Role of Indomethacin in the Treatment of Pericardial Effusion after Cardiac Surgery

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ABSTRACT

Background: Pericardial effusion is a serious complication post cardiac surgery and often leads to significant morbidity. Hence, it is important to counter the rapid progression of effusion. Indomethacin is a potential therapy to heal any effusion of inflammatory origin.

Aim: To assess the efficacy of indomethacin in managing pericardial effusion in the post cardiac surgery period.

Methods: A prospective randomized-controlled trial was conducted on 138 patients who underwent cardiac surgery at Queen Alia Heart Institute during the period between 2019-2020. The mean age of the patients was 50.4 ± 6.2 years and they were predominantly males (54.3%). There were two groups: Group I, who received indomethacin and Group II, the placebo group. The mean pericardial effusion was evaluated at discharge, 7 and 14 days' post hospital discharge. The split plot ANOVA mixed design was used for group-wise comparison, while multiple linear regression was used to determine the effects of risk factors on effusion.

Results: At discharge, both groups demonstrated comparable mean pericardial effusion (15.34 vs. 15.99 mm). However, at one-week follow-up period, the mean pericardial effusion in indomethacin group was significantly lower (~2-fold) than that in control group and continued to decrease until last follow-up day (Week 2).

Conclusion: Pericardial effusion after cardiac surgery can be managed effectively with indomethacin in the first week period. However, it is important to ascertain the underlying cause before prescribing indomethacin because of their propensity to cause bleeding.

Keywords: pericardial effusion, echocardiography, indomethacin, cardiac surgery

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INTRODUCTION

Symptomatic pericardial effusion is a frequent sequelae of cardiac operative interventions. Although its implications are usually not too severe and the condition may be seen in 50-85% of the patients postoperatively, rarely, the effusion may progress to cardiac tamponade. [(1)] The significance of the threat posed by this condition is evident by its high prevalence (22%) among cardiac surgery patients even after the 20 days' post-surgery. [(2)] Previous studies have reported that an important risk factor of a delayed cardiac tamponade is the size of the early detected effusion. Although such effusion is reversible, it is still considered to be extremely life-threatening. Postoperative monitoring has revealed that small-sized effusions often resolve uneventfully, while larger pericardial effusions may progress to tamponade in about 11% of the patients. [(2)]

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Previous studies have used indomethacin, a non-steroidal anti-inflammatory drug (NSAID), to mitigate the clinical effects and reduce the effusion size.[3] The rationale behind using NSAIDs postoperatively is that the underlying inflammation has been found to be responsible for triggering as well as progression of the effusion post-surgery.[4,5] Patients who have recently undergone a cardiac surgery are under stress conditions and NSAIDs are administered for a short period to prevent the fluid build-up in the pericardial cavity may be of value. Furthermore, a short-term therapeutic course could help to avoid severe side effects from NSAIDs, including myocardial infarction, acute heart failure, [6,7] acute renal failure, [8] and upper gastrointestinal tract bleeding. [9]

This investigation aims to determine the efficacy of indomethacin therapy in decreasing the size of pericardial effusions persisting even after a week post-cardiac surgery using the extent change in the pericardial effusion score from baseline and the number of subjects with a minimum of 1-point reduction in the effusion score with a median modification in the width of the effusion.

METHODS

This prospective, randomized-controlled double-blind investigation [10] was conducted at the Queen Alia Heart Institute, KHMC, Amman, Jordan, in the period between 2019 and 2020. 138 patients (mean age: 50.4 years, SD+/- 6.2) having mild, moderate, or large pericardial effusion (indicated by a score >1 on an echocardiogram scale) persisting beyond 1-week after their cardiac surgeries (coronary artery bypass graft, valve replacement, or congenital heart defect repair), also different co morbidities (risk factors) comorbidities are outlined as in (Table I).

