Efficacy of betaine + polyhexanide as anti-septic wound irrigating solution prior to subcutaneous layer and skin closure of cesarean section in preventing surgical site infection*

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ABSTRACT

Background: Surgical site infection (SSI) after cesarean section occurs in 3-15% of cases. Surgical irrigation has been widely used as a measure of reducing SSI, however, there are no official guidelines for its practice.

Objective: To determine the efficacy of Betaine + Polyhexanide (Prontosan) as anti-septic wound irrigating solution prior to subcutaneous layer and skin closure of cesarean section in preventing surgical site infection.

Methodology: One hundred thirty-two women who underwent cesarean section were included from April to October 2017. The cesarean section was done according to the standard operating procedure of the hospital. All subjects were given prophylactic antibiotics prior to the cesarean section. Subjects were then randomly assigned, 66 in Prontosan and 66 in Saline as irrigating solution prior to closure of subcutaneous layer and skin. Post-operatively, subjects were monitored and evaluated for signs and symptoms of superficial surgical site infection on Day 3, 7-10 and 30.

Results: There was no demographic difference identified between the two groups (age, prepregnancy BMI, obstetric parameters and comorbidities) except that saline group had a higher proportion of emergency cesarean section (84% vs 70%). The incidence of surgical site infection 2 was similar in the two groups (15.15% vs 9.09 % on Day 3, 7.84 % vs 6.78% on Day 7-10, 3.23% vs 0 on Day 30).

Conclusion: Betaine + Polyhexanide (Prontosan) and Saline wound irrigation showed no reduction in the incidence of superficial surgical site infection in women undergoing cesarean section.

Keywords: cesarean section, infection, wound irrigation

INTRODUCTION

Surgical site infection (SSI) is defined as an infection that occurs in the part of the body where the surgery took place[1]. It may be caused by contamination with micro-organisms from the patient's own body during the surgery[5].

In January 2016, according to the Center for Disease Control and Prevention (CDC), SSI was the most common health care associated infection (HAI) accounting to 31% of HAIs among hospitalized patients[1]. Various comorbidities of surgical patients and the emergence of antimicrobial-resistant pathogens increase the cost and challenges of treating SSIs[12].

Cesarean section (CS) is one of the most frequent surgical procedure worldwide[3] and its incidence has increased globally during the past three decades[13]. SSI after cesarean section is a major cause of morbidity and mortality causing prolonged hospital stay and increasing hospital costs. SSI following cesarean section occurs in 3-15% of cases[13]. The wide range of reported SSI rates is accounted for by the population being studied, methods used and appropriate antibiotic prophylaxis administered[2]. Some of the risk factors of post-cesarean SSI are prolonged labor, premature rupture of membranes, frequent internal examination, manual extraction of the placenta, premature births, chorioamnionitis, obesity as well as comorbidities such as severe anemia and gestational diabetes mellitus[2].

SSI usually affects the superficial tissues only. However, there are some cases with serious infection that affect the deeper tissues or other parts of the body

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handled during the procedure. Most SSIs are evident within 30 days of an operation and mostly between the 5th and 10th post-operative day[4]. According to CDC, superficial SSIs are infections that occur within 30 days after the surgery that involve only the skin and subcutaneous tissue of the incision site and have at least one of the following: 1) 4 purulent discharge from the superficial incision with or without laboratory evidence, 2) with organism isolated from an aseptically cultured fluid or tissue in the superficial incision, 3) with at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat 4) diagnosis of superficial incisional SSI given by a surgeon or attending physician[1].

Even with the advances in technology in infection control, such as practices involving sterilization method, surgical technique and availability of antimicrobial prophylaxis, SSI remains to be a significant cause of morbidity and prolonged hospital stay. The majority of which are preventable with measures that can be taken in the pre-, intra- and post-operative phases of care to reduce the risk of infection[5].

