Effect of Low-dose Dexamethasone on Extra Vascular Lung Water in Patients Following On-pump Elective Primary Coronary Artery Bypass Graft Surgery

Abstract

Background: The primary objective was to compare the effect of a low-dose dexamethasone as against a saline placebo on extravascular lung water index (EVLWI) in patients undergoing elective primary coronary artery bypass surgery. The secondary endpoints were to assess the effect of dexamethasone on other volumetric parameters (pulmonary vascular permeability index, global end diastolic volume index, and intrathoracic blood volume index), Vasoactive Inotrope Scores, hemodynamic parameters and serum osmolality in both groups. Settings and Design: Prospective observational study performed at a single tertiary cardiac care center. Materials and Methods: Twenty patients were randomized to receive either dexamethasone (steroid group, n = 10) or placebo (nonsteroid group, n = 10) twice before the institution of cardiopulmonary bypass (CPB). EVLWI and other volumetric parameters were obtained with the help of VolumeView™ Combo Kit connected to EV 1000 clinical platform at predetermined intervals. Hemodynamic parameters, vasoactive-inotropic Scores, hematocrit values were recorded at the predetermined time intervals. Baseline and 1st postoperative day serum osmolality values were also obtained. Results: The two groups were evenly matched in terms of demographic and CPB data. Intra- and inter-group comparison of the baseline EVLWI including other volumetric and hemodynamic parameters with those recorded at subsequent intervals revealed no statistical difference and was similar. Generalized estimating equation model was obtained to compare the changes between the groups over the entire study period which showed that on an average the changes between the steroid and nonsteroid group in terms of all volumetric parameters were not statistically significant. Conclusions: There were no beneficial effects of low-dose dexamethasone on EVLWI or other volumetric parameters in patients subjected to on-pump primary coronary bypass surgery. Hemodynamic parameters were also not affected. Probably, the advanced hemodynamic monitoring aided in optimal fluid management in the nonsteroidal group impacting EVLW accumulation.

Keywords: Anti-inflammatory agents/pharmacology, dexamethasone/administration and dosage, extravascular lung water, heart diseases/surgery, inflammation/prevention and control

Introduction

Cardiac surgery performed on cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response resulting in organ dysfunction, and even multisystem organ failure. Glucocorticoids have anti-inflammatory activity. These drugs are low-cost, potent anti-inflammatory agents and therefore represent an appealing treatment option in this scenario. It, therefore, seems reasonable to try to attenuate the inflammatory response with long-acting corticosteroids such as intravenous methylprednisolone or dexamethasone during cardiac surgery for a better outcome. Studies have shown that corticosteroids may improve pulmonary gas exchange and reduce the need for postoperative inotropic support by attenuating increases in serum inflammatory markers. Corticosteroids administration has also been shown to improve myocardial or pulmonary cell integrity with a reduction in the expression of endothelial adhesion molecules, complement activation, and cytokine release. Despite the uncertainty about the effectiveness of corticosteroids in the reduction of major adverse events, corticosteroid administration during cardiac surgery is part of routine care in many European hospitals. High-dose (1 mg/kg) dexamethasone could result in inadequate
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serum glucose control and an increased re-thoracotomy to name a few adverse effects.\cite{11-13} Low-dose corticosteroids were found to attenuate the systemic inflammation associated with CPB.\cite{14} Small-dose dexamethasone therapy (8 mg at the start of anesthesia and CPB) enhanced patient-perceived quality of recovery scores in elective cardiac surgical patients.\cite{15} The authors assumed that tissue edema is an indicator for inflammatory mediator activation and extravascular lung water index (EVLWI) could be considered as a surrogate marker of tissue edema following CPB. EVLWI can be measured perioperatively by transpulmonary thermodilution technique with the help of VolumeView/EV1000™ system (Edwards Lifesciences, Irvine CA, USA). It was hypothesized that a small dose of dexamethasone would attenuate inflammatory response as reflected by a reduction in EVLWI during open heart surgery.

The primary objective was to compare the effect on EVLWI measured at predetermined intervals of a low-dose intravenous dexamethasone (0.1 mg/kg) administered twice before the commencement of CPB as against a saline placebo in patients undergoing elective primary coronary artery bypass surgery. The secondary endpoints were to assess the effect of dexamethasone on other volumetric parameters pulmonary vascular permeability index (PVPI), global end-diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI), vasoactive inotrope score (VIS), hemodynamic parameters, and serum osmolality.

