 [11]. These rates were reduced by 80% for herniorrhaphies ($p = 0.049$) and 74% for cholecystectomies (p = 0.270) in 2007 due to a better adherence to infection control practices and a shift to minimally invasive surgeries [11]. The last annual report from the Infection Control Department in our institution, King Saud University Medical City in Riyadh, revealed an increase in the overall rate of SSIs following hysterectomy procedures to 9.7% (S. Alqahtani, personal communication, 28 April 2019).

The administration of prophylactic antibiotics in a single dose, in patients undergoing hysterectomy regardless of the route of surgery, is the standard of care and is always recommended to minimize the rate of postoperative infections and help prevents the adverse effects of long-term antibiotic treatment. The American College of Obstetricians and Gynecologists (ACOG) recommends, for patients not allergic to Penicillin and undergoing hysterectomy procedures, a first-generation Cephalosporin (e.g. Cefazolin) 2-3 grams based on body weight [12]. On the other hand, in patients allergic to Penicillin and due to the cross reactivity that often occurs in these patients with Cephalosporins, a combination of a single dose of Metronidazole 500 mg or Clindamycin 900 mg plus Gentamicin 5mg/kg or Azternam 2 gm is recommended [12]. However, there are yet no standardized protocols implemented in Saudi Arabia and there are no published national or regional studies assessing SSIs following gynecological surgeries; despite their continuous impact on patients and hospitals. Moreover, local hospital protocols may differ from other national or international recommendations in terms of the level of adherence, type of antibiotics, frequency or even doses. The role of antibiotic prophylaxis prior to a hysterectomy procedure is unquestionable and the administration of more than a dose is recommended only in certain circumstances such as prolonged surgeries or when bleeding is expected to be equal to or more than 1.5 liters [13,14]. However, hysterectomy remains the most common gynecological procedure causing SSIs in King Saud University Medical City (S. Alqahtani, personal communication, 28 April 2019) and due to this relatively high rate and the demographical characteristics of the Saudi patients where obesity, prediabetes and diabetes are prevalent and represent major health issues [15-17], we aimed to assess whether the recommended single dose is enough or that more doses may be needed in reducing SSIs in our population.

The primary objective of our study was to compare the efficacy of a single dose *vs.* 24-hour multiple doses of Cefazolin in patients who underwent an elective hysterectomy for benign or malignant causes. The secondary objective was to identify risk factors for the development of SSIs in gynecological patients.

Figure 1. Patients' flow chart.



Methodology

The case files of one gynecological oncologist (KA) were retrospectively reviewed for all elective hysterectomies done in our hospital; whether the procedures were done through a laparotomy or using a minimally invasive surgery. A total of 167 cases were found between November 2016 and January 2019 and 141 patients were included based on the following criteria (Figure 1).

The inclusion criteria were:

- Patients who underwent an elective hysterectomy for benign or malignant reasons (abdominal, vaginal, laparoscopic and robotic surgeries).
- Patients operated by the same surgeon (KA) under the same sterilization techniques.
- Patients received either a single dose of Cefazolin (2-3 gm) 30-60 minutes before skin incision as recommended by ACOG [12], or multiple doses of Cefazolin (2-3 gm) 8 hours pre-incision, (2-3 gm) 30-60 minutes before skin incision and (2-3 gm) 8 hours post incision; based on their known risk factors e.g. a previous history of SSI, morbid obesity or diabetes mellitus.
- Patients with available follow up data for a at least one month postoperatively.

The exclusion criteria were:

- Patients who underwent an emergency hysterectomy
- Immunocompromised patients
- Patients with known allergies to β-lactams
- Patients with incomplete documentation of prophylactic antibiotic administration
- Patients who lost follow up post-operatively.

Table 1. The demographic and clinical characteristics of patients.

