

Kardiyak Cerrahi Sonrası Postoperatif Mediastinit Tedavisi Sonuçları: Yıkamalı ve Yıkamasız Metodlarla Yapılan Negatif Basıncılı Yara Tedavilerinin Karşılaştırılması

Treatment Outcomes of Postoperative Mediastinitis After Cardiac Surgery: A Comparison of Negative Pressure Wound Therapy Performed with Instillation Method and Non-Instillation Method

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ÖZ

Amaç: Kalp cerrahisi sonrası gelişen mediastinit potansiyel olarak yıkıcı bir komplikasyondur. Bu klinik durum için çeşitli tedavi modaliteleri önerilmiştir ve vakum yardımcı kapatma bunlardan biridir. Bu çalışmada yıkamalı ve yıkamasız yöntemlerle gerçekleştirilen vakum destekli kapatmanın sonuçlarını karşılaştırmayı amaçlanmıştır.

Materyal ve Metot: Ocak 2015-Haziran 2019 tarihleri arasında sternotomi ile kalp cerrahisi gerçekleştirilen ve sonrasında mediastinit gelişen toplam 60 hasta çalışmaya dahil edildi. Grup 1 ve Grup 2, sırası ile yıkamasız ve yıkamalı negatif basınçlı yara tedavisi uygulanan 30 hastadan oluşturuldu. Gruplar arasında demografik özellikler ve tedavi sonuçları karşılaştırıldı.

Bulgular: Hastaların demografik verileri benzerdi. Bakteriyolojik kültürler, her iki gruptaki hastaların büyük çoğunluğunda stafilocok varlığını gösterdi (Grup 1, % 61,6; Grup 2, %70). Tedavi, enfeksiyon eradikasyonu, yara kapanma ve hasta taburculuğu süreleri Grup 2'de istatistiksel olarak daha düşüktü ($p<0,05$) Yara kapanma oranı Grup 2'de istatistiksel olarak daha yüksekti ($p<0,05$).

Sonuç: Yıkama metodu kullanılarak uygulanan vakum destekli negatif basınç tedavisi, mediastinit tedavisinde uygulanabilen bir yöntemdir ve yıkamasız yöntemle göre üstünlükleri mevcuttur.

Anahtar Kelimeler: Enfeksiyon, mediastinit, negatif basınçlı yara tedavisi, vakum yardımcı kapatma, yara iyileşmesi

ABSTRACT

Objective: Mediastinitis following cardiac surgery is potentially devastating complication. Various treatment modalities were suggested for this clinical situation and vacuum assisted closure is one of them. In the study it was aimed to compare outcomes of vacuum assisted closure performed with instillation and non-instillation methods.

Materials and Methods: From January 2015 to June 2019, a total of 60 patients who had mediastinitis after cardiac surgery performed via sternotomy were included to the study. Both Group 1 and Group 2 was consisted of 30 patients to whom negative pressure wound therapy performed without and with instillation, respectively. Demographic characteristics and treatment outcomes were compared between the groups.

Results: Demographic data of the patients were similar. Bacteriologic cultures showed the presence of staphylococci in the majority of the patients in both groups (Group 1, 61.6%; Group 2, 70%). Duration of treatment, eradication of the infection, wound closure and patients discharge were statistically lower in Group 2 ($p<0.05$). Rate of the patients with healed wound was statistically significantly higher in Group 2 ($p<0.05$).

Conclusion: Vacuum assisted negative pressure therapy via instillation is a reliable method that can be performed in the treatment of mediastinitis and has superiority over non-instillation method.