**Materials and Methods**

After obtaining the Institutional Medical Ethics and Scientific Research Committee approval (MESRC#4/2016) and an informed consent, 20 adult patients undergoing elective on-pump primary coronary artery bypass surgery were prospectively included in the study. Patients weighing <40 kg and those with valvular abnormalities and/or arrhythmias were excluded from the study. Patients who were to undergo emergency coronary bypass surgery, combined bypass surgery and valve procedures, those patients on preoperative inotropic agents or needing intra-aortic balloon counter pulsations perioperatively, patients on steroid therapy, poorly controlled diabetes patients, patients with pulmonary disease or renal impairment and those with ejection fraction (EF) <30% were also excluded from the study. The 20 patients were allocated by computer-generated block randomization numbers using the block sizes of 2, 4, 6 to either the steroid group (n = 10) or the nonsteroid group (n = 10). Two qualified anesthesiologists were allotted for each case.

A nurse anesthetist who is aware of the randomization code prepared either the intervention drug or normal saline in a 5 ml syringe labeled with the patient’s hospital identity number. One anesthesiologist who was blinded to the randomization conducted the anesthesia for the patient and a second anesthesiologist also blinded to the drug administered collected all the data. Based on the randomization code, two syringes each containing either the intervention drug (dexamethasone [0.1 mg/kg drawn up to 5 ml total volume]) or saline (drawn up to 5 ml total volume) were kept ready by the nurse anesthesiologist to be administered at the appropriate time.

All patients were premedicated as per the institutional protocol. Under standard American Society of Anesthesiologists recommended monitoring modalities, general anesthesia was administered after adequate pre-oxygenation and following right radial artery cannulation under topical anesthesia. Anesthesia was induced with thiopental (2 mg/kg), midazolam (1–5 mg), and fentanyl (1–2 mcg/kg). Neuromuscular blockade was achieved with rocuronium (1–1.5 mg/kg). Pressure controlled mechanical ventilation was used in all patients. The respiratory rate, pressure control limits, inspired oxygen concentration, and positive end-expiratory pressure were adjusted to ensure a minimum tidal volume of 6–8 ml/kg, oxygen saturation of >95%, and end-tidal carbon dioxide levels of 36–38 mm Hg. Anesthesia was maintained with isoflurane in oxygen-enriched air, propofol infusion (2–5 mg/hr), and intermittent fentanyl boluses.

Intraoperative transesophageal echocardiography was used routinely. In all patients, the right internal jugular vein was accessed with a quadruple lumen central venous catheter (8.5 Fr, ARROWâ® Catheter, Arrow International, Inc., Reading, PA 19605 USA) and left femoral artery was cannulated with a VolumeView femoral artery catheter, from the femoral catheter kit (5Fr, VLVFC520, Edwards Lifesciences LLC, Irvine, CA, USA) provided in the VolumeView™ Combo Kit (VLV8R520, Edwards Lifesciences LLC, Irvine, CA, USA). All cannulations were performed aseptically under ultrasound guidance. The femoral arterial line was connected to a VolumeView sensor. The central venous line was connected to VolumeView thermistor manifold and the TruWave pressure transducer that was provided in the venous injectate kit by the manufacturer (VLVVKDT, Edwards Lifesciences LLC, Irvine, CA, USA). The femoral arterial line and the central venous line were in turn connected to EV1000 clinical platform. Bolus injections of 20 ml of cold saline (<8°C) through the thermistor manifold attached to the central venous line were used to obtain cardiac output values. The arterial pressure waveform derived continuous cardiac output monitoring system was then calibrated by accepting the mean of the three cardiac output readings that were obtained by transpulmonary thermodilution technique. Subsequent to calibration, the EV1000 clinical platform continuously displayed the patient’s hemodynamic and volumetric data. Once the baseline data were collected the first bolus of dexamethasone or saline placebo was administered to the patient by the second anesthesiologist which was
about 30 min from the skin incision. The second bolus of dexamethasone was administered before the institution of CPB.

The volumetric parameters (EVLW, PVPI, GEDVI, and ITBV) and hemodynamic parameters (heart rate, mean arterial pressure, central venous pressure, stroke volume variation, calibrated cardiac output, calibrated stroke volume, and systemic vascular resistance) were recorded at predefined time intervals: T1: Baseline once the system was in place and before bolus of the drug or placebo administration, T2: Before institution of CPB and after the second bolus of drug or placebo administration, T3: After separation from CPB and protamine administration, T4: before shifting from operating room, T5: 6 h after aortic cross-clamp release and T6: 24 h after aortic cross-clamp release.

