Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

# Effect of topical Vancomycin on consolidation of sternum surgical fracture in open-heart surgery

Luis Alberto Machuca Maldonado[1], Luis Félix Campos Musquiz[1], Gloria Andrea Vaca Braña[1], Mario Sánchez Godínez[1], Cristian Alejandro Castillo López[1], Guillermo Díaz Quiroz[1], Rafael Vilchis López[1], José Luis[1], Aceves Chimal[1]

*[1]Cardiologist, Cardiovascular Department. National Medical Center "20 de Noviembre" ISSSTE, México City, México.*

**ARTICLE INFO**

*Article type:*
*Original article*

*Article history:*
Received: 10 Sept 2019
Revised: 26 Sept 2019
Accepted: 19 Nov 2019

*Keywords:*
*Open Heart Surgery*
*Surgical Fracture Consolidation*
*Topical Vancomycin,*

**ABSTRACT**

**Introduction**: The physiological process of sternum surgical fracture consolidation in patients undergoing cardiac surgery could be prolonged by the invasion of gram-positive saprophytic bacteria which perpetuates the local inflammatory process despite the standardized aseptic and antiseptic measures in cardiac surgery. In this regard, the topical application of Vancomycin can exert a positive effect and prevent the perpetuation of the local inflammatory process by the elimination of these bacteria which in turn reduces bone consolidation time. The purpose of the current study was to determine the effect of topical Vancomycin on sternum surgical fracture consolidation in patients undergoing to open-heart surgery.

**Materials and Methods:** Patients who underwent open heart surgery were assigned into groups receiving the topical application of bone wax or Vancomycin mass in the spongy tissue exposed by surgical sternotomy, prior to sternal closure. The bone consolidation processes were assessed by two expert radiologists with simple chest computed tomography (CT) in the postoperative period (4, 8, and 12 weeks).

**Results:** The study was conducted on 55 patients in Vancomycin (n=33) and bone wax group (n=19). The computerized axial tomography (CAT) scan revealed a higher number of patients with early bone consolidation (Medullar and bone continuity, and callus bone) in Vancomycin group, as compared to bone wax group (p values between 0.004-0.02 at 4 weeks and 0.01-0.06 at 8 weeks). However, no difference was observed at 12 weeks (P=0.09-0.11). Moreover, The magnitude effect of topical Vancomycin was high (>90%) at 3, 8, and 12 weeks of follow up, compared to the patients who received bone wax (<90%).

**Conclusion:** The topical Vancomycin application had a positive effect on sternal surgical fracture and promotes an early bone consolidation in patients undergoing open-heart surgery.

►*Please cite this paper as:*
*Maldonado L.A.M, Musquiz L.F.C, Braña G.A.V, Godínez M.S, López C.A. C, Quiroz G.D, Aceves Chimal R.V.J.L . Effect of topical Vancomycin on consolidation of sternum surgical fracture in open-heart surgery. J Cardiothoracic Med. 2019; 7(4): ):523-529*

## Introduction:

Surgical sternum fracture is essential for the treatment of anterior mediastinum boarding in open-heart surgery which usually heals at least in 12 weeks. During this time patients are at great risk of developing dehiscence, local infection, osteomyelitis, and mediastinitis. An

*Corresponding *author: José Luis Aceves Chimal, Cardiovascular Department. National Medical Center "20 de Noviembre" ISSSTE, México City, México.. Tel: 52005003 ext. 14323 and 14324; E-mail: luis.aceves@issste.gob.mx*

inflammatory reaction is involved after any fracture during the process of bone consolidation which is usually self-limited in the absence of the factors that prolong inflammatory conditions [1.2].

Some authors reported the invasion of deep tissues of mediastinum by gram-positive bacteria, such as saprophytic flora resulting from sternotomy, tissue manipulation, and bone trauma during closure sternotomy despite standardized aseptic and antiseptic measures in cardiac surgery, however despite of this measures considered as gold standard, this bacterial invasion promotes an inflammatory stage which prolongs bone consolidation in the sternum [3-6].