Total number of patients (n = 141)		**Group 1: Single dose of Cefazolin**		**Group 2: 24-hour multiple doses of Cefazolin**		***p*-value**
		N = 68		**N = 73**		
Age (mean ± SD; in years)		54.03 ± 8.71		55.14 ± 9.43		0.471
BMI (mean ± SD; kg/m^2)		33.25 ± 6.02		34.77 ± 6.83		0.167
		N	**Percentage (%)**	**N**	**Percentage (%)**	
History of diabetes	Diabetic	15	22.06	33	45.21	**0.004***
	Non diabetic	53	77.94	40	54.79	
Control of diabetes	Controlled	13	86.67	20	60.61	0.067
	Uncontrolled	2	13.33	13	39.39	
Previous incisions	Yes	22	33.85	25	35.21	0.867
	No	43	66.15	46	64.79	

* Significant *p*-value; BMI: body mass index; kg: kilogram; N: number; m: meter; SD: standard deviation.

Table 2. The intra-operative and post-operative characteristics of patients.

Total number of patients (n = 141)	**Group 1: Single dose of Cefazolin**		**Group 2 24-hour multiple doses of Cefazolin**		***p*-value**
	N = 68		**N = 73**		
Blood loss (mean ± SD; in ml)	392.65 ± 341.78		492.05 ± 410.84		0.122
Duration of surgery (mean ± SD; in minutes)	129.29 ± 49.92		150.99 ± 52.66		**0.013***
Duration of hospital stay (mean ± SD; in days)	4.68 ± 3.69		5.70 ± 3.87		0.111
	N	**Percentage (%)**	**N**	**Percentage (%)**	
Indication for surgery					
Benign causes	47	69.1	39	53.4	0.056
Malignant causes	21	30.9	34	46.6	
Surgical approach					
Laparotomy	44	64.71	53	72.60	0.312
Minimally invasive surgery	24	35.29	20	27.40	
Type of laparotomy incision					
Pfannenstiel or Maylard incision	25	56.82	19	35.85	**0.039***
Midline incision	19	43.18	34	64.15	
The presence of intra-operative complications					
Yes	5	7.4	6	8.2	0.848
No	63	92.6	67	91.8	
Types of intra-operative complications					
Vascular injury	0	0.0	2	33.3	0.848
Bowel injury	0	0.0	2	33.3	
Urinary bladder injury	2	40.0	1	16.7	
Bleeding	2	40.0	0	0.0	
Bowel, urinary bladder injury and blood transfusion	1	20.0	0	0.0	
Urinary bladder injury and blood transfusion	0	0.0	1	16.7	
The presence of surgical drainage					
Yes	14	20.6	15	20.5	0.995
No	54	79.4	58	79.5	
The presence of SSI					
Yes	9	13.2	9	12.3	0.872
No	59	86.8	64	87.7	
Classification of SSI (N=9)					
Superficial	9	100.0	8	88.9	0.303
Deep	0	0.0	1	11.1	
Organ/space	0	0.0	0	0.0	

* Significant *p*-value; ml: milliliter; N: number; SD: standard deviation; SSI: surgical site infection.

The electronic medical records of all included patients were revised for demographic and clinical variables including: age, body mass index (BMI), blood sugar levels, immunity status, allergies, history of previous surgeries, duration of hospital stay, surgical approach, the duration of the operation, intraoperative complications, blood loss, surgical drainage, final pathology results, SSIs classification and causative pathogen when present. SSIs were classified as suggested by the Center for Disease Control and Prevention into: superficial incisional SSIs, deep incisional SSIs and organ/space SSIs [18].

The study was approved by King Saud University Internal Review Board and the confidentiality of the data was retained under strict privacy.