The echocardiogram scoring ranged from 0 to 4, wherein the score equalized a loculated effusion >1 cm or a circumferential effusion of any size [11] (Table I). Patients who are known to have gastroduodenal ulcer disease and/or renal failure, and/or previous cardiac surgery more than one month before the first echocardiogram, or harboring a pericardial effusion that required drainage were excluded from the study.

Ethical approval was obtained from the Ethical and Research Board Review Committee, Royal Jordanian Medical Services, Jordan. All participants provided written informed consent before commencement of the study. All demographics and baseline clinical data were recorded during the pre-procedural assessment.

The recruited patients were divided into two groups - Group I participants received 0.3-0.6 mg/kg/day indomethacin administered orally three times a day, while Group II was the control group [1], which was administered a placebo agent twice-a-day for 2 weeks. The patients and the data collector were blinded to the drug used.

The first echocardiogram was performed on the day of discharge after the surgery, the second echocardiogram was performed after first week in the clinic, and the third echocardiogram was performed two weeks' post-discharge in order to assess the potential effect of the investigated therapy on the size of effusion. Besides the interventional drug that was given on the day of discharge and continued until the effusion subsided by echocardiogram, low-dose aspirin was administered to patients undergoing a coronary artery bypass graft (CABG), while oral Vitamin-K antagonists were administered for anticoagulation in patients who had valve replacement. M-mode, cross-sectional, and Doppler echocardiogram was used. Pulsed and continuous Doppler echocardiograms of the mitral, aortic, and tricuspid flows were obtained. Pericardial effusion during diastole was recorded as an echo-free space around the heart and categorized as circumferential or loculated along the right or left cardiac chambers, following by measurement of the effusion width at the largest volume.

The primary outcome was the extent of change in the pericardial effusion score from baseline till 2 weeks post intervention. Secondarily, the number of subjects with a minimum of 1-point reduction

in the effusion score and the median modification in the width of the effusion was also recorded. Lastly, pericardial drainage was recorded 2 weeks' post-surgery.

Table I: Socio-demographic data of study sample N=138

Variable	Frequency (%)
Gender	
Male	75(54.3%)
Female	63(45.7%)
HTN	
Yes	71(51.4)
No	67(48.6)
DM	
Yes	54(39.1)
No	84(60.9)
PVD	
Yes	56(40.6)
No	82(59.4)
Surgery	
CABAG	84(40.9)
MVR	19(13.8)
AVR	19(13.8)
Congenital	16(11.6)
Anti-inflammatory drugs	
Indomethacin	71(51.4)
Control	67(48.6)
	Mean±SD
Pericardial effusion on discharge	15.65±3.11mm
Pericardial effusion at one week	7.29±3.25mm
Pericardial effusion at 2week	2.88±1.8mm
Age/years	50.4±6.2

STATISTICAL ANALYSIS

Frequency and percentages were used to represent the categorical data, while mean ± SD were used to represent the continuous data. The Kolomgrove Siminarove test was used to assess the normality of the data. Split Plot ANOVA (mixed design) was used to assess the significance of the inter-group differences. Multiple linear regression was used to assess risk factors significantly associated with pericardial effusion. The statistical significance was set at $\alpha \leq 0.05$ with 80% of study power. SPSS IBM software v.25 was used for statistical analysis.

Data management

A standard data scanning was conducted to check if there were any outliers, or missing or undefined values before the analysis. In addition, each inferential test was checked for its assumptions, the data were found normally distributed, and no assumptions were violated.

RESULTS

Study Participants

This study included 138 patients who underwent cardiac surgery at the Queen Ali Heart Institute during 2019-20. The mean age of the patients was 50.4 ± 6.2 years, predominantly comprising male patients (n = 75; 54.3%). The indomethacin group and the control group comprised 71 (51.45%) and 67 (48.6%) patients respectively. Of all the participants, 71 (51.4%), 54 (39.1%), and 56 (40.6%) patients had hypertension (HTN), diabetes mellitus (DM), and peripheral vascular disease (PVD), respectively. majority of the procedures were CABG surgery (n = 84; 60.9%).