Surgical irrigation has been widely used as a measure of reducing SSI[4]. Microorganism that have grown from the incised skin edges in the course of surgery or those that have contaminated the wound from the environment can be washed away[4]. It is usually done at the end of the procedure and prior to closure of the wound. Normal saline solution is the most common form of irrigant fluid used. It has been long debated as a potentially important intraoperative measure to be done to prevent the development of SSI[8]. There are also several types of additives used in combination with irrigation fluid such as antibiotics, surfactant and antiseptics in an attempt to optimize infection prevention[8]. However, in comparison to other SSI prevention efforts, there are no official practice guidelines or recommendations from any medical group for the practice of surgical irrigation[8].

Betaine + Polyhexanide solution (Prontosan), is an irrigating solution commonly used as a surface active wound cleanser on chronic wounds. It is a combination of Polyhexanide which functions as a preservative that inhibits the growth of microorganism and Betaine which is a surface active cleanser that provides immediate debridement[11].

OBJECTIVES

2.1. General Objective

2.1.1. The main objective of this study is to determine the efficacy of Betaine + Polyhexanide (Prontosan), as an antiseptic wound irrigating solution prior to subcutaneous layer and skin closure in preventing surgical site infection.

2.2. Special Objectives

2.2.1. To compare the surgical site infection rate among patients who underwent cesarean section that used Betaine + Polyhexanide (Prontosan) as surgical wound irrigation solution prior to subcutaneous layer and skin closure versus Saline Solution.

2.2.2. To determine the association of select demographic and clinical factors (i.e. age, previous CS operations, present comorbidities, BMI, number of internal examinations performed, surgery type, length of OR procedure) to surgical site infection among patients who underwent cesarean section.

MATERIALS AND METHODS

This randomized controlled trial was carried out in all pregnant women who underwent cesarean section from April to October 2017. The study was approved by the Institutional Review Board. The drug information along with the risk and possible complications were thoroughly explained to all subjects and a written informed consent was secured. Exclusion criteria included those with known hypersensitivity reaction to Betaine + Polyhexanide (Prontosan) solution. A minimum of 132 subjects were required for this study, or 66 per arm, based on a level of significance of 5% and a power of 80% with an assumed incidence of SSI in control group of 12.6% [10]. The expected magnitude of decrease of SSI incidence is half of the control, based from the assumed reduction of 50% of the SSI which is 6.3%.

The cesarean section was done according to the standard operating procedure of the hospital. All subjects were given prophylactic antibiotics prior to the cesarean section. Propan-2-ol, Benzalkonium Chloride (Cutasept-F) was used as pre-operative and post-operative skin disinfectant. Closure of the uterus, peritoneum, fascia, subcutaneous tissue and skin were done according to the standard operating procedure of the department. Subjects were then randomly assigned by numbered envelopes as to the type of irrigating solution used, intervention group: Betaine + Polyhexanide solution (Prontosan), and control group: normal saline solution as irrigating solution prior to closure of subcutaneous layer and skin during cesarean section.

For the Intervention group: Betaine + Polyhexanide solution (Prontosan), Polyhexanide functions as a preservative that inhibits the growth of microorganism and Betaine is a surface active cleanser that provides immediate debridement[11]. A 40 mL ampule was used as an irrigating solution at the subcutaneous layer for 1 minute. The area was then dried using a sterile gauze prior to suturing of the subcutaneous layer and skin.

For the Control group: Normal Saline, an isotonic solution, is the most commonly used wound irrigating agent due to its safety and physiologic characteristics. 200 mL of Normal saline was used as an irrigating solution at the subcutaneous layer for 1 minute. The area was then dried using a clean sterile gauze prior to suturing of the subcutaneous layer and skin.

Post-operatively, subjects were monitored for superficial surgical site infection and fever while in the ward. They were evaluated by junior residents (1st and 2nd year residents who were not present during 7 the surgery) along with a data collection form as guide for presence of surgical site infection. They were followed up at the clinics and outpatient department 7-10 days and 30 days after the surgery. They were asked and examined for presence of fever (Temperature >37.8°C), signs and symptoms of superficial surgical site infection as defined by CDC such as discharge from the wound, pain or tenderness, localized swelling, redness or heat and wound disruption in the skin and subcutaneous tissue of the incision site. Both evaluators and investigators were blinded as to what irrigating solution was used.

