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FULL PAPER

Topical Rifampicin versus Povidone-Iodine for the Prevention of Incisional Surgical Site Infections Following Benign Gynecologic Surgery: A Prospective, Randomized, Controlled Trial

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SUMMARY

In this prospective, randomized, controlled study we investigated the effect of subcutaneous rifampicin and povidone-iodine irrigation on incisional surgical site infection.
Superficial incisional surgical site infection (SSI) following gynecologic surgery is a serious problem for both patient and surgeon in terms of increased morbidity, length of hospital stay, anxiety, and costs.
Three hundred patients scheduled for abdominal surgery due to various benign gynecological pathologies were randomly assigned to one of three groups of 100 members each, as follows: the subcutaneous tissue was irrigated with saline in group 1; saline + rifampicin in group 2; saline +10% povidone iodine in group 3. Patients were invited to follow-up once every 10 days in a 30-day period for evaluation. Patients who developed a superficial incisional SSI were recorded.
The superficial incisional SSI rate increased significantly with the use of saline alone ($p = 0.006$). There was no significant difference between saline +10% povidone iodine and saline + rifampicin ($p=0.055$).
The results suggest that the incidence of superficial incisional SSI is significantly reduced when irrigation is performed using rifampicin and povidone-iodine compared with using saline alone.

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INTRODUCTION

The incidence of surgical site infections (SSIs) is 5-16%, and they are seen in 1.6- 3% of all hysterectomies (Leaper *et al.*, 2017; Mahdi *et al.*, 2014; Quiroga-Garza *et al.*, 2017). For reasons such as elderly patients who have chronic diseases and who undergo surgery more than previously, and complicated surgical procedures being performed, there has been a recent increase in both the incidence and severity of SSIs (Hawn *et al.*, 2011; Nelson *et al.*, 2016).
The US Centers for Disease Control and Prevention (CDC) introduced standard definitions for purposes of diagnosing postoperative infections on the basis of specific criteria and eliciting more accurate statistical data, and the use of the term SSI was recognized at that time (Berrios-Torres *et al.*, 2017). Based on the standard definitions introduced by the CDC, SSIs were divided into two groups: incisional and organ/site infection. Incisional SSIs were further subdivided into superficial and deep SSIs. Deep incisional infection includes fascia, muscle, or deep soft tissues associated with the incision site, whereas superficial incisional infection involves cutaneous/subcutaneous tissues and is observed within 30 days following surgery. Superficial incisional infections represent two thirds of gynecological SSIs (Mahdi *et al.*, 2014).
For infection to develop in a surgical wound, micro-organism numbers and virulence must be at a level that can disrupt the wound-healing process and local defense mechanisms. Factors involved in this balance include bacterial, wound-related, and patient-related agents. Pathogens are endogenous flora frequently originating from the patient's skin, mucosal membranes, or intestinal system (Anderson *et al*., 2014). Therefore, broad-spectrum antibiotic prophylaxis, local preoperative cleansing, removal of debris when closing the cutaneous incision, abundant washing of the wound, and provision of appropriate local antisepsis can reduce the risk of superficial incisional SSI (Webster *et al*., 2015; Menderes *et al*., 2012; Allegranzi *et al*., 2016).
Chronic diseases, advanced age, smoking, hypoalbuminemia, malnutrition, hypothermia, hyperglycemia, prolonged hospital stay, perioperative blood transfusion, and corticosteroids and other immunosuppressive agents can increase superficial incisional SSI rates by adversely affecting the host defense. At the same time, the architectural characteristics and ventilation of the operating room, surgical clothing, surgical hand-washing, preparation of the incision site under appropriate conditions, prophylactic antibiotic use, surgical technique, materials used, and length of surgery also affect superficial incisional SSI rates (Lake *et al*., 2013; Leaper *et al*., 2015).

Key words:
Gynecologic surgery; povidone-iodine; rifampicin; surgical site infection.

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The aim of this study was to compare the efficacy of rifampicin with that of povidone-iodine for preventing superficial incisional SSI in benign gynecological surgery, excluding oncological pathologies and emergency gynecological surgery. Furthermore, other factors that could cause SSI were evaluated.

MATERIALS AND METHODS

We conducted this prospective, randomized clinical trial from May 2017 to April 2018 at Gaziantep University Medical Faculty Department of Obstetrics & Gynecology Clinic. The Ethical Committee of Gaziantep University approved the study protocol (2018/156), and written informed consent was obtained from all patients before enrollment.

Three hundred patients scheduled for abdominal surgery due to various benign gynecological pathologies were randomly assigned to one of three groups of 100 members each. Each patient operated in the above-mentioned period was included in the groups in turn. The subcutaneous agent to be administered to each patient was determined on a random basis.