Data was analyzed using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). Continuous variables were expressed as means ± standard deviation and categorical variables were expressed as percentages. The *t*-test was used for continuous variables and the chi-square test was used for categorical variables. Univariate and multivariate logistic regression were used to assess the risk factors. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 141 patients were included in this retrospective analysis. The clinical and demographic data are summarized in Table 1. The mean age of patients receiving a single dose of Cefazolin (group 1) and patients receiving 24-hour multiple doses of Cefazolin (group 2) were 54.03 years and 55.14 years, respectively (*p* = 0.471). There were no statistically significant differences between both groups in regards to age, BMI, previous history of incisions and the control of blood sugar levels in diabetic patients. Diabetes mellitus is a historical risk factor for SSIs, thus more diabetic patients, as per the practice of the treating gynecological oncologist, were included in group 2 (15 patients in group 1 *vs.* 33 patients in group 2, *p* = 0.004). The rate of developing SSIs was 13.2% in group 1 *vs.* 12.3% in group 2 (*p* = 0.872) (Table 2). Nine patients in each group developed SSIs; all 9 SSIs were superficial in group 1, 8 were superficial in group 2 and 1 was a deep SSI in group 2.

Table 3. Risk factors for surgical site infections; a univariate logistic regression analysis.

Risk factor	OR	95 % CI		*p*-value
		Upper	Lower	
Age	1.03	0.97	1.08	0.357
BMI	1.12	1.03	1.22	**0.006***
Control of diabetes				
Controlled**	1.00			
Uncontrolled	1.85	0.47	7.32	0.381
Previous incisions				
Yes	1.24	0.45	3.45	0.679
No**	1.00			
A malignant indication for surgery				
Yes	1.29	0.48	3.51	0.613
No**	1.00			
Surgical approach				
Laparotomy	9.14	1.18	71.02	**0.034***
Minimally invasive surgery**	1.00			
The presence of intraoperative complications				
Yes	0.66	0.08	5.53	0.705
No**	1.00			
The presence of surgical drainage				
Yes	2.17	0.74	6.40	0.159
No**	1.00			
Blood loss				
≥ 500 ml	2.92	1.06	8.09	**0.038***
< 500 ml**	1.00			
Duration of surgery	1.00	0.99	1.01	0.868
Duration of hospital stay				
≥ 7 days	2.92	1.02	8.38	**0.046***
< 7 days**	1.00			

* Significant *p*-value; ** Used as a reference; BMI: body mass index; CI: confidence interval; ml: milliliter; OR: odds ratio.

Table 4. Risk factors for surgical site infections; a multivariant logistic regression analysis.

Risk factor	OR	95 % CI		*p*-value
		Upper	Lower	
BMI	1.176	1.066	1.296	**0.001***
Duration of hospital stay				
≥ 7 days	1.737	0.542	5.569	0.353
< 7 days**	1.00			
Surgical approach				
Laparotomy	16.023	1.725	148.818	**0.014***
Minimally invasive surgery**	1.00			
Blood loss				
≥ 500 ml	1.576	0.505	4.921	0.434
< 500 ml**	1.00			

* Significant *p*-value; ** Used as a reference; BMI: body mass index; CI: confidence interval; ml: milliliter; OR: odds ratio.

Table 5. Types of pathogens cultured from patients with surgical site infections in both groups.

Type of pathogen	Group 1: Single dose of Cefazolin		Group 2: 24-hour multiple doses of Cefazolin		*p*-value
	N = 9	Percentage (%)	N = 7	Percentage (%)	
Escherichia Coli/Enterobacter cloacae	0	0.00	1	14.29	
Enterobacter cloacae	0	0.00	1	14.29	
Enterobacter gergoviae	1	11.11	0	0.00	
Klebsiella pneumonia	0	0.00	1	14.29	
Klebsiella pneumonia	0	0.00	1	14.29	
Klebsiella pneumonia	2	22.22	0	0.00	0.379
Klebsiella pneumonia	1	11.11	0	0.00	
Klebsiella pneumoniae	1	11.11	0	0.00	
Staphylococcus aureus	2	22.22	1	14.29	
Staphylococcus lugdunensis	0	0.00	1	14.29	
No culture	2	22.22	1	14.29	

N: number.