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Independent sample T-test, Mann-Whitney U test and Chi-Square/Fisher's exact test were used to determine the difference of mean, median and frequency between groups, respectively.

Crude and adjusted risk ratio and the corresponding 95% confidence interval from Binary logistic regression was computed to determine the significant predictors of superficial surgical site infection.

All valid data will be included in the analysis. Missing variables were neither replaced nor estimated. Intention to treat analysis was planned but was unnecessary for this study. Null hypotheses were rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 132 subjects were recruited for randomization from April to October 2017. Eleven subjects were lost to follow up during their assigned schedules.

Subjects were randomly allocated on a 1:1 basis to receive either Betaine + Polyhexanide (Prontosan) or normal saline. The two groups were similar in terms of age, BMI, obstetric parameters and comorbidities. However, the normal saline group had a higher proportion of emergency CS (84% versus 70%, p = 0.038) (Table 1).

The Betaine + Polyhexanide (Prontosan) group had 6 subjects who had fever on Day 3, which was significantly more than one subject in the normal saline group (p = 0.0017). However, fever may not be specific for SSI and may be caused by other infections such as endometritis, mastitis or phlebitis.

Table 1. Clinical and demographic profile of patients who underwent caesarean section given Betaine + Polyhexanide and Normal Saline as irrigating solution prior to subcutaneous layer closure, (n= 132)

	Betaine + Polyhexanide (n= 66)	Normal Saline (n= 66)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
Age (years)	31.48 ± 5.18	31.4 ± 4.79	0.958*
BMI (pre-pregnancy)	22.55 ± 2.27	22.47 ± 1.93	0.837*
Gravidity			
Primigravida	22 (33.33)	21 (31.82)	0.853§
Multigravida	44 (66.67)	45 (68.18)	
Parity			
Nulliparous	25 (37.88)	23 (34.85)	0.696§
Primiparous	29 (43.94)	27 (40.91)	
Multiparous	12 (18.18)	16 (24.24)	
Numbers of IE	1 (0 – 6)	1 (0 – 6)	0.271‡
Hours of labor	1 (0 – 20)	2 (0 – 25)	0.085‡
Operative time	1.3 (1.1 – 2.3)	1.3 (1 – 3)	0.514‡
Number of previous surgeries			
0	31 (46.97)	28 (42.42)	0.557§
1	29 (43.94)	28 (42.42)	
2	6 (9.09)	10 (15.15)	
Comorbidities:			
Diabetes mellitus	22 (33.33)	13 (19.70)	0.076§
Anemia	10 (15.15)	6 (9.09)	0.286§
Meconium stained amniotic fluid	9 (13.64)	5 (7.58)	0.258§
Status of amniotic membrane			0.315§
Ruptured BOW	14 (21.21)	19 (28.79)	
Intact BOW	53 (78.79)	47 (71.21)	
Type of CS			
Emergency CS	46 (69.70)	56 (84.85)	0.038§
Elective CS	20 (30.30)	10 (15.15)	

*Statistical test used: * - Independent sample t-test; ‡- Mann-Whitney U test; § - Chi square test*

In terms of superficial surgical site infections, there was insufficient evidence to demonstrate a difference in incidence between the two groups. The number of

subjects given Betaine + Polyhexanide and Normal saline as irrigating solution prior to skin and subcutaneous closure who presented with signs and symptoms of SSI was not statistically significant. (Table 2, Figure 1).