Keywords: Infection, mediastinitis, negative pressure wound therapy, vacuum-assisted closure, wound healing

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INTRODUCTION

Deep sternal wound infections (DSWI), known as mediastinitis, is a major complication after cardiac operations performed with sternotomy. Mediastinal fascia and the deep-seated retrosternal tissues are the involved areas.¹ The incidence of the mediastinitis was reported between 0.6% and 5% in different series and despite adequate medical and surgical treatments it has mortality rates ranging from 10% to 45%.² Multifactorial process involves in the pathogenesis of the mediastinitis that includes various risk factors and pathogenic microorganisms. These factors related to either patient characteristics or the procedure.³

Different treatment modalities can be performed for mediastinitis. Prophylactic and/or microorganism-oriented antibiotherapy is one of the most important tools in the treatment regimens. Besides, surgical revision with primary closure or open dressings, closed irrigation, reconstruction with soft tissue flaps, and negative pressure wound therapy (NPWT) are the other treatment alternatives for mediastinitis.⁴ NPWT can be performed with instillation method or standard method without instillation.⁵

Purpose of this study is to evaluate the treatment outcomes of the NPWT with and without instillation methods in patients with mediastinitis after cardiac surgery performed via sternotomy.

MATERIALS AND METHODS

Ethical Status: Written informed consent was taken from all participants and this single center retrospective study was approved by Gaziantep University Ethics Committee of Clinical Trials (Date: 03/07/2019, decision no: 2019/196) and complies with the declaration of Helsinki.

From January 2015 to June 2019, hospital records of the patients who were treated with NPWT after cardiac operation performed via sternotomy were investigated. Patients performed emergent surgery, re-do surgery, beating heart surgery, underwent thoracic aortic surgery extended to the descending aorta, more than one valve interventions, coronary artery bypass with valve interventions, under 18 years old, diagnosed any kind of neoplasia, had evidences related to the infection but with negative substernal bacterial wound culture or without mediastinitis were not included to the study. A total of 60 patients diagnosed with mediastinitis after cardiac surgery and treated with NPWT with or without instillation methods were involved to the study.

Study was consisted of two groups. Both Group 1 and Group 2 were consisted of 30 patients to whom NPWT was performed without or with instillation method. Demographic data, laboratory findings and echocardiographic results in terms of ejection frac-

tion of the patients, comorbidities, kind of operations performed (coronary artery bypass graft operation, aort valve replacement, mitral valve replacement), classification of the wound, duration of operation and aortic cross-clamp, results of bacterial wound cultures and treatment outcomes of NPWT were compared. Cefazolin sodium 1gr was administered to the patients during induction of anesthesia via venous way and ordered three times a day after postoperative period. Antibiotherapy was revised to suitable one which of the detected pathogen in the surgical site was sensitive. Sternum was closed in classical way after operation but Robitschek method was performed for sternal fixation in the necessity of revision surgery.

Mediastinitis was defined according to Centers for Disease Control and Prevention guidelines.⁶ Diagnosis of mediastinitis requires at least one of the following criteria; presence of organisms cultured from mediastinal fluid or tissue, evidence of mediastinitis on histopathological and gross anatomical examination, and at least one of the signs or symptoms including fever ($>38^{\circ}\text{C}$), sternal instability or chest pain and additionally at least one of the following; mediastinal widening on imaging or purulent drainage from mediastinal site. El Oakley⁷ classification was used for post-sternotomy mediastinitis.

Statistical Method: The normality of distribution of continuous variables was tested by Shapiro Wilk test. Mann-Whitney U test was used for comparison of two independent groups of variables with a non normal distribution. Chi-square test was used to assess relation between categorical variables. The categorical variables were expressed as percentages and continuous variables were expressed as the mean SD. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Statistical significance was defined as $p < 0.05$ with a two tailed test.

RESULTS

Both groups were consisted of 30 patients and there were no statistically differences in demographic, laboratory and clinical data prior to the treatment (Table 1).

In addition to the data above, there were no statistically significant differences in body mass index (BMI) (Group 1, $n=17$; Group 2, $n=18$) and immunosuppressive treatment between the groups.

All the patients were underwent open heart surgery by using cardiopulmonary bypass pump. Type of operations, duration of cross-clamp and operations were given in Table 2.

Post-sternotomy wound classification was evaluated according to the recommendations of El-Oakley et al and summarized in Table 3.