The subcutaneous tissue was irrigated with different agents after the fascia was closed, as follows:

– group 1: saline alone (control group);
– group 2: saline + rifampicin;
– group 3: saline +10% povidone iodine.

All subcutaneous tissues were irrigated with 250 ml of saline. Then 500 mg/6 ml of rifampicin in group 2 and 10 ml of povidone iodine in group 3 was applied directly on the subcutaneous tissue without dilution. The excess liquid was cleaned off and the subcutaneous tissue scrubbed with gauze. A six-point gynecological perioperative infection prevention bundle was applied in all groups (Crolla *et al.*, 2012). All groups underwent surgery in the same operating room under the same technical conditions. Subcutaneous thickness was divided into three groups: thin: 4 cm or less; medium: 5 to 9 cm; thick: 10 cm or more. 10-Fr hemovac drains (400 cc) were inserted subcutaneously in the medium and thick groups, and sutures (2-0 polyglactin 910; Vicryl®) were used for subcutaneous closure in patients with subcutaneous thicknesses of 5 cm or more. Subcuticular 3-0 modified glycolic acid (Monosyn®) was used for the skin in pfannenstiel incisions, and subcuticular 3-0 polypropylene (PP, Premilene®) or staple was used for the skin in midline incisions. Age, length of hospital stay, comorbidity, preoperative leukocyte count, hemoglobin, amount of preoperative blood loss and blood transfusion if applicable, smoking status, and incision type were recorded for all patients. After discharge, all patients were sent home with oral Cefazolin 1 g/day, naproxen sodium 550 mg/day, and wound site care advice. Patients were invited to follow-up once every 10 days for 30 days. SSI was diagnosed according to the following criteria: purulent discharge, positive culture, presence of at least one of the following signs: pain, swelling, redness, warmth and wound-opening (Emori *et al.*, 1991). Wound swabs were taken when clinically indicated. Patients developing superficial incisional SSI during this period were recorded.

Statistical Analysis

Compatibility with normal distribution of numerical data was assessed using the Shapiro-Wilk test. Analysis of variance (ANOVA) and the least significant difference (LSD) test were used to compare normally distributed variables in the three groups. Relations between categorical variables were analyzed using the chi-square test. Analyses were performed on SPSS 22.0 software. p values <0.05 were regarded as statistically significant.

RESULTS

The operation types and rates were as follows: 106 myomectomies (35.3%), 85 ovarian cystectomies (28.3%), 79 total abdominal hysterectomies (TAH) (26.3%), 18 salpingectomies (6.0%), and 12 oophorectomies (4.0%). The baseline characteristics of the patients are shown in *Table 1*.

The total SSI number in the entire patient group was 19 (6.3%) (group 1: 12, group 2: 1, group 3: 6). The risk factors that may play a role in SSI formation are shown in *Table 2*.

Superficial incisional SSI rates differed significantly between the control and case groups (p=0.006). It was sig-

Table 1 - *Baseline characteristics of the patients.*

Variables		*Saline (n=100)*	*Saline+Rifampicin (n=100)*	*Saline + 10% povidone-iodine (n=100)*	*P values*
Age† (yr)		36.26±11.33	37.33±13.51	33.92±11.09	0.124
Hospital stay† (day)		1.97±0.5^B	2.21±0.74^A	1.99±0.66^B	0.014*
SC thickness† (cm)		4.99±1.49	4.76±1.79	4.72±1.25	0.402
Leukocytes† (/mm^3)		6561±2014.64	6164±1841.31	6346±1736.15	0.324
CRP†		6.16±2.35	5.77±2.59	5.61±2.53	0.278
PO blood loss† (ml)		213.2±161.08^B	382±306.62^A	200.7±155.92^B	0.001*
BMI†		22.16±2.81^B	23.08±3.59^A	21.87±2.57^B	0.013*
Hemoglobin† (g/dl)		10.81±1.13	10.97±1.23	11±1.41	0.522
Comorbid disease‡		14 (14)	14 (14.1)	16 (16)	0.906
SC drain‡		12 (12)	24 (24)	14 (14)	0.051
SC suture‡		69 (69)	63 (63)	69 (69)	0.581
İncision‡	Pfannenstiel	90 (90)	89 (89)	91 (91)	0.895
	Midline	10 (10)	11 (11)	9 (9)	
Smoking‡		24 (24)	20 (20)	23 (23)	0.779

†mean±st.deviation. ‡Count(percent). *Significant at 0.05 level. (A is significantly higher than B).
Abbrevations: SC: Subcutaneous; PO: Peroperative; BMI: Body Mass Index; CRP: C reactive protein.