In comparison to the subjects who had signs and symptoms of SSI on day 3, there was no significant difference between those given Betaine + Polyhexanide (Prontosan) and Saline in factors influencing wound infection, including pre-pregnancy BMI (24.3 ± 4.03 vs 25.16 ± 2.64), numbers of IE (0-5 hours vs 1-6 hours), operative time (1.3-2.3 hours vs 1.3-2 hours), presence of comorbidities like Diabetes mellitus (5 out of 10 vs 3 out of 6) (Table 3). Moreover, there was no significant difference

Table 2. Distribution of rate of infection at 3rd, 7th-10th and 30th days among subjects who underwent cesarean section given Betaine + Polyhexanide (Intervention group) and Normal Saline (Control group) as irrigating solution prior to subcutaneous layer closure. (n= 132)

	Betaine + Polyhexanide (n= 66)	**Normal Saline (n= 66)**	**P-value**
	Frequency (%)		
Day 3			
Fever	6 (9.09)	1 (1.52)	0.115₴
Superficial Surgical Site Infection*			
Redness	8 (12.12)	7 (10.61)	0.784§
Localized swelling	4 (6.06)	4 (6.06)	1.000§
Tenderness	3 (4.54)	1 (1.52)	0.619₴
Wound discharge	3 (4.55)	2 (3.03)	1.000₴
Pain	0	0	-
Heat	0	0	-
Wound disruption	0	0	-
Day 7-10 (n=122) (10 subjects were lost to follow-up)	[n= 63] (3 subjects were lost to follow-up)	[n= 59] (7 subjects were lost to follow-up)	
Fever	1 (1.59)	0	1.000₴
Superficial Surgical Site Infection*			
Redness	3 (4.76)	1 (1.69)	1.000₴
Localized swelling	2 (3.17)	2 (3.39)	1.000₴
Tenderness	1 (1.59)	0	1.000₴
Wound discharge	4 (6.35)	2 (3.39)	0.681₴
Pain	0	0	-
Heat	0	0	-
Wound disruption	3 (4.76)	1 (1.6)	0.620₴
Day 30 (n=121) (11 subjects were lost to follow-up)	[n= 62] (4 subjects were lost to follow-up)	[n= 59] (7 subjects were lost to follow-up)	
Fever	0	0	-
Superficial Surgical Site Infection*			
Redness			
Localized swelling			
Tenderness			
Wound discharge			
Pain			
Heat			
Wound disruption			

**Multiple signs and symptoms (Subjects may present with multiple signs and symptoms at the same time)*
Statistical tests used: § - Chi square test; ₴ - Fisher's exact test

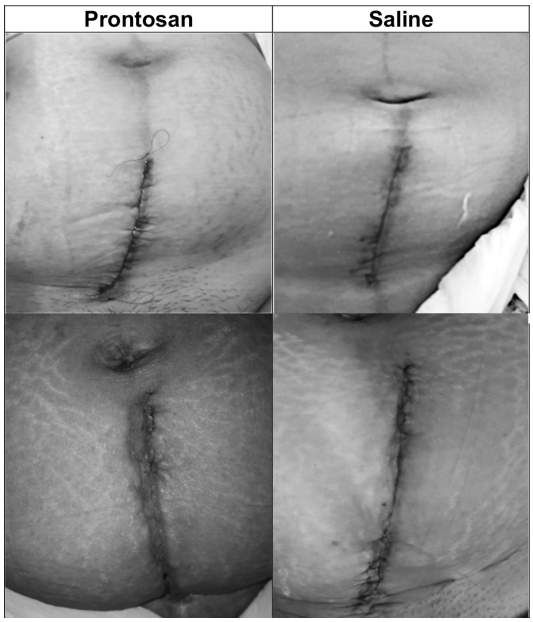

Figure 1. Wound discharge, localized swelling and redness on Day 3 with Prontosan and Saline

in subjects with SSI on day 7-10 and day 30 on both groups. (Table 4).

The incidence of SSI on both groups were similar on Days 3, 7-10 and 30. Overall, both Betaine + Polyhexanide (Prontosan) and Saline had no significant reduction in preventing surgical site infection after cesarean section (Table 5).