No adverse event was reported in various clinical trials regarding topical Vancomycin. On the contrary, Vancomycin was found to reduce the incidence of local infection by up to 45% which may be attributed to the elimination of residual gram-positive bacteria in the surgical incision [7]. Accordingly, bacterial elimination in the surgical fracture of sternum could promote a faster evolution of the primary bone consolidation and reduce the risks of complications related to surgical sternotomy. The current study reported the result of a clinical trial in which Vancomycin was applied topically to sternotomy surgery at the end of surgical procedure in patients undergoing open-heart surgery to identify the effect of topical Vancomycin in the speed of sternal consolidation after open heart surgery.

### *Materials and Method*

This was a randomized blind clinical trial conducted from January 2018 to June 2019. The study as approved by the National Medic Center " 20 de Noviembre" ISSSTE, Mexico city. Research Ethics Committee with number register 012.2018. All patients signed informed consent and accepted to undergo -heart surgery performed in Cardiology and Cardiothoracic Surgery Departments. The patient's randomization was made using the identification number of clinical records to assign them to each group: 1) Case group: patients with odd end number that received 1 gr. of topical Vancomycin. 2) Control group: patients with even end number that received topical bone wax. The sample size was calculated using the recommendation made by Cohen J [8], whose proposes a high probability to reach a normality distribution of data with at less 30 subjects. Patients prone to surgical re-exploration due to excessive bleeding were eliminated from the study.

The standardized preoperative protocol was covered by all patients, including septic focus eradications, blood biometrics, blood chemistry, respiratory function tests, liver function tests, general urine tests, chest radiographs, electrocardiogram, serological tests (HIV, hepatitis, HPV, CMV, and Chagas disease), hormonal thyroid and parathyroid profile.

Once the patients were prepared for surgery in the operating room, the heart electric activity was continuously monitored by DII and V5 ECG, arterial oxyhemoglobin saturation was determined by pulse oximetry, and heart rate and blood pressure were obtained with a catheter introduced into the left radial artery connected to an arterial pressure transducer. Under general anesthesia, a median sternotomy was performed to gain access to the anterior mediastinum. Thereafter, the pericardium was marsupialized using silk suture to obtain access to the heart. Systemic anticoagulation was carried out with Sodic heparin (Hep-Tec®) at 100 U/kg and, and one cannula was then inserted in the ascending aorta and another one in the inferior and/or superior vena cava. The patient was weaned from extracorporeal bypass and protamine was administered to revert anticoagulation. Additionally, the sternotomy closure was made with stainless steel wire and muscle planes with poliglactina 910 (Vicryl®) suture in the conventional way.

### *Experimental Procedure*

Sternotomy closure was performed with sterile spatula bone wax (Control group) or Vancomycin mass (case group) on the spongy matrix of the sternum, as depicted in Figure 1. The topical Vancomycin was prepared by mixing 1 mg powdered Vancomycin with a physiologic solution until reaching a solid mass and the bone wax Atramat® 2.5 gr.

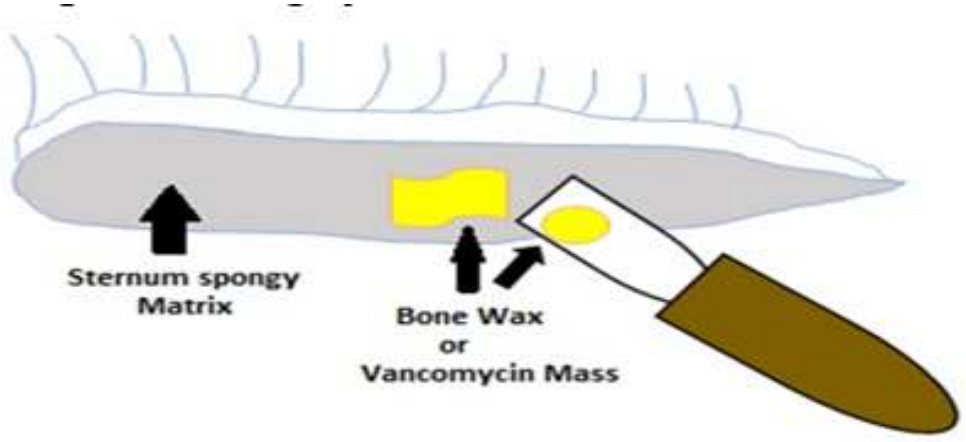


Figure1: Vancomvcin paste and bone wax application technique. From Original Drawing by Machuca Maldonado LA etal.

