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Efficacy of Local Vancomycin Application in Prevention of Poststernotomy Wound Infection in High-Risk Coronary Artery Bypass Grafting Patients

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ABSTRACT

Background: Poststernotomy mediastinitis is a challenge in each cardiac surgery, especially CABG, with severe effect on the patient and increased costs for health authorities.We aim at evaluation of the efficacy of local vancomycin application in prevention of poststernotomy infection and mediastinitis in high-risk CABG patients, who have one or more risk factor for SWI.

Methods: Our study was performed from 2019 to the end of 2020. It included 80 high risk CABG patients for SWI divided into two equal groups: vancomycin and control groups. The vancomycin group had local sternal vancomycin paste application prior to reinforced sternal closure prepared by mixing 2.5 grams of powdered vancomycin with 3 ml normal saline and stirred until a paste was formed. The control group had reinforced closure technique without vancomycin paste application. All cases were followed up for symptoms and signs of SWI.

Results: Results shows a significantly increased prevalence of poststernotomy superficial wound infection among patients of control group (P-value=0.02). Purulent discharge was detected in 8 cases of control group versus no cases in vancomycin group (20% , 0.0% respectively), serous discharge (1 case in control group (2.5%) versus 2 cases in vancomycin group(5%)) and early partial sternal rocking (1 case in the control group (2.5%) versus 2 cases in the vancomycin group (5%)). 1 case had late sternal dehiscence with deep mediastinitis in the control group (2.5%) versus no cases of deep mediastinitis in the vancomycin group (0.0%) (p-value=0.496).

Conclusion: Application of local sternal vancomycin significantly reduces poststernotomy wound superficial wound infection and possibly prevents deep mediastinitis.

Keywords: Poststernotomy, Infection, Mediastinitis, Vancomycin, Local.

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BACKGROUND

Median sternotomy has been the preferred way to gain access to mediastinal organs. The procedure is quick and efficient but has two major complications: sternal infection (1–3% of patients) and non-union (2–8% of patients). **(19)** SWI is one of the most dangerous complications after cardiac surgery, it may lead to serious morbidities and even mortality. **(13)**

According to extent and depth of infection, SWI can be generally classified into superficial and deep wound infection. **(14)** According to El Okaley classification, Sternal complications are categorized as follows:Non-infected dehiscence (El Oakley class-1), SWI without sternal dehiscence (El Oakley class-2A) and DSWI with or without sternal dehiscence (El Oakley class-2B) **(4).** Prevention of SWI by the use of prophylactic systemic or local antibiotics is widely applied policy in cardiac surgery centres**(2).** Topical application combines the benefit of higher effective concentration at the sternum, and less possibility of systemic side effects. **(11)**

Vancomycin is one of the most efficiently used local antibiotic for SWI prevention. It is a potent bactericidalglycopeptide antibiotic against methicillin resistant Staphylococcus aureus (MRSA) and methicillin resistant coagulase negative Staphylococcus species. **(2)** Inspite of guidelines recommendation of local vancomycin application (class IIb) in 2007, it is still not widely used protocol in many cardiac centers. As regard its penetration into the sternal bone and adjacent tissues, it was found that the concentrations of vancomycin in sternal bones were always above the MICs for staphylococci, streptococci, and enterococci.**(3).** Inflammatory and sepsis biomarkers such as CRP and procalcitonin were suggested to be important tools in early diagnosis and guiding management of SWI and mediastinitis **(5)**. In this study, we aim at evaluation of the safety and efficacy of topical vancomycin application in prevention of SWI in high-risk CABG patients.

Patients and methods:

From February 2019 to February 2020, a total of 80 CABG patients were included in our study , all of them were operated in cardiothoracic surgery department at Zagazig University hospital. All of them had one or more criterion of high risk for SWI like DM, obesity (BMI>30 mg/dl), elderly, COPD, harvesting of LITA, long CPB, long operation time, intraoperative IABP use, re-exploration for bleeding and long ICU and hospital stays. Patients were divided into two groups. The first group (Vancomycin Group) included 40 patients who had topical application of vancomycin paste before reinforced sternal closure. The second group (Control Group)

included 40 patients who had only reinforced sternal closure. All patients included in our prospective study had LITA harvested during their operation.

Preoperative preparation:

All patients signed an informed consent after getting approval of the study from our ethical committee. Routine preparation was done including full history taking, clinical examination, full laboratory and radiological investigations including coronary angiography, echocardiography and plain Chest X-ray.