DISCUSSION

Surgical site infection is still one of the significant burdens on the health care system[8] and one of themost common complication of cesarean section. It has many negative effects including pain, longer hospital stay or readmission, need for antibiotics and increasing costs[7]. Substantial efforts have been done to lessen the rate of SSI after cesarean section and these include the following: pre-operative prophylactic antibiotics, antiseptic solutions for skin and vaginal preparation and use of negative pressure dressing. Surgical wound

Table 3. Comparison of patients with signs of SSI on Day 3 post-op (n=16)

	Prontosan: Day 3 Positive SSI (n= 10)	Saline: Day 3 Positive SSI (n= 6)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
Age (years)	30.7 ± 5.36	31.33 ± 7.19	0.842*
BMI (pre-pregnancy)	24.3 ± 4.03	25.16 ± 2.64	0.648*
Gravidity			0.869§
Primigravida	2 (20)	1 (16.67)	
Multigravida	8 (80)	5 (83.33)	
Parity			0.355§
Nulliparous	3 (30)	1 (16.67)	
Primiparous	4 (40)	1 (16.67)	
Multiparous	3 (30)	4 (66.67)	
Numbers of IE	1 (0 – 5)	1 (1 – 6)	0.605‡
Hours of labor	2 (0 – 20)	2 (2 – 12)	0.925‡
Operative time	2 (1.3 – 2.3)	2 (1.3 – 2)	
Number of previous surgeries			0.411§
0	5 (50)	1 (16.67)	
1	2 (20)	2 (33.33)	
2	3 (30)	3 (50)	
Comorbidities:			
Diabetes mellitus	5 (50)	3 (50)	1.000§
Anemia	1 (10)	0	1.000ǂ
Meconium stained amniotic fluid	4 (40)	0	0.234ǂ
Status of amniotic membrane			0.869§
Ruptured BOW	2 (20)	1 (16.67)	
Intact BOW	8 (80)	5 (83.33)	
Type of CS			0.500§
Emergency CS	8 (80)	6 (100)	
Elective CS	2 (20)	0	

*Statistical test used: * - Independent sample t-test; ‡- Mann-Whitney U test; § - Chi square test; ǂ - Fisher's exact test*

Table 4. Association between clinical characteristics with significant SSI symptoms persisting for at least seven days post-op (n= 9)

	Prontosan: Day 7-10 or Day 30 Positive SSI (n= 5)	Saline: Day 7- 10 or Day 30 Positive SSI (n= 4)	Crude Risk Ratio (95% Confidence Interval)	P-value
	Frequency (%); Mean ± SD; Median (Range)			
Age (years)				
> 35	2 (40)	0	-	-
< 35	3 (60)	4 (100)	(reference)	-
BMI (prepregnancy)				
> 25	5 (100)	3 (75)	1.33 (0.76 – 2.35)	0.236
< 25	0	1 (25)	(reference)	-
Gravidity				
Primigravida	1 (20)	1 (25)	(reference)	-
Multigravida	4 (80)	3 (75)	1.067 (0.52 – 2.18)	0.858
Parity				
Nulliparous	1 (20)	1 (25)	(reference)	-
Primiparous	2 (40)	2 (50)	1.000 (0.32 – 3.10)	1.000
Multiparous	2 (40)	1 (25)	1.333 (0.27 – 6.61)	0.709
Numbers of IE				
> 2	0	1 (25)	-	-
< 2	5 (100)	3 (75)	(reference)	-
Hours of labor				
> 6	0	1 (25)	-	-
< 6	5 (100)	3 (75)	(reference)	-
Operative time (hours)				
> 2	4 (80)	2 (50)	1.6 (0.55 – 4.68)	0.343
< 2	1 (20)	2 (50)	(reference)	-
Number of previous surgeries				
0	2 (40)	1 (25)	(reference)	-
1	2 (40)	3 (75)	0.667 (0.22 – 2.07)	0.465
2	1 (20)	0	-	-
Comorbidities:				
Diabetes mellitus	4 (80)	1 (25)	3.2 (0.55 – 18.47)	0.099
Anemia	1 (20)	1 (25)	0.80 (0.07 – 9.18)	0.858
Meconium stained amniotic fluid	1 (20)	0	-	-
Status of amniotic membrane				
Ruptured BOW	1 (20)	1 (25)	(reference)	-
Intact BOW	4 (80)	3 (75)	1.067 (0.52 – 2.18)	0.858
Type of CS				
Emergency CS	3 (60)	3 (75)	0.80 (0.32 – 1.99)	0.635
Elective CS	2 (40)	1 (25)	(reference)	-