Demographic data such as age, BSA, BMI, EuroSCORE II, EF, and CPB data (total CPB time and aortic cross-clamp time) were recorded for each patient. For all patients, VIS, hematocrit at the predetermined time intervals was obtained along with the baseline and 1st postoperative day serum osmolality values. The VIS was calculated as described in the literature.\[^{[16]}\] The formula used was as follows:

\[
\text{Inotrope Score (IS)} = \text{Dopamine dose (mcg/kg/min)} + \text{Dobutamine dose (mcg/kg/min)} + 100 \times \text{Epinephrine dose (mcg/kg/min)}
\]

\[
\text{Vasoactive-Inotropic Score (VIS)} = \text{IS} + 10 \times \text{Milrinone dose (mcg/kg/min)} + 10,000 \times \text{Vasopressin dose (units/kg/min)} + 100 \times \text{Norepinephrine dose (mcg/kg/min)}
\]

Baseline arterial blood gas values and blood sugar levels were obtained following radial arterial cannulation with patients receiving supplemental oxygen through a face mask. These were compared with those obtained following separation from CPB between both groups. Mean arterial pressure was maintained within 20% of the baseline values. Hypertension was treated with attempts at deepening the planes of anesthesia or by vasodilation. Fluid management in both the groups was based on the dynamic variables that were displayed on the EV1000 monitor. The objective of fluid administration in this study was to maintain the stroke volume variation <10%–13% to achieve a stroke volume index ≥35 ml/m² and a cardiac index >3l ts/m². Lactated Ringer’s was often the crystalloid of choice and the volume of fluid administered was recorded for each patient. Vasopressors were administered only if patients were hypotensive with low cardiac output variables despite adequate volume optimization. The total intraoperative urine output was recorded and compared between both groups.

**Statistical analysis**

Data were analyzed using Statistical Package for Social Sciences version 22 (IBM Corp. Chicago, Illinois, USA). For descriptive purposes, continuous variables are presented as Mean and Standard Deviation. The outcome variables at the predetermined time intervals were compared using nonparametric approach using Mann–Whitney “U” test. Generalized estimating equation model was obtained to compare the average of changes between the groups over the time period. \(P < 0.05\) was considered statistically significant.

The values of serum osmolality, blood sugar, and arterial blood gas parameters were analyzed using Mann–Whitney test. The differences in the pre- and post-CPB values were compared and a \(P < 0.05\) was considered as statistically significant.

**Results**

Twenty patients completed the study. In view of the small sample size and to compare the variables between the two groups, the sum of ranks and the mean ranks were obtained using Mann–Whitney Test. The idea of applying the Mann–Whitney test was to rank the data for each condition, and then appreciate how different the two rank totals are. If there was a systematic difference between the two groups, then most of the high ranks would belong to one group, and most of the low ranks would belong to the other one. As a result, the rank totals would be quite different. On the other hand, if the two groups are similar, then high and low ranks would be distributed fairly evenly between the two groups and the rank totals would be quite similar.

There was no difference in demographic and CPB data between the groups [Table 1]. Between the two groups, there was no difference in the baseline arterial blood gas values and blood sugar levels as compared to those obtained following separation from CPB [Table 2]. The volume of fluid administered before CPB institution was comparable between the two groups [Table 1]. The urine output was also comparable [Table 2]. The hemodynamic parameters obtained following calibration by transpulmonary thermodilution of the arterial pressure waveform derived continuous cardiac output monitoring system were considered as baseline values. These values were compared with values obtained at the subsequent predetermined time intervals both within the groups as well as between the two groups [Table 3]. The results indicated that the mean ranks of each hemodynamic variable at the baseline as compared with subsequent readings within the group as well as between the two groups were comparable. The baseline VIS values were comparable at all subsequent time points between the groups. The mean ranks hematocrit values were also comparable throughout the study. Serum osmolality values were not normally distributed. Hence, a nonparametric approach using Mann–Whitney test for obtaining statistical significance was adopted. The baseline mean rank values of serum osmolality were comparable to those obtained on the 1st postoperative day in both groups \((P = 0.796)\) [Table 3].
Generalized estimating equation model was obtained to compare the changes between the groups over the entire study period [Figure 1]. Generalized estimating equation is a general statistical approach to fit a marginal model for longitudinal/clustered data analysis in biomedical studies. Generalized estimating equation is used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes. Under mild regularity conditions, parameter estimates from the generalized estimating equation are consistent even when the covariance structure is misspecified. Generalized estimating equation model was obtained to compare the changes between the groups over the time period for EVLWI, PVPI, GEDVI, and ITBVI [Figure 1]. On an average, the changes between the steroid and non-steroid group in terms of EVLWI, PVPI, GEDVI, and ITBVI were not statistically significant.