Table 1. Comparison of pre-treatment status between groups.

Variables*	Group 1 (n =30)	Group 2 (n = 30)	p
Age (years)	59.40 ± 10.29	57.13 ± 11.64	0.571
Gender (male/female)	13/17	12/18	0.835
Patients with DM	11	10	0.837
Patients with COPD	6	7	0.726
Patients with renal failure	2	2	>0.99
EF (%)	47±2.3	49±2.7	0.784
Wound area (cm ²)	173.00 ± 123.73	127.33 ± 137.87	0.341
Albumin (gr/dL)	2.364 ± 0.325	2.350 ± 0.823	0.954
CRP (mg/L)	42.44±8.52	46.56±7.61	0.896
WBC count/ml	13.9	13.7	0.965

NPWT; negative pressure wound therapy, DM; diabetes mellitus, WBC; white blood cell *Mean ± SD.

Table 2. Type of operations and duration of operations and cross-clamp.

	CABG(n)	AVR(n)	MVR(n)	Duration of Operation (min)	Duration of cross-clamp (min)
Group 1	18	5	7	160.3±12.4	45.2±3.7
Group 2	19	4	7	156.6±11.7	43.4±4.1
P	0.844	0.786	>0.99	0.934	0.925

CABG; coronary artery bypass graft, AVR; aortic valve replacement, MVR; mitral valve replacement.

Table 3. Post-sternotomy El-Oakley mediastinitis classification.

El Oakley Class	Group 1 (n=30)		Group 2 (n=30)	
	N	%	N	%
I	-	-	-	-
II	6	20.0	5	16.6
IIIA	9	30.0	9	30.0
IIIB	15	50.0	16	53.4
IVA	-	-	-	-
IVB	-	-	-	-
V	-	-	-	-

Bacteriologic wound cultures revealed the presence of staphylococci in the majority of the patients in both groups and results were given in Table 4.

Duration of treatment, bacterial eradication, wound closure, and hospital discharge were statistically

significantly lower in Group 2. Wounds of all patients totally healed in Group 2 however, 66.7% of the patients had totally healed wounds in Group 1 (Table 5).

Table 4. Culture-verified deep sternal wound infection pathogens.

Bacterial strains	Group 1 (n=30)		Group 2 (n=30)	
	N	%	N	%
Staphylococcus aureus	12	40.0	13	43.3
Escherichia coli	1	3.3	-	-
Staphylococcus epidermidis	6	20.0	7	23.3
Metisin resistance Staphylococcus aureus	6	20.0	5	16.6
Pseudomonas aeruginosa	3	10.0	2	6.6
Acinetobacter baumannii	2	6.6	3	10.0

Table 5. Comparison of treatment outcomes between groups.

Outcomes	Group 1 (n =30)	Group 2 (n = 30)	p
Days treated*	36.47 ± 13.07	9.87 ± 4.31	0.001**
Days wound eradicated from clinical infection*	26.40 ± 6.58	6.05 ± 1.48	0.001**
Wound healed (%)	65.7	100	0.006**
Days to wound closure*	28.65 ± 6.62	13.24 ± 6.58	0.001**
Days to patient discharge*	39.28 ± 12.14	14.76 ± 9.25	0.001**

NPWT, negative pressure wound therapy. *Mean ± SD. ** p < 0.05 compared with control group.

DISCUSSION AND CONCLUSION

Mediastinitis is a life-threatening complication after median sternotomy. Several risk factors have been defined in the literature and of those obesity and diabetes remain the most important.⁸ Most of the participants in our study were involved in overweighted and obesity class I groups according to the BMI classification and DM was the most prevalent concomitant disease. Besides, advanced age, COPD, left ventricular dysfunction, female sex and renal failure were additional preoperative risk factors mentioned in the literature.² Most of the patients were female and had decreased EF and advanced age in our study. COPD was the second prevalent concomitant disease and there were four patients with renal failure. Prolonged duration of surgery and aortic-cross clamp time was accepted as intra-operative risk factors for mediastinitis.⁹ Duration of operation and aortic cross-clamp time was within normal limits parallel with the literature in our study, because of exclusion of surgeries required more than one cardiac structure interventions and redo.