Pericardial Effusion

Pericardial effusion was recorded at three different time points during the study. (Table 1). The mean effusions at the time of discharge, at Week 1 during follow-up, and at Week 2 during follow-up were 15.65 mm ± 3.11, 7.29 mm± 3.25, and 2.88 mm ± 1.8, respectively (Table I; Figure 1).

The inter-group differences in the effusion sizes were assessed using the split plot ANOVA, which revealed a statistical significant interaction effect across all the three observation points (Wilks' lambda: 0.835, F (df =135): 13.318, $p < 0.001$). In addition, partial eta square (η_p^2) = 28.5% indicated a medium effect size based on Cohen effect size classification

As shown in (Table II), the mean effusion at the time of discharge was comparable between Groups I and II (15.34 mm and 15.99 mm, respectively). At the end of Week 1 during the follow-up, the effusion in Group I was significantly lower (~2-fold) compared to that in Group II. The effusion in Group I continued to decrease across Week 2 during the follow-up (Table II).

Table II Mean and standard deviation of pericardial effusion=138

Time	Group	N	Mean± SD
On discharge	Indomethacin	71	15.34±6.86mm
	Control	67	15.99±7.38mm
Week 1	Indomethacin	71	4.49±4.08 mm
	Control	67	10.27±6.66 mm
Week 2	Indomethacin	71	0.45±1.16 mm
	Control	67	5.46±3.93 mm

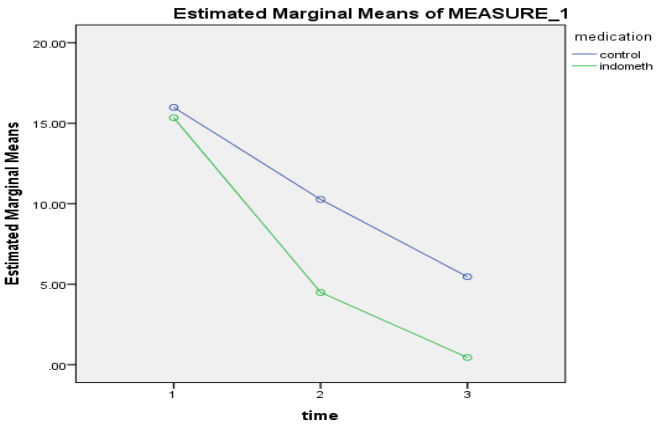

Fig.1

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Table III: Split plot ANOVA test result for groups mean differences

Time	Groups (I)	Groups (J)	Mean differences (I-J)	Sig
Discharge	Control	Indomethacin	0.643	0.598
One week	Control	Indomethacin	5.775	0.000
2 week	Control	Indomethacin	5.017	0.000

Risk Factors

To determine the significant risk factors for pericardial effusion, multiple linear regression analysis was performed at Week 2 of follow-up. For this analysis, we examined the association of age and other co-morbidities (HTN, DM, and PVD) with the mean size of effusion. As shown in (Table IV), of all the factors, only the age of the patient was significantly associated with the degree of effusion at Week 2 during the follow-up" as the age increase by one year, there was proportional increase in size of pericardial effusion (B=0.042 mm (p = 0.046).