Table 6. Recommended guidelines for antibiotic prophylaxis prior to hysterectomy procedures.

Organization	Antibiotic of choice	Alternatives	Timing before the procedure	Dose	Frequency
SOGC* [13]	1^{ST} or 2^{nd} generation Cephalosporin	Clindamycin Erythromycin or Metronidazole	15 to 60 minutes prior to skin incision	1-3 gram (depends on weight)	Single dose unless, lengthy (4 hours or more) surgery or massive blood loss (1.5 Liters or more)
ACOG** [14]	Cefazolin	Quinolones or Vancomycin	Within 1 hour for Cefazolin; Within 2 hours for alternatives	1-3 gram (depends on weight)	Single dose unless, lengthy (4 hours or more) surgery or massive blood loss (1.5 Liters or more)

*SOGC: The Society of Obstetricians and Gynaecologists of Canada; **ACOG: The American College of Obstetricians and Gynecologists.

None of the patients included in the study developed an organ/space SSI. Patients in group 2 tended to have longer surgeries than those in group 1 (p = 0.013). Although there was no statistically significant difference between both groups, patients who underwent a laparotomy procedure were more common than those who underwent a minimally invasive surgery (44% *vs.* 24% in group 1 and 72.6% *vs.* 27.4% in group 2, p = 0.312). Both groups were comparable in terms of the amount of blood loss, duration of hospital stay, indication for surgery, the presence or absence of surgical drainage and intraoperative complications. Table 2 summarizes the intra-operative and post-operative characteristics of both groups of patients. The results of a univariate analysis (Table 3) reveal that BMI (p = 0.006), a laparotomy surgical approach (p = 0.034), blood loss ≥ 500 ml (p = 0.038) and a hospital stay ≥ 7 days (p = 0.046) are significantly associated with a higher risk of developing SSIs. However, in a multivariant analysis, shown in Table 4, only BMI and a laparotomy surgical approach remain statistically significant risk factors for developing SSIs (p = 0.001 and 0.014, respectively). Table 5 shows the types of pathogens cultured from the wounds of patients with SSIs. There was no statistical difference between group 1 and group 2 in terms of the causative organisms (p = 0.379).

Discussion

A surgical site infection is one of the most common postoperative complications and comprises 25% of all reported nosocomial infections [19].

Although the role of antibiotic prophylaxis has been established and recommended in all surgical guidelines as shown in Table 6, few publications have emerged during the past few years assessing the optimal prophylactic antibiotic regimens in different surgical specialties [20-22].

An evaluation of the use of antibiotic prophylaxis in 34,133 Medicare patients with a major surgical procedure revealed that only 55.7% had an antimicrobial dose administered within one hour before incision [20]. The antibiotic was discontinued within 24 hours of the surgery end time for only 40.7% of patients [20]. The authors concluded that considerable prospects exist to expand the use of prophylactic antibiotics for patients undergoing major surgeries to avoid SSIs and they also highlighted the importance of implementing standardised protocols to reduce the risk of SSIs [20]. Another randomized multicenter study, evaluating elective colorectal surgeries, showed that the administration of three-dose Cefmetazole is significantly more effective than a single dose for the prevention of SSIs [22]. The same results were achieved in cardiac surgeries [23].

SSIs in the field of obstetrics and gynecology pose a different challenge in that the source of pathogens can be the skin or the vagina and endocervix depending on the surgical approach used. Therefore, SSIs related to gynecological procedures tend to be polymicrobial and include gram-positive as well as gram-negative bacteria. A prospective randomized comparative study showed that the preoperative prophylactic use of a single-dose Cefazolin prior to a gynecological surgery was as effective as four doses of Cefazolin for preventing postoperative infections [19]. Another study focused on patients who underwent cesarean sections and the authors concluded that the evidence was inadequate to decide whether there is a difference between a single *vs.* multiple-dose antibiotic regimens in reducing the incidence of infections after caesarean sections [24]. Our findings support some of the previously published data [19]. We found no statistically significant difference in the rate of SSIs between patients receiving a single dose or 24-hour multiple doses of prophylactic Cefazolin in elective hysterectomies. The properties of Cefazolin have made it an appropriate prophylactic antibiotic in several fields of surgeries, due to its wide antimicrobial range, its inexpensive price, its sufficiently long half-life and its tendency to concentrate in subcutaneous tissues [19,25,26].