### Discussion

Low-dose dexamethasone did not have any effect on EVLWI in patients who had coronary bypass surgery on CPB. The hypothesis that low-dose dexamethasone would reduce inflammatory response as reflected by a reduction in a surrogate marker, i.e., EVLWI was rejected.

Cardiac surgery and CPB induce an acute inflammatory response contributing to postoperative morbidity. This inflammatory response often leads to tissue edema and organ failure. Corticosteroids are anti-inflammatory drugs that can reduce the inflammatory response and suppress the immune response. It has been suggested that steroids exhibit a cytoprotective effect in patients undergoing CPB. Steroids inhibit increases in interleukin 6 and 8 levels during open heart surgery. Corticosteroid treatment before CPB was shown to have cardioprotective effects due to the reduction of perioperative release of systemic and myocardial inflammatory mediators. Corticosteroid prophylaxis during cardiac surgery was associated with a salutary effect on pulmonary function. These beneficial effects of steroid therapy may be attributed to the attenuation of the perioperative systemic inflammatory response syndrome.

| Data                               | Steroid group (n=10) | Nonsteroid group (n=10) | Mean ranks* | U     | P*   |
|------------------------------------|----------------------|-------------------------|-------------|-------|------|
| Age (years)                        | 60.8±11              | 61.6±11                 | 10.68       | 11.35 | 51.50| 0.809|
| BSA                                | 1.8±0.12             | 1.8±0.17                | 11.23       | 9.61  | 41.50| 0.552|
| BMI                                | 25.6±2.7             | 26.4±4.7                | 10.86       | 11.15 | 53.50| 0.918|
| Euroscore II                       | 1.3±0.8              | 1.3±0.41                | 9.14        | 11.19 | 34.50| 0.442|
| EF %                               | 52.7±6.47            | 48.5±4.7                | 12.86       | 8.95  | 34.50| 0.152|
| CPB time (min)                     | 108.7±18.02          | 106.80±20.92            | 11.14       | 10.85 | 53.50| 0.918|
| ACC time (min)                     | 65.5±16.12           | 71.3±25.44              | 10.68       | 11.35 | 51.50| 0.809|
| Pre CPB fluid (ml/kg)              | 8.2±2.14             | 7.2±1.8                 | 12.59       | 9.25  | 37.50| 0.223|

*Mann–Whitney test. BSA: Body surface area, BMI: Body mass index, CPB: Cardiopulmonary bypass, EF: Ejection fraction, ACC: Aortic cross clamp.

#### Table 2: Comparison of the arterial blood gas parameters, blood sugar levels and urine output between steroid group and nonsteroid group

| Variables                     | Mean ranks | U     | P*   |
|-------------------------------|------------|-------|------|
| Arterial blood gas values     |            |       |      |
| pH                            | 11.9       | 9.1   | 36   | 0.315|
| Pre. CPB**-Post. CPB***       |            |       |      |
| pO2                           | 12.3       | 8.7   | 32   | 0.190|
| Pre. CPB**-Post. CPB***       |            |       |      |
| pCO2                          | 12.9       | 8.1   | 26   | 0.075|
| Pre. CPB**-Post. CPB***       |            |       |      |
| Lactate                       | 7.3        | 13.7  | 18   | 0.015|
| Pre. CPB**-Post. CPB***       |            |       |      |
| Blood sugar levels            | 11.9       | 9.1   | 36   | 0.315|
| Pre. CPB**-Post. CPB***       |            |       |      |
| Urine output                  | 11.50      | 9.50  | 40   | 0.481|

*Mann–Whitney test. **Pre. CPB: Baseline values following arterial line insertion with the patients on oxygen supplementation thorough a face mask prior to CPB institution, ***Post. CPB: Values at 30 min following separation from CPB, ****Post. CPB: Highest blood sugar values recorded following separation from CPB and prior to shifting to the ICU.

| Table 2: Comparison of the arterial blood gas parameters, blood sugar levels and urine output between steroid group and nonsteroid group

The baseline mean rank values of volumetric variables were compared with subsequent values obtained at the predetermined time points [Table 4]. The baseline EVLWI values were comparable between the steroid and nonsteroid groups [P = 1.0]. The subsequent mean rank values of EVLWI that were recorded at various time points were comparable in each group. Following separation from CPB, neither intra- nor inter-group differences in mean rank values of EVLWI were found as compared to their baseline values. There were no intra- or inter-group differences in PVPI, GEDVI, ITBVI values during the study.
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Therefore, the specific action of dexamethasone on inflammatory cascade was what was investigated in this study.