Use of bilateral internal mammarian artery for vascular graft in coronary artery bypass graft operations is also associated with postoperative mediastinitis. Harvesting of both mammarian arteries damages to sterna collateral blood supply and increases the vulnerability to infections.¹⁰ In our study only left internal mammarian artery was used in patients who underwent coronary artery bypass graft operation.

Mediastinitis was classified into five categories according to time of presentation and presence of risk factors by El-Oakley et al.⁷ All of the participants in both groups in our study were involved in group II, IIIA and IIIB.

The most common microorganism detected in wound infections is staphylococcus aureus and causing up to 80% of mediastinitis after cardiac surgery.¹¹ Similarly, S.aureus was the major pathogen detected in the bacteriologic wound cultures of the patients in both groups in our study.

Various treatment modalities were defined in the

literature for mediastinitis. Despite the choice of antibiotic, optimal dose, duration and timing remain controversial, preoperative antibiotic prophylaxis is one of the most important tools in the treatment.¹² Surgical debridement, drainage, irrigation, plastic reconstruction and NPWT are the other techniques established previously.¹³

NPWT is a newer method consists of an open-cell foam dressing covered with an adhesive drape. Sub-atmospheric pressure is created and maintained by the dressing connected to a vacuum pump.¹⁴ It can be used in different wound types including acute wounds such as traumatic or dehisced surgical wounds and flaps and grafts, and chronic wounds such as diabetic, pressure and vascular ulcers.¹⁵ Wound drainage, stabilization of the chest wall, isolation of the chest cavity to prevent contamination, granulation stimulation, maintenance of a moist environment, and increased blood flow to the tissues can be achieved by using NPWT when applied for the mediastinitis after sternotomy.¹⁶ It also plays a critical role in cell proliferation, modulation of inflammation and decreasing in bacterial levels.¹⁵ NPWT with antibiotic was suggested as a first line therapy for mediastinitis in a study conducted by Kaul.¹⁷ In addition, initiation of NPWT is a class II recommendation by the guidelines of American Association of Thoracic Surgery (AATS) in patients to whom delayed sternal closure is planned following mediastinitis.¹⁸ Cefazolin sodium (iv) was administered to the patients before operation and antibiotic therapy was regulated according to the microorganisms detected in the bacterial wound culture in post-operative period in our study.

NPWT can be performed by a standard way without instillation or with instillation method which allows automated, intermittent, volume controlled instillation of a topical wound solution during the therapy. Although several solutions were recommended in the literature for instillation, saline was the preferred one because of the outcomes similar to other types of solutions.¹⁹ Saline was used for instillation in our study.

NPWT with instillation has been suggested in the treatment of infected or contaminated wounds in necrotizing fasciitis, upper and lower extremity wounds, ulcers, breast reconstruction and other complex wounds as well as mediastinitis.²⁰ Singh et al.²¹ compared the outcomes of patients with mediastinitis treated with NPWT with and without instillation. Control of wound infection and early granulation tissue formation was better in patients treated with NPWT with instillation. Similarly, in a study designed by Chowdhry et al.²⁰, days to wound closure and the number of therapy days were fewer in NPWT with instillation group. In our study, days to wound closure were significantly fewer and the duration of the treatment were significantly lesser in the patients treated via NPWT with instillation. Karaca et al.²² reported a case of mediastinitis caused by *Mycoplasma hominis*. NPWT with instillation method was performed and patient was treated with a success in that study. Gabriel et al.²³ emphasized that NPWT with instillation has a positive impact on decreasing the bacterial colonization in acute or chronic wounds. Thus, this method can be useful for the eradication of infection in mediastinitis with appropriate antibiotics. Duration of the eradication of the wound was lesser in NPWT with instillation group in our study. According to the study designed by Hehr et al.²⁴, successful clearance of infection and healed wounds in 89% of the patients were achieved with sternal, spinal and extremity infections via NPWT with instillation. Sternal wounds were healed in all of the patients treated via NPWT with instillation in our study. NPWT with instillation has also been shown to shorten the overall hospital stay.²⁵ Patients were statistically significantly discharged earlier to whom NPWT with instillation method was performed in our study.