Table 2 - *Risk factors in SSI formation.*

Variables		*SSI (n=19)*	*No SSI (n=281)*	*P values*
Age† (yr)		51.63±11.66	34.77±11.35	0.001*
Hospital stay† (day)		2.42±0.76	2.03±0.63	0.044*
Sc thickness† (cm)		4.89±1.76	4.82±1.51	0.977
Leukocytes† (/mm³)		6021.05±1249.7	6379.72±1902.42	0.360
CRP†		5.74±2.13	5.85±2.52	0.919
PO blood loss† (ml)		371.05±367.54	258.15±220.99	0.235
BMI†		22.58±3.44	22.36±3.03	0.876
Hemoglobin† (g/dl)		11.11±1.52	10.91±1.25	0.668
Comorbid disease‡		15 (78.9)	30 (10.7)	0.001*
SC drain‡		5 (26.3)	45 (16.0)	0.272
SC suture‡		14 (73.7)	187 (66.5)	0.522
İncision‡	Pfannenstiel	16 (84.2)	254 (90.4)	0.416
	Midline	3 (15.8)	27 (9.6)	
Smoking‡		5 (26.3)	62 (22.1)	0.672
Groups‡				
Saline		12 (63.2)	88 (31.3)	0.006*
Saline+Rifampicin		1 (5.3)	99 (35.2)	
Saline+Povidone-iodine		6 (31.6)	94 (33.5)	

†mean±st.deviation. ‡Count(percent). *Significant at 0.05 level.
Abbrevations: SSI: Surgical Site Infection; SC: Subcutaneous; PO: Peroperative; BMI: Body Mass Index; CRP: C reactive protein.

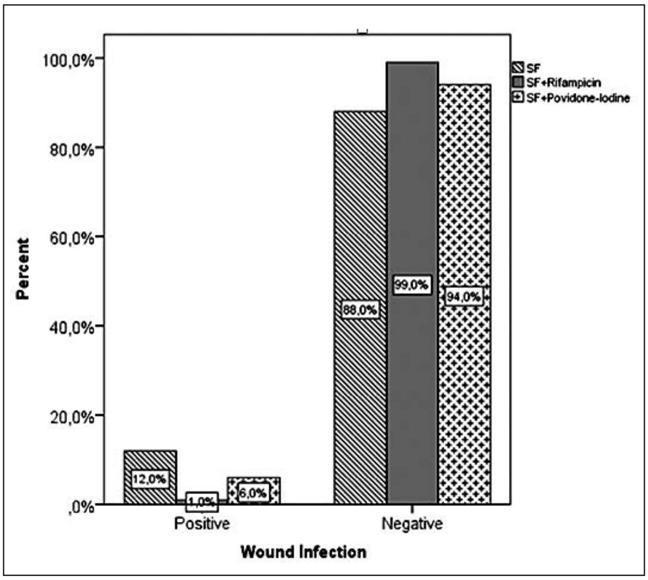

Figure 1 - *Relationship between subcutaneous agents and SSI.*

nificantly higher with the use of saline solution alone than with saline +10% povidone-iodine or with saline + rifampicin use (p=0.006). There was no significant difference in terms of infection between saline +10% povidone-iodine and saline + rifampicin (p=0.055) (*Figure 1*).

DISCUSSION

Superficial incisional surgical site infections are one of the principal problems of surgery. It is impossible to correct all patient-based factors, but almost all risk factors concerning the surgical procedure can be ameliorated. A knowledge of all risk factors leading to superficial incisional SSI and the requisite precautions to take will reduce the incidence of these infections.

One of the most important methods for reducing superficial incisional SSIs involves observation and evaluation by hospital infection control committees (Ortega *et al.*, 2012). Superficial incisional SSI rates for the entire hospital and for specific departments, and the antibiotic sensitivity of agent pathogens, need to be determined for that purpose. It must not be forgotten that sensitivity profiles may not match the values given in books, and that they may differ for each hospital, and even for each department. The results of these assessments must be shared with the surgical team, and constant quality improvement activities must be introduced to reduce infections.