Table IV: Multiple linear regression for associated factor that impact on week two pericardial effusion

P value	T value	B coefficients	predictors	ANOVA		R^2	Dependent variable
				P value	F		
0.046	2.015	.042	Age	0.041	4.891	0.085	Week two pericardial effusion
0.530	-.629	-.483	HTN				
0.868	-.167	-.132	DM				
0.356	-.927	-.681	PVD				

DISCUSSION

This study aimed to assess the efficacy of indomethacin, a non-steroidal anti-inflammatory drug, in managing pericardial effusion post cardiac surgery. During 2-weeks follow-up period, only 10% of our patient's cohort exhibited moderate to large pericardial effusion and required operative pericardiocentesis. As evident from our results, indomethacin was able to completely resolve the effusion if it was continuously administered for 7 days postoperatively. Eighty-five patients were scheduled to a control group receiving oral placebo or to an indomethacin group having 25 mg oral indomethacin three times daily for one week befor surgery. No patient in both groups experienced pericardial effusion following the first day after surgery. At the end of the first week, 2 patients experienced pericardial effusion; at the end of the second week following discharge, 3 patients experienced pericardial effusion; and at the end of the sixth week following discharge, 4 patients experienced pericardial effusions. One of the patients who had pericardial effusion at the end of the sixth week had indomethacin; the others were all in the control group ($P < 0.019$) **(12)**.

Etiologically, early effusion in the pericardial sac results from intraoperative hemorrhage, while delayed effusion, which is more common, could be attributed to other factors, among which inflammation is the principal causal factor**.(13)** Hence, indomethacin can be used to manage delayed pericardial effusion.(2,3) Corroborating the results of the previous studies, our study showed an improvement of 0.6 mm in the effusion score of the control group, while on the other hand, indomethacin administration led to a significant improvement in effusion scores and median pericardial effusion size as well.

It is noteworthy that in cardiac surgery patients other administered medications often exhibit certain side effects when administered with NSAIDs. For instance, patients undergoing a heart valve surgery utilizing oral anticoagulants to prevent the risk of valve thrombosis and distal embolization, when combined with NSAIDs, these agents can lead to serious gastrointestinal bleeding. Similarly, patients suffering from coronary artery disease are prescribed angiotensin-converting enzyme inhibitors, which may cause renal failure if combined with NSAIDs. (1) Hence, the use of NSAIDs after a CABG may have certain hazards to be taken in consideration. Furthermore, selective COX-2 inhibitors and nonselective NSAIDs may increase the risk for a cardiovascular event as well as the mortality and re-infarction risk in patients suffering from coronary artery disease. (6) It is known that the administration of COX-2 inhibitors post-CABG surgery is associated with a high frequency of cardiovascular hazards. (13).

Indomethacin does not counteract the irreversible platelet inhibition generated by aspirin (almost 70% of our participants were given low-dose, 81 mg aspirin), has less side effects such as hemorrhage and renal failure, and has a higher cost-effectiveness, can be given with angiotensin converting enzyme inhibitors drug without harmful effects on the kidney.(14) We used the interventional drug after the first postoperative week since early pericardial effusions are less frequent than delayed effusions and cannot be managed through NSAIDs. In 95% of cases, delayed effusions were recorded between the 1st and the 4th postoperative week. (5)

It is known that pericardial effusion after cardiac surgery is frequent and possibly intense, consequently, the moderate to large pericardial effusions (score 2-4) observed within the first 4 weeks postoperatively have serious ramifications, and 10% of these patients required surgical pericardiocentesis in the 2 weeks after inclusion. However, another important consideration is that inflammation may not be the sole reason for delayed effusions.

Unfortunately, there is no available non-invasive test that can differentiate between inflammatory and bleeding effusions, and hence, indomethacin cannot be prescribed in all cases without determining the underlying etiology and clinical correlation. In cases where the clinical picture after surgery is unknown, it is better to resort to conservative methods, especially when the cause of most of the pericardial effusions is non-inflammatory. (15)

The main limitation of our investigation is that it was conducted at a single center.

CONCLUSION

Pericardial effusion that occurs within the first week and second week after surgery can be adequately controlled with indomethacin. Indomethacin is superior conservative treatment in patients with pericardial effusion (placebo). Also, indomethacin is safe with less adverse sequels and improves pericardial effusion outcome. However, it is important to ascertain the underlying cause before prescribing indomethacin because of their propensity to cause bleeding.

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