**Basal and follow up studies**

To see osteoporotic status in each patient as possible bias in the process of bone consolidation, bone densitometry was performed before surgical procedure using Hologic QDR 4500 Elite Dual Energy X-Ray Absorptiometry (DXA) for the determination of mineral concentration (gr) and mineralized bone density (gr / cm3) in the hip and lumbar spine (L1-L4).

The T score and Z scale were identified according to reference values in the Mestizo-Mexican population. At 4, 8 and 12 weeks after surgical procedure, a chest computerized tomography (CT) scan was performed using Siemens CT Scaner and Syngo CT 2006A multislice software. (Figure 2).

The axial cut images were evaluated every 5 mm by an expert radiologist and a radiologist cardiologist in PACs (Picture Archiving and communication system) and KDS (Kanteron Systems version 3.1b2) Osirix Team 2004-2007. The intra and inter-observer variability was assessed with independent images prior to the recruitment, indicating variability of 5 and 8%, respectively.

It is worthy to mention that the radiologists were blinded to the assessment of TC images concerning bone wax or Vancomycin mass applied in each group.

**Results**

The current study was conducted on 52 patients who were assigned into two groups of case (n=33) and control (n=19), the remain patients (n = 11) in this group were eliminated by volume of bleeding that required surgical exploration. The preoperative, surgical and postoperative variables did not show significant differences, as indicated in in Table 1.

The postoperative CAT assessment showed significant higher number patients with early bone consolidation (Medullar and bone continuity, and callus bone) to 4 and 8 weeks in Vancomycin group, compared with bone wax group (p values between 0.004-0.02 at 4 weeks and 0.01-0.06 at 8 weeks). However, no difference was detected after 12 weeks (p value between 0.09-0.11), as indicated in Table 2.

In the Figure 2, showed the CAT images comparison between a case of the vancomycin group and another case of the bone wax group at 4, 8 and 12 postoperative weeks. The magnitude effect of topical Vancomycin was high at 4, 8 and 12 weeks than bone wax on postoperative bone consolidation, as indicated in Table 3.