Our results also pointed to several actual and potential risk factors for SSIs e.g. obesity as reflected in BMI measurements and a laparotomy surgical approach. In fact, a cross-sectional analysis of the 2005-2009 American College of Surgeon's National Surgical Quality Improvement Programs patient files showed that a BMI greater than 30 kg/m^2 is associated with a higher rate of SSIs in gynecological and obstetric surgeries [27]. Despite the strong clinical evidence and obvious advantages of minimally invasive surgeries including fewer complications, shorter hospital-stay and lesser costs, the rate of abdominal hysterectomy is higher than those done with minimally invasive procedures. This has been demonstrated in an analysis from the United States in 2007; which showed that abdominal hysterectomies are performed in 66% of cases, vaginal hysterectomies in 22% and laparoscopic hysterectomies in 12% [28]. The preference of a laparotomy surgical approach can still be noted even in recent data with a rate of 51.2% for laparotomy and 31.8% and 16.9% for laparoscopic and vaginal hysterectomies, respectively [29]. Our results are not far from these figures as 68.79% of all patients underwent a laparotomy although they were being treated in a university tertiary hospital, and thus higher rates are expected in other less equipped centers or rural areas. Our data showed that the surgical approach (laparotomy *vs.* minimally invasive surgery) is strongly linked to a higher rate of SSIs (p = 0.014). These findings are supported by several studies including the findings from King Abdul-Aziz Medical City in herniorrhaphy and cholecystectomy surgeries [27,29,11] as well as the data from Roy *et al* who demonstrated a higher overall incidence of SSIs with abdominal procedures; whereas minimally invasive procedures were associated with fewer complications, re-admissions and costs [3]. The duration of surgery was not associated with a statistically significant increase in SSIs, which can be explained by the administration of a second dose of antibiotic during surgeries exceeding three hours.

Although our results are limited by the retrospective nature of this study and the number of included patients, we aimed to find new ways of reducing our SSIs rates. The literature revealed that it is an international challenge; where authorities and guideline-generating bodies are trying to standardize and implement strict infection control protocols. Clinicians and surgeons should consider the increasing evidence of the benefits of stratifying patients before surgeries; taking into consideration their pre-existing or potential risk factors as well as the benefits of minimally invasive procedures. Reducing weight, achieving a low HbA1C level, personal hygiene and avoiding dermal herbs are some of the preventive measures that can be advocated prior to surgeries. Finally, we strongly encourage hospitals to conduct patients' educational sessions before elective surgeries and to utilize the social media in promoting awareness to SSIs and ways to prevent their occurrence or reduce their rates.

Conclusion

A single dose antibiotic prophylaxis is adequate, cost-effective and remains the gold standard in preventing SSIs in patients undergoing elective hysterectomies for benign or malignant conditions. There is no difference between the efficacy of a single dose or 24-hour multiple doses of Cefazolin in reducing SSIs. However, risk stratification after preoperative screening can be done and the prophylactic regimen must be tailored for each patient in a cost-effective manner and using a multidisciplinary approach. Minimally invasive surgeries remain the gold standard approach for hysterectomy whenever indicated and feasible.

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Authors' contributions

M Arafah is considered a co-first author and contributed equally to the first author. K Akkour, M Arafah and S Iqbal contributed in the concept, design and drafting the paper. M Alhulwah, R Badaghish, H Alhalal, N Alayed and S Alqahtani contributed in collecting and analyzing the data. All authors have reviewed and approved the final manuscript.

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