Underlying mechanism of NPWT with instillation on wound healing and bacterial eradication can be explained as follows; NPWT with instillation allows to lower wound fluid viscosity, enabling the washout of necrotic tissue, clots and fibrin in addition to removal of excess fluid and increased granulation. NPWT alone supplies a mechanical stress for stimulation of underlying cell proliferation, while NPWT with instillation allows new cells to be set on healthy tissue. It removes inhibitory factors such as metalloproteases and destroys glycocalyx responsible for resistance to antiseptics.^{26,27}

In conclusion, efficiency of NPWT on the treatment of mediastinitis after sternotomy was known previously. NPWT with instillation is a recently introduced treatment modality and performed NPWT with irrigation solution. Evidences are available in the literature related to its positive effects on cell proliferation and granulation which maintain wound healing and prevention of drug resistance. It has su-

periority over NPWT without instillation in the terms of duration of the therapy, wound closure, eradication of the infection and patient discharge. Further studies with larger population are required for additional effects of this therapy.

Ethics Committee Approval: Our study was approved by Gaziantep University Ethics Committee of Clinical Trials (Date: 03/07/2019, decision no: 2019/196).

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REFERENCES

1. Ma JG, An JX. Deep sternal wound infection after cardiac surgery: a comparison of three different wound infection types and an analysis of antibiotic resistance. *J Thorac Dis.* 2018;10(1):377-387. doi:10.21037/jtd.2017.12.109
2. 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;20:1168-1175. doi:10.1016/s1010-7940(01)00991-5
3. Lepelletier D, Bourigault C, Roussel JC, et al. Epidemiology and prevention of surgical site infections after cardiac surgery. *Med Mal Infect.* 2013;43:403-409. doi:10.1016/j.medmal.2013.07.003
4. Cotogni P, Barbero C, Rinaldi M. Deep sternal wound infection after cardiac surgery: Evidences and controversies. *World J Crit Care Med.* 2015;4(4):265-273. doi:10.5492/wjccm.v4.i4.265
5. Kim PJ, Attinger CE, Steinberg JS, et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg.* 2014;133(3):709-716. doi:10.1097/01.prs.0000438060.46290.7a
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol.* 1999;20:250-278.
7. El Oakley RM, Wright JE. Postoperative mediastinitis: classification and management. *Ann Thorac Surg.* 1996;61(3):1030-1036. doi:10.1016/0003-4975(95)01035-1
8. Abu-Omar Y, Kocher GJ, Bosco P, et al. European Association for Cardio-Thoracic Surgery