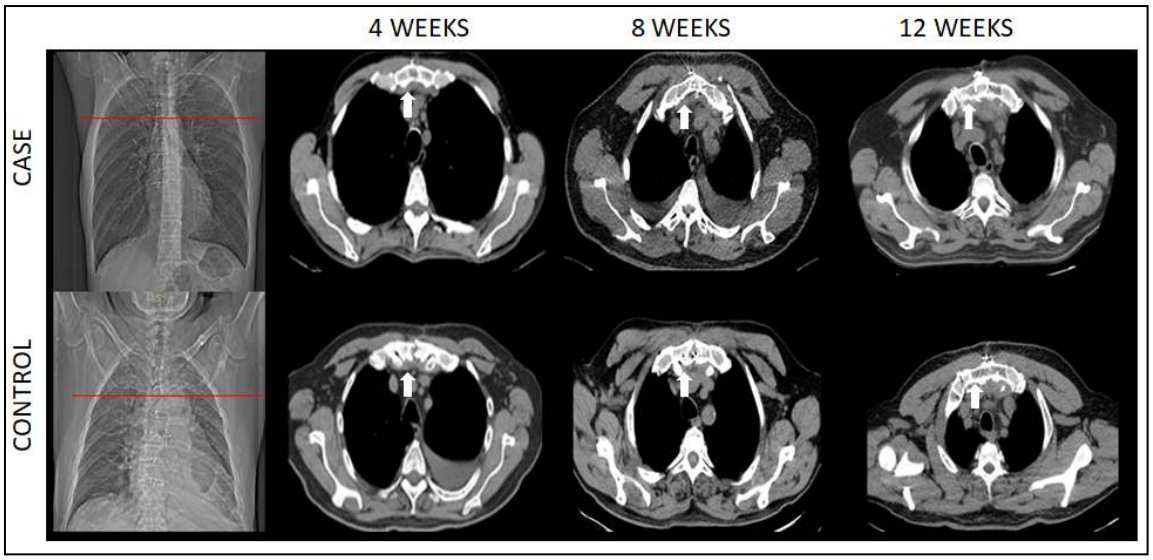


Figure 2: From computed axial tomography of one patient from cases group and other from control group. Axial Tomographic images show medullar and bone continuity at 4 and 8 weeks in case above, compared with control (Below) only with medullar continuity at 8 weeks; at 12 weeks callus bone was present in patients of both groups.

Table 1. Demographic, surgical and postoperative variables

| | Vancomycin group | Bone wax group | p-Value |
|---|---|---|---|
| **Demographic variables** | | | |
| Age (years) | 61±9 | 63±4 | 0.55 |
| Weight (kg) | 74±14 | 75±10 | 0.67 |
| Index Body Mass | 27±3 | 28±2 | 0.82 |
| Diabetes Mellitus (n / %) * | 22/66 | 13/68 | 0.45 |
| Hypertensión (n/ %) * | 17/51 | 9/47 | 0.56 |
| Dyslipidemia (n / %) * | 20/60 | 11/57 | 0.34 |
| Bone densitometry (gr/cm2) | 11.8±6.7 | 13.6±2.4 | 0.27 |
| Alkaline phosphatase (UI/l) | 92.6±5.3 | 78.6±4 | 0.55 |
| Aspartate Aminotransferasa (IU/l) | 76.3±16.3 | 26.5±6.8 | 0.47 |
| Alanin Aminotransferase (IU/l) | 54±10 | 28±5.4 | 0.56 |
| Ureic Nitrogen (mg/dl) | 17.6±8.2 | 22.6±8.8 | 0.21 |
| Creatinine (mg/dl) | 0.9±0.05 | 0.9±0.03 | 0.93 |
| **Surgical variables** | | | |
| Surgical time (min) | 237±64 | 243±47 | 0.80 |
| Extracorporal Bypass time (min) | 70±4 | 89±6 | 0.40 |
| Aorta clamping time (min) | 44± 4 | 62±2 | 0.10 |
| **Postoperative Variables** | | | |
| Hospital estancia (days) | 7±2 | 9±2 | 0.22 |
| Sternal dehiscence (n) | 0 | 0 | - |
| Sternal Instability (n) | 0 | 0 | - |
| Surgical wound infection (n) | 0 | 0 | - |
| Adverse events (n) | 0 | 0 | - |

P value was calculated with Student's t-test and Chi-squared test*

Table 2. Postoperative bone consolidation stages evaluated with images of Computed axial tomography

| | Vancomycin group (n) | Bone wax group (n) | p-value |
|---|---|---|---|
| **Post-Surgical 4 weeks** | | | |
| Medullar continuity | 31 | 12 | 0.004 |
| Bone continuity | 30 | 13 | 0.02 |
| Bone callus | 26 | 3 | 0.001 |
| **Post-Surgical 8 weeks** | | | |
| Medullar continuity | 33 | 16 | 0.01 |
| Bone continuity | 33 | 16 | 0.01 |
| Bone callus | 32 | 17 | 0.05 |
| **Post-Surgical 12 weeks** | | | |
| Medullar continuity | 33 | 19 | 0.09 |
| Bone continuity | 33 | 19 | 0.10 |
| Bone callus | 33 | 19 | 0.11 |