Table 5. Incidence of SSI

	Prontosan (n= 66)	Saline (n= 66)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
SSI at day 3	10 (15.15)	6 (9.09)	0.286§
SSI at day 7 – 10	5 (7.84)	4 (6.78)	1.000ǂ
SSI at day 30	2 (3.23)	0	0.496ǂ

Statistical test used: § - Chi square test; ǂ - Fisher's exact test

irrigation before skin and subcutaneous closure is also being incorporated as an easy and economical measure to decrease the incidence of SSI however there is currently no official practice guidelines or recommendations from any major medical group to have this implemented[14].

According to the latest official guidelines for prevention of SSI by CDC and World Health Organization, intraoperative wound irrigation with saline is not effective but wound irrigation with povidone-iodine solution may have a beneficial effect in preventing SSI. However, these current recommendations are weak and supported by evidences suggesting a trade-off between clinical benefits and harms.

In a meta-analysis performed by Tara Mueller et al. on abdominal surgery with intraoperative wound irrigation with saline, povidone-iodine and anibiotics, they noted a risk reduction of 46% in the treatment group. The SSI incidence was half at 9% in the group where surgical wound irrigation was done as compared to the untreated group with 16%[14].

There are several irrigating fluids being used such as normal saline solution, antibiotics, sterile water, surfactant and antiseptics but there is no strict ruling as for the delivery method, volume and solution additives[7].

Prontosan irrigating fluid contains Betaine, a surfactant which acts as a surface-active cleanser that provides immediate debridement and Polyhexanide, a preservative which is also found in contact lens solution that inhibits bacterial growth. This product works as a wound cleanser to help reduce necrotic debris, control exudate and remove foreign materials that impede healing. It is usually used in chronic wounds for optimal wound conditioning, effective removal of wound coatings and absorption of wound odors[11].

This study determined the efficacy of Betaine + Polyhexanide (Prontosan), as an antiseptic wound irrigating solution prior to wound closure, this time in acute wounds such as in cesarean section. Our analysis showed that there was no significant reduction of SSI in cesarean section after using Betaine + Polyhexanide (Prontosan) or saline solution as wound irrigating solution prior to wound closure. Both groups were similar in terms of age, BMI, obstetrical parameters and comorbidities. Demographic profiles of subjects presented with SSI were usually obese with pre pregnancy BMI > 25, based on the WHO Asia Pacific classification, with concomitant diabetes mellitus and underwent emergency cesarean section, however these predictors were noted to be not statistically significant prepregnancy BMI (24.3 ± 4.03 vs 25.16 ± 2.64), presence diabetes mellitus (5 out of 10 vs 3 out of 6).

In the study done by Kassam Mahomed called "The Betadine Trial" in Australia, which included 1520 women who underwent cesarean section with Betadine wound irrigation and 1507 without Betadine, there was no significant reduction on the incidence of SSI after Betadine wound irrigation[7]. Likewise, according to the study by K. Gungorduk which included a total of 520 women who underwent cesarean section with 260 women who had saline wound irrigation prior to wound closure, there was no significant difference between the groups in terms of factors known to influence wound infection and is of no benefit in preventing SSI.

CONCLUSION

In conclusion, our study showed that Betaine + Polyhexanide (Prontosan) or saline wound irrigation before wound closure do not reduce the infection rate in patients undergoing cesarean delivery.

LIMITATIONS

This study was conducted to compare Betaine + Polyhexanide (Prontosan) and Saline only for preventing SSI. Patients with no irrigation fluid used prior to wound closure were not studied.

RECOMMENDATIONS

Further studies may be done with or without wound irrigation fluid in acute wounds such as cesarean section.

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