- expert consensus statement on the prevention and management of mediastinitis. *Eur J Cardiothorac Surg.* 2017;51:10-29. doi:10.1093/ejcts/ezw326
9. Fowler VG, O'Brien SM, Muhlbauer LH, Corey GR, Ferguson TB, Peterson ED. Clinical predictors of major infections after cardiac surgery. *Circulation.* 2005;112(9 Suppl):1358-1365. doi:10.1161/CIRCULATIONAHA.104.525790
 10. Ruka E, Dagenais F, Mohammedi S, et al. Bilateral mammary artery grafting increases postoperative mediastinitis without survival benefit in obese patients. *Eur J Cardiothorac Surg.* 2016;50(6):1188-1195. doi:10.1093/ejcts/ezw164
 11. Mekontso-Dessap A, Kirsch M, Brun-Buisson C, Loisançe D. Poststernotomy mediastinitis due to *Staphylococcus aureus*: Comparison of methicillin-resistant and methicillin-susceptible cases. *Clin Infect Dis.* 2001;32:877-883. doi:10.1086/319355
 12. Kreter B, Woods M. Antibiotic prophylaxis for cardiothoracic operations: Metaanalysis of thirty years of clinical trials. *J Thorac Cardiovasc Surg.* 1992;104:590-599.
 13. Petzina R, Hoffmann J, Navasardyan A, et al. Negative pressure wound therapy for post-sternotomy mediastinitis reduces mortality rate and sterna re-infection rate compared to conventional treatment. *Eur J Cardiothorac Surg.* 2010;38(1):110-113. doi:10.1016/j.ejcts.2010.01.028
 14. Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. Negative pressure wound therapy: a vacuum of evidence? *Arch Surg.* 2008;143(2):189-196. doi:10.1001/archsurg.2007.54
 15. Orgill D, Bayer L. Update on negative-pressure wound therapy. *Plast Reconstr Surg.* 2011;127:105-115. doi:10.1097/PRS.0b013e318200a427
 16. Sjögren J, Malmsjö M, Gustafsson R, Ingemansson R. Poststernotomy mediastinitis: A review of conventional surgical treatments, vacuum-assisted closures therapy and presentation of Lund University Hospital mediastinitis algorithm. *Eur J Cardiothorac Surg.* 2006;30:898-905. doi:10.1016/j.ejcts.2006.09.020
 17. Kaul P. Sternal reconstruction after post sternotomy mediastinitis. *J Cardiothorac Surg.* 2017;12:94-103. doi:10.1186/s13019-017-0656-7
 18. Lazar HL, VanderSalm TV, Engelman R, Orgill D, Gordon S. Prevention and management of sterna wound infections. *J Thorac Cardiovasc Surg.* 2016;152(4):962-972. doi:10.1016/j.jtcvs.2016.01.060
 19. Teot L, Boissiere F, Fluieraru S. Novel foam dressing using negative pressure wound therapy with instillation to remove thick exudate. *Int Wound J.* 2017;14(5):842-848. doi:10.1111/iwj.12719
 20. Chowdhry SA, Wilhelmi BJ. Comparing negative pressure wound therapy with instillation and conventional dressings for sternal wound reconstruction. *Plast Reconstr Surg Glob Open.* 2019;71:e2087. doi:10.1097/GOX.0000000000002087
 21. Singh H, Mahendru S, Khazanchi RK. Negative pressure wound therapy with instillation on sterna wound: is it really worrisome? *Ind J Thorac Cardiovasc Surg.* 2019;34(4):594-595. doi:10.1007/s12055-019-00834-x
 22. Karaca S, Kalangos A. Vacuum-assisted closure (VAC)-Instill with continuous irrigation for the treatment of *Mycobacterium hominis* mediastinitis. *Int Wound J.* 2015;12:595-597. doi:10.1111/iwj.12234
 23. Gabriel A, Shores J, Bernstein B, et al. A clinical review of infected wound treatment with Vacuum Assisted ®(V.A.C.®) Therapy: experience and case series. *Int Wound J.* 2009;6:1-25. doi:10.1111/j.1742-481X.2009.00628.x
 24. Hehr JD, Hodson TS, West JM, et al. Instillation negative pressure wound therapy: An effective approach for hardware salvage. *Int Wound J.* 2020;17(2):387-393. doi:10.1111/iwj.13283
 25. Gabriel A, Kahn K, Karmy-Johnes R. Use of negative pressure wound therapy with automated instillation for the treatment of extremity and trunk wounds: clinical outcomes and potential cost-effectiveness. *Eplasty.* 2014;14:e41.
 26. Gilbert V, Kelly T, Grossi R. Source control and graft preservation using negative pressure wound therapy with antibiotic instillation. *Cureus.* 2016;8(10):e855. doi:10.7759/cureus.855
 27. Gabriel A, Shores J, Heinrich C, et al. Negative pressure wound therapy with instillation: a pilot study describes a new method for treating infected wounds. *Int Wound J.* 2008;5:339-413. doi:10.1111/j.1742-481X.2007.00423.x