*P value was calculated with Chi-squared test.*

Table 3. Effect Size of Vancomycin and bone wax on postoperative bone consolidation of sternotomy by Computed Axial Tomography

| | **Vancomycin group (%)** | **Bone wax group (%)** | **p-value** |
|---|---|---|---|
| **Post-Surgical 4 weeks** | | | |
| Medullar continuity | 91 | 65 | 0.001 |
| Bone continuity | 91 | 67 | 0.001 |
| Bone callus | 93 | 66 | 0.001 |
| **Post-Surgical 8 weeks** | | | |
| Medullar continuity | 95 | 82 | 0.01 |
| Bone continuity | 95 | 81 | 0.01 |
| Bone callus | 96 | 93 | 0.05 |
| **Post-Surgical 12 weeks** | | | |
| Medullar continuity | 98 | 95 | 0.06 |
| Bone continuity | 98 | 95 | 0.06 |
| Bone callus | 98 | 97 | 0.09 |

*Effect Size (d) was calculated using Cohen Delta test, p value was obtained with Chi-squared test.*

## Discussion

The sternal surgical fracture healing is an event requiring sequenced physiological processes which must take place to avoid postoperative complications in open-heart surgery. These processes are usually carried out smoothly for at least 12 weeks. However, as evidenced by the literature, surgical fracture healing may be delayed by microbial contamination in the sternal surgical wound that leads to a prolonged inflammatory immune phenomenon. The efficiency of topical Vancomycin (30 mg) in the reduction of postoperative infections has been suggested by several studies. This efficiency can be attributed to the elimination of microorganisms that invade the sternal surgical wound despite the standardized aseptic and antiseptic processes in open heart surgery [7, 9, 10]. Based on the results of the present study, apart from preventing the development of a local infectious process, Vancomycin

promotes conditions that allow natural healing of sternal surgical fracture at a faster rate. In this regard, bone and medullar continuity, as well as, bone callus was observed within 4 and 8 weeks in more patients in Vancomycin group, compared to the patients who received conventional bone wax (p values between 0.004-0.02 at 4 weeks and 0.01-0.06 at 8 weeks). These results strongly suggest that the elimination of an antigenic source that prolongs the local inflammatory process allows for a physiological process of tissue reconstitution in less time.

Contrary to above mentioned, several studies have reported that bone wax, which is used in a standardized way to perform hemostasis in sternum spongy bone, is a non-absorbable material that keeps the wound environment moist which permits microorganisms lodged during the surgical procedure to survive. Moreover, surgical trauma and extracorporeal bypass used for open-heart surgical procedures were reported to have an adverse effect on the organism's immune response. Consequently, they can alter the immuno-modulatory defense mechanisms, allowing the invasion and survival of gram-positive microorganisms from saprophytic flora usually observed in local infections [11-14].

In cardiac surgery, major risk factors of sternal surgical fracture healing include obesity and osteoporosis status in each patient, extracorporeal bypass circulation time, aortic clamping time, and preoperative levels of hepatic enzymes (AST, ALT, and TGO) [11-20]. All these imply the possibility of modifying the positive effect of topical Vancomycin on reducing the time needed for postoperative surgical sternal fracture healing. However, neither preoperative demographic nor metabolic conditions showed significant differences between groups and topical vancomycin showed a marked effect on the early healing within the first 8 postoperative weeks processes of bone reconstitution, showing a very high magnitude effect (> 90%), compared to the effect size observed in patients who received conventional bone wax (<90%).

**Strengths and limitations**

The study shows the additional utility of topical vancomycin that in addition to its antimicrobial effect, contributes with conditions that promote bone consolidation in a shorter time, representing an advantage for the patient which undergoing open heart surgery, reducing the likelihood postoperative complications related to sternotomy.

No cultures of the sternotomy edges were performed to identify the residual presence of bacterial contamination; however, the findings showed a process of bone consolidation in less time, suggests other possible effects of vancomycin on cellular processes that should be studied in future research.

**Conclusion**

The topical Vancomycin application had a positive effect on sternal surgical fracture and promotes an early bone consolidation in patients undergoing open heart surgery.

**Acknowledgment**

We would like to thank Rosa María Rosales, Uvea MD, Cardiac Radiology Department, for all her help with image evaluation and Densitometry Department of National Medic center “20 de Noviembre” ISSSTE, México City.

**Conflict of interest:**

The authors declare that they have no competing interest.