Careful glycemic control for the diabetic patients according to guidelines to keep blood sugar less than 180 mg/dl. All measures advised by guidelines for prevention of surgical site infection were applied. Prophylactic antibiotic was given for both groups 1 hour before skin incision in the form of cefotaxime 1gram by intravenous infusion and another dose was given with the start of cardiopulmonary bypass.

Surgical technique: All patients had classic median sternotomy followed by harvesting LITA, meanwhile saphenous vein segments were harvested. CABG procedure was done in classic On- pump technique.

Techniques of sternotomy closure:

Vancomycin Group: Patients in this group had local sternal vancomycin paste. **Vancomycin paste was prepared by mixing** 2.5 grams of powdered vancomycin with 3 milliliter of normal saline and stirred until a paste was formed. It was applied on both sternal halves similar to bone wax just prior to sternal wiring. Bone wax was removed before application of vancomycin paste.

In both groups, the sternum was closed by reinforced sternal closure with modified Robiscek technique in each half of the divided sternum in addition to simple sternal wires.

During ICU stay, postoperative prophylactic antibiotics in the form of 2 grams of cefotaxime daily given intravenously and Good glycemic control maintained. Patients' data during ICU and hospital stay were recorded. Patients were followed up for detection of the occurrence of poststernotomy wound infection during hospital stay and after discharge in our outpatient clinic for 3 months.

Clinical criteria of sternotomy wound infection were searched for included: fever, sternotomy pain, and hyperemia of sternotomy scar, skin and subcutaneous tissue dehiscence, sternal instability, presence of discharge in the sternotomy wound and worsening of general health. Laboratory investigations were done for detection of presence of markers of poststernotomy infection in the form of leucocytosis, elevated CRP, elevated ESR, and elevated serum procalcitonin level at the third postoperative day and at discharge time. Other samples for CRP and procalcitonin were taken as needed in patients showing criteria of wound infection. Swab from the discharge or infected wound -when present- was taken for culture and sensitivity to detect the causative organism and applicate the appropriate antibiotics.

Statistical methods:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data was then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis.

RESULTS

Preoperative Data:

Table 1. There was no significant relation between occurrence of SWI in patients of both studied groups and their preoperative characteristics except obesity only in the control group which was statistically significantly linked to occurrence of SWI (P- value = 0.003).

Variables	Mean SD		t-test	P-value
	Control Group N=40	VancomycinGroup N=40		
Age (years) Mean ±SD	58.2 ± 5.73	57.6 ± 6.07	0.45	0.65 NS
	N (%)	N (%)	X^2	
Sex Male Female	30 (75%) 10 (25%)	29 (72.5%) 11 (27.5%)	0.25	0.62 NS
Obesity	16 (40%)	19 (47.5%)	0.054	0.82 NS
DM	28 (70%)	31 (77.7%)	0.58	0.45 NS
COPD	10 (25%)	7 (17.5%)	0.67	0.42 NS

NS: P-value>0.05 is not significant

Inrtaopeartive Data:

Table 2. Long operation time >180 minutes was the only operative variable that significantly statistically associated with SWI in control group (P-value= 0.006), however this variable did not show significance in vancomycin group patients (p-value = 0.2).

	Control Group N=40	Vancomycin Group N=40	t-test	P-value
Ischemic time (minutes) Mean ±SD	**56.6 ± 14.3**	**59.7 ± 14.7**	0.96	0.34 NS
CBP time (minutes) Mean ±SD	**96.1 ± 24.7**	**100.7 ± 27.3**	1.87	0.06 NS
Total operation time (minutes) Mean ±SD	**190 ± 34.7**	**205 ± 39.1**	1.81	0.07 NS
long operation time (minutes) ≤180 minutes >180 minutes	**N(%) 8 (20%) 32 (80%)**	**N(%) 9 (22.5%) 31(77.5%)**	X^2 0.62	0.43 NS
Number of grafts Mean ±SD	**2.93 ± 0.68**	**2.95 ± 0.69**	0.33	0.75 NS
	N (%)	**N (%)**		P
IABP use	**1 (2.5%)**	**1 (2.5%)**	Fisher	1.0 NS
Re-exploration for bleeding	**4 (10%)**	**2 (5.0%)**	Fisher	0.396 NS

NS: P-value>0.05 is not significant

There was no statistically significant difference among both studied groups regarding intraoperative data (p-value>0.05).

Postopeartive Data:

Table 3. The control group showed a staistitically significant relationship between vasopressor duration (P-value=0.001), long postoperative ICU stay for more than 3 days (p-value=0.008) and occurrence of postsernotomy infection. However, in the vancomycin group, these risk factors showed non-significant statistical relationship to poststernotomy infection.