When compared to systemic antibiotic therapy, topical antibiotics have many potential advantages for minimizing SSIs, as well as some disadvantages, such as hypersensitivity or contact dermatitis (Heal *et al.*, 2017). The advantages of topical use are: providing high and continuous concentrations at the surgical site, limiting systemic absorption and toxicity, decreasing amounts of antibiotic use, and, perhaps, reducing possible antibiotic resistance. Agents that cannot be applied systemically may be used topically. Topical antibiotics may be used in different forms, such as solutions, gels, powders, creams, beads or implants. The most frequently used antibiotics are cephalosporins, aminoglycosides, glycopeptides, chloramphenicol, rifampicin and bacitracin (Karaarslan *et al.*, 2018). It is difficult to determine which agent to use, how much, for how long and in what form, for prophylaxis in different types of surgical wounds. For this reason, the efficacy and limits of topical antibiotic use at the surgical site have not yet been clarified (McHugh *et al.*, 2011). Besides topical antibiotics, the efficacy of local anesthetics and local antiseptics has been observed in various studies (Mueller *et al.*, 2015; Quiroga-Garza *et al.*, 2017).

Most studies in the field of gynecological surgery have involved post-cesarean SSIs (De Nardo *et al.*, 2016; Shrestha *et al.*, 2014, Wang *et al.*, 2014; Conner *et al.*, 2014; Tuuli *et al.*, 2016). There have been limited numbers of studies of superficial incisional SSIs developing in benign gynecological cases (Lachiewicz *et al.*, 2015; Steiner *et al.*, 2017; Uppal *et al.*, 2017), but the results and approaches for cesareans may be regarded as acceptable in terms of similar incision procedures and inclusion in the same surgical wound class.

In this study, the aim of which was to compare the effectiveness of wound site irrigation of saline + rifampicin with saline + 10% povidone iodine, used by us for several years, superficial incisional SSIs decreased significantly when irrigation was performed using these two agents compared with the use of saline alone. Fewer superficial incisional SSIs were observed in patients receiving rifampicin compared with those receiving povidone-iodine, although the difference was not statistically significant. Nevertheless, rifampicin may be recommended for subcutaneous irrigation against potential metabolic side effects, the risk of allergic reaction, and potential problems with sterilization of povidone-iodine. In addition, although the length of hospital stay was longer in the group receiving rifampicin irrigation compared with the other groups, the lower incidence of superficial incisional SSI compared with povidone-iodine, albeit not statistically significant, also supports our recommendation of rifampicin.

The rate of superficial incisional SSI in all groups (6.3%) was slightly higher than that in the previous literature. However, this may be due to all patients being referred to our center for close monitoring, since patients may present to centers other than that where surgery is performed if superficial incisional SSI develops after discharge. Also, our center is a tertiary research center that accepts high-risk patients, who are likely to be elderly or have chronic diseases.

We observed that superficial incisional SSI rates increased with age, and this agrees with several previous studies. This can probably be attributed to natural defense mechanisms decreasing with age and to chronic diseases, particularly diabetes, increasing with age. Indeed, we observed more superficial incisional SSI in patients with chronic disease. An increase in superficial incisional SSI rates in line with length of hospital stay is an expected outcome, because an increase in micro-organisms in the cutaneous flora occurs in patients with prolonged hospitalization, and this flora may include resistant micro-organisms encountered in the hospital. For that reason, discharging patients as early as possible in the postoperative period will reduce the risk of superficial incisional SSI.

We did not find any positive effect of hemovac drains on the incidence of SSI. We can conclude that the use of subcutaneous drains is useless if we consider the discomfort and cost involved. These results are comparable to studies focusing on other indications like cesarean delivery (Magann *et al*., 2002). On the other hand, studies demonstrating the benefit of subcutaneous drainage are also available (Panici *et al*., 2003). Therefore, a definite conclusion cannot be reached concerning the general use of prophylactic subcutaneous drainage in surgery.

Contrary to the general opinion, we found no effect of the subcutaneous thickness and the presence of subcutaneous suture on the SSIs. The fact that the wound was in the clean/clean contaminated group and that the study group consisted of benign cases may have generated this result. In addition, considering potential negative effects like bacterial contamination or tissue reaction, subcutaneous sutures should be questioned.

This study may contribute to raising the still inadequate levels of evidence concerning SSI in benign gynecological cases, and may be a guide to subsequent studies on this subject. The limitations of our study include low patient number and the fact that all the operations were not performed by the same team. Furthermore, there are some unpredictable factors, such as the possible presence of team members with active infection and a lack of knowledge of patients' hygiene status in the perioperative period.

In conclusion, superficial incisional SSI decreased significantly when irrigation was performed using rifampicin or 10% povidone-iodine compared to the use of saline alone. Less superficial incisional SSI was observed in patients receiving rifampicin compared with those receiving povidone-iodine, although the difference was not statistically significant. Nevertheless, rifampicin may be recommended in wound site irrigation against potential metabolic side effects, the risk of allergic reaction, and potential problems with sterilization of povidone-iodine.

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