**References**

1. Puga FJ. La cirugía convencional sigue siendo la mejor opción en el tratamiento quirúrgico de la valvulopatía aórtica. Argumentos a favor. Rev Esp Cardiol. 2000; 53:479-82.
2. Tsiridis E, Upadhyay M, Giannoudis P. Molecular aspects of fracture healing: which are the important molecules. Injury. 2007; 38: S11-25.
3. De Feo M, Gregorio R, Della Corte A, Marra C, Amarelli C, Renzulli A, et al. Deep sternal wound infection: the role of early debridement surgery. Eur J Cardiothorac Surg. 2001; 19:811-6.
4. Ridderstolpe L, Gill H, Granfeldt H, Ahlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. Eur J Cardiothorac Surg. 2001; 20:1168-75.

5. Braxton JH, Marrin CA, McGrath PD, Morton JR, Norotsky M, Charlesworth DC, et al. 10-year follow-up of patients with and without mediastinitis. Sem Thorac Cardiovasc Surg. 2004; 16:70-6.
6. Pezzella T. Mediastinitis following open heart surgery: introduction. Sem Thorac Cardiovasc Surg. 2004; 16:51-2.
7. Friberg O, Svedjeholm R, Soderquist B, Granfeldt H, Vikerfors T, Källman J. Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial. Ann Thorac Surg. 2005; 79:153-61.
8. Cohen J. Statistical power analysis for the behavioral sciences. Second editionPsychology Press Taylor & Francis Group; 2009
9. Lilly E, Company, Ltd. Manufacturers of vancomycin hydrochloride as brand name vaccine. Basingstoke: Hampshire RG21 6XA; 2002.
10. Hafermann MJ, Kiser TH, Lyda C, Fish DN, Barber GR, Wempe MF, et al. Weight-based versus set dosing of vancomycin for coronary artery bypass grafting or aortic valve surgery. J Thorac Cardiovasc Surg. 2014; 147:1925-30.
11. Pezzella T. Mediastinitis following open heart surgery. Sem Thorac Cardiovasc Surg. 2004; 16:51-2.
12. Veitch SW, Findlay FC, Hamer AJ, Blumsohn A, Eastell R, Ingle BM. Changes in bone mass and bone turnover following tibial shaft fracture. Osteoporos Int. 2006; 17:364-72.
13. Wildemann B, Schmidmaier G, Ordel S, Stange R, Haas NP, Raschke M. Cell proliferation and differentiation during fracture healing are influenced by locally applied IGF-I and TGF-beta1: comparison of two proliferation markers, PCNA and BrdU. J Biomed Mater Res B Appl Biomater. 2003; 65:150-6.
14. Schmidmaier G, Wildemann G, Heegere J, Gäbelein T, Flyvbjerg A, Bail HJ, et al. Improvement of fracture healing by systemic administration of growth hormone and local application of insulin-like growth factor-1 and transforming growth factor-$\beta$1. Bone. 2002; 31:165-72.
15. Moghaddam A, Muller M, Roth HJ, Wentzensen A, Grutzner A, Zimmermann G. TRACP 5b and CTX as osteological marker soft delayed fracture healing. Injury. 2011; 42:758-64.
16. Zimmermann G, Henle P, Kusswetter M, Moghaddam A, Wentzensen A, Richter W, et al. TGF-$\beta$1 as a marker of delayed fracture healing. Bone. 2006; 38:456-7.
17. Sarahrudi K, Thomas A, Mousavi M, Kaiser G, Köttstorfer J, Kecht M, et al. Elevated transforming growth factor-beta1(TGF-$\beta$1) levels in human fracture healing. Injury. 2011; 42:833-7.
18. Stoffel K, Engler LH, Kuster M, Riesen W. Changes in biochemical markers after lower limb fractures. Clin Chem. 2007; 53:131-4.
19. Kurdy NM. Serology of abnormal fracture healing: The role of PIIINP, PICP, and BsALP. J Orthop Trauma. 2000; 14:48-3.
20. Seibel MJ. Biochemical markers of bone turnover. Part II: clinical applications in the management of osteoporosis. Clin Biochem Rev. 2006; 27:123-38.