	Control Group N=40	Vancomycin Group N=40	MW test*	P-value
Mechanical ventilation period\ hours Mean ±SD	**6.96 ± 9.4**	**6.16 ± 5.4**	0.26	0.82 NS
Blood transfusion units(Packed RBCs) Mean ±SD	**2.94 ± 1.3**	**2.84 ± 1.3**	0.41	0.68 NS

Total tube drainage \ml **Mean ±SD**	**418.9 ± 263.97**	**412.4 ± 224.8**	0.29	0.77 NS
Vasopressor duration (days) **Mean ±SD**	**1.3 ± 0.71**	**1.2 ± 0.46**	0.52	0.61 NS
Postoperative ICU stay (days) **Mean ±SD**	**2.5 ± 0.98**	**2.3 ± 0.65**	0.72	0.47 NS
Postoperative ICU stays **<3 days** **≥3 days**	**N (%)** **29 (72.5%)** **11 (27.5%)**	**N (%)** **25 (62.5%)** **15 (37.5%)**	X^2 0.91	 0.34 NS

NS: P-value>0.05 is not significant

There was non-significant difference regarding the ICU data in both studied groups (p-value>0.05).

Table 4. Long hospital stay ≥ 10 days were found to be statistically associated with more SWI in both studied groups: In vancomycin group (P-value= 0.02) and in control group (P-value= 0.03).

	Control Group N=40	**Vancomycin Group N=40**	**X^2 t-test***	**P-value**
Total hospitalization period **Mean ±SD**	**11 ± 3.57**	**10.3 ± 2.33**	1.04*	0.302 NS
Total hospital stays. **<10 days** **≥10 days**	**N (%)** **20 (50.0%)** **20 (50.0%)**	**N (%)** **25 (62.5%)** **15 (37.5%)**	1.27	0.26 NS

NS: P-value>0.05 is not significant

Vancomycin group patientshad slightly shorter hospital stay, in comparison to control group. However, it did not reveal statistical significance.

There was no mortality in patients of both studied groups.

Table 5. The presence of two or more risk factors has significant relation to the occurrence of poststernotomy infection in Control group (P- value=0.01). But in the vancomycin group, presence of two or more risk factors showed non-significant relationship to infection (P-value=0.33) .

	Control Group N=40	**Vancomycin Group N=40**	**X^2 t-test***	**P-value**
Not infected	**30 (75%)**	**36 (90%)**	**Fisher**	**0.07** **NS**
Superficial sternotomy infection **Serous discharge** **Purulent discharge** **Early Sternal Rocking**	 **1 (2.5%)** **8 (20%)** **1 (2.5%)**	 **2 (5%)** **0 (0.0%)** **2 (5%)**	**7.47**	**0.02** **S**
Late sternal dehiscence with Deep mediastinitis	**1 (2.5%)**	**0 (0.0%)**	Fisher	0.496 NS

NS: P-value>0.05 is not significant S: P-value<0.05 is significant

There is a statistically significant increased prevalence of superficial sternotomy infection with purulent discharge among Control group patients (20% versus 0% of Vancomycin group patients). There was 1 case of late sternal dehiscence with deep mediastinitis (2.5%) in the control group versus no cases of deep mediastinitis in the vancomycin group. Regarding the safety of vancomycin use, there was no statistically significant difference between preoperative and

average postoperative measures of serum creatinine and urea levels in the vancomycin group of patients. (P-value=0.921, 0.712 , respectively) No patients complained from auditory symptoms (tinnitus, hearing defects), allergies, rash nor neural symptoms. Regarding Laboratory Data, CRP was found to be statistically significantly linked to SWI in both studied groups: In vancomycin group (P-value=0.004),and in control group (P-value<0.001) Procalcitonin was found positive only in one patient who developed poststernotomy deep mediastinitis in control group. It was not detected in any patient in the vancomycin group.

DISCUSSION

In cardiac surgery patients, mediastinitis incidence is 0.4% to 5% . It is a devastating complication leading to increased morbidity and mortality. **(8)** Cardiac surgery performed during the COVID-19 pandemic will force surgeons to operate in certain circumstances. Strict following of the guidelines will decrease postoperative infections, reduce complications, and improve survival. **(11)**

In our study, we tried to evaluate the safety and efficacy of local sternal vancomycin application in prevention of SWI in high-risk CABG patients.

Results of our study showed that there is significant relationship between obesity and poststernotomy infection in control group of patients. However , it did not represent a significant risk factor for SWI when topical sternal vancomycin paste was applied. Other authors found that there is increase in mediastinitis risk by (3% for each additional Kgm body mass per square meter body surface) **(3).Raja s. et al.** found that female gender and obesity are predictors of poststernotomy wound infection in CABG patients. **(15)** However, othersmentioned that obesity is the only modifiable preoperative risk factor for mediastinitis **(16)**.

In the control group in our study, long operation time > 180 minutes, long vasopressor duration and prolonged ICU stay were found to be possible risk factors for poststernotomy infection. However, in vancomycin group, the aforementioned data were not linked to poststernotomy infection.**(12)**

Multiple studies evaluated the effect of intraoperative variables on poststernotomy mediastinitis. Theyfound that long ischemic time, long cardiopulmonary bypass time, intraopeartive insertion of intra-aortic balloon pump and long operation time are risk factors for poststernotomy wound infection. **(17)** Additionally, authors found that prolonged ventilation time and ICU stay duration are risk factors for poststernotomy infections **(18).Lu J et al.** suggested that reexploration for bleeding have been associated with sternal wound infections.

Presence of two or more risk factors for infection was found to carry more risk for poststernotomy infection in our control group. But in vancomycin group -even- presence of multiple risk factors did not show a significant relationship to occurrence of poststernotomy infection. Thus, confirming the efficacy of topical vancomycin in prevention of SWI in high risk patients with multiple risk factors.

Our study results revealed a significant relationship between long hospital stay and poststernotomy superficial infection in both studied groups. However, in vancomycin group, it not related to deep mediastinitis. Our patients with superficial sternotomy wound infection showed only superficial serous discharge negative for bacterial contamination and sternal rocking. **Sá M. et al.** found that patients who developed mediastinitis stayed more time in the intensive care unit and had a higher length of hospital stay (statistically significant) compared with those who did not develop mediastinitis **(18).** **Jadhao M. et al.** found that vancomycin paste application over sternal edges is an effective method to prevent DSWI. The use of local vancomycin paste application is recommended especially in patients with co morbidities like diabetes mellitus and morbidly obese (BMI>30) patients **(7)**

Additionally, **Lazar H. et al.** found that topical sternal vancomycin application with perioperative antibiotics administration and strict glycemic control decreased both SSWIs and DSWIs in postcardiac surgery patients **(10).**

Results of our study showed that in the vancomycin group, poststernotomy superficial infections were in the form of superficial serous discharge negative for bacterial contamination and early partial/limited sternal rocking. Frequent sterile dressing and thoracic support vest was enough for management. No late sternal dehiscence nor deep mediastinitis was detected on follow up. In the control group, poststernotomy superficial infections were superficial serous discharge , early sternal rocking and purulent discharge with positive culture (staphylococcus aureus and epidermidis were the causative pathogens) . One case developed late sternal dehiscence with deep mediastinitis that needed surgical management in the form of debridement of infected tissue, sternal rewiring with reinforced closure and mediastinal irrigation.

Results of our study proved that topical sternal vancomycin paste is effective in prevention of post sternotomy deep mediastinitis and superficial infected discharge. There was no renal complication recorded with the used dose of vancomycin in the local vancomycin paste.

In our study, there is a statistically significant relationship between the occurrence of infection and CRP levels in patients. CRP is a well-known biomarker for infection and inflammation **(6)** .

Procalcitonin was found positive in one severely ill patient with deep mediastintis in control group, but it was not found to be posititive in any case with superficial sternotomy wound infection. It was found that procalcitonin kinetics peaked on postoperative day 2 and fell more sharply than CRP kinetics, which peaked at postoperative day 3.**(2)** **Kopterides P et al.** mentioned that PCT may be useful in antibiotic guidance to minimize the inappropriate use of antibiotics **(9).**Meta analysisby **Wacker C. et al.** revealed that PCT is an important marker in early sepsis diagnosis in severely ill patients; with sensitivity and specificity [77% (95% CI: 72–81%) and 79% (95% CI: 74–84%)], respectively **(20)** .

CONCLUSION

Local vancomycin paste application had the power to decrease the incidence of poststernotomy wound infection even in high-risk CABG patients who had one or multiple risk factors for infection and mediastinitis.

Fortunately, this was in conjunction with excellent safety profile of this technique in concern with possible theoretical adverse systemic effect of vancomycin which was not reported in our series of patients.

These results suggested that this technique can offer superior protection of high-risk patients under excellent umbrella of safety.

CRP is an important marker for detection and follow up of poststernotomy infections.

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