A small dose of dexamethasone (8 mg) administered twice to cardiac surgical patients improved the quality of recovery scores after elective cardiac surgery.[15] The authors of the present study assumed that since a small dose of a corticosteroid appears to be efficacious in suppression of inflammatory cascade and also shown to improve the recovery scores, probably a patient weight-adjusted low-dose dexamethasone could be investigated. Hence, dexamethasone at a dosage of 0.1 mg/kg was investigated in this current study. A rapid fall in plasma levels of corticosteroids on the initiation of CPB because of hemodilution was described earlier.[15] Based on this observation, weight-adjusted dexamethasone or bolus steroid administration over a prolonged duration might not be necessary.

Dexamethasone was found to enhance patient comfort through several direct mechanisms such as reducing nausea/vomiting, shivering, and fatigue.[15] The indirect mechanisms might be due to its beneficial action of attenuation of inflammation.[15] This specific action of dexamethasone on inflammatory cascade was what was investigated in this study.

### Table 3: Comparison of hemodynamic parameters at each time point between steroid group and nonsteroid group using Mann-Whitney test

| Variables* | Mean ranks |  U  |  P  |
|------------|------------|-----|-----|
| HR         |            |     |     |
| HR1-HR2    | 11.64      | 10.30 | 48.0 | 0.65 |
| HR1-HR3    | 11.91      | 10.00 | 45.0 | 0.51 |
| HR1-HR4    | 13.09      | 8.70  | 32.0 | 0.11 |
| HR1-HR5    | 12.36      | 9.50  | 40.0 | 0.31 |
| HR1-HR6    | 9.86       | 12.30 | 42.0 | 0.39 |
| MAP        |            |     |     |
| MAP1-MAP2  | 10.95      | 11.05 | 54.5 | 0.97 |
| MAP1-MAP3  | 9.86       | 12.25 | 42.5 | 0.39 |
| MAP1-MAP4  | 11.68      | 10.25 | 47.5 | 0.61 |
| MAP1-MAP5  | 10.64      | 11.40 | 51.0 | 0.51 |
| MAP1-MAP6  | 10.55      | 11.50 | 50.0 | 0.76 |
| CVP        |            |     |     |
| CVP1-CVP2  | 9.14       | 13.05 | 34.5 | 0.15 |
| CVP1-CVP3  | 9.41       | 12.75 | 37.5 | 0.22 |
| CVP1-CVP4  | 11.55      | 10.40 | 49.0 | 0.71 |
| CVP1-CVP5  | 11.05      | 10.95 | 54.5 | 0.97 |
| CVP1-CVP6  | 10.86      | 11.15 | 53.5 | 0.92 |
| SVV        |            |     |     |
| SVV1-SVV2  | 12.00      | 9.90  | 44.0 | 0.47 |
| SVV1-SVV3  | 12.73      | 9.10  | 36.0 | 0.20 |
| SVV1-SVV4  | 12.45      | 9.40  | 39.0 | 0.28 |
| SVV1-SVV5  | 12.45      | 9.40  | 39.0 | 0.28 |
| SVV1-SVV6  | 12.73      | 9.10  | 36.0 | 0.20 |
| CI         |            |     |     |
| CI1-CI2    | 11.64      | 10.30 | 48.0 | 0.65 |
| CI1-CI3    | 9.00       | 13.20 | 33.0 | 0.13 |
| CI1-CI4    | 11.09      | 10.90 | 54.0 | 0.97 |
| CI1-CI5    | 10.55      | 11.50 | 50.0 | 0.76 |
| CI1-CI6    | 9.41       | 12.75 | 37.5 | 0.22 |
| SIV        |            |     |     |
| SIV1-SIV2  | 11.00      | 11.00 | 55.0 | 1.00 |
| SIV1-SIV3  | 9.18       | 13.00 | 35.0 | 0.17 |
| SIV1-SIV4  | 10.32      | 11.75 | 47.5 | 0.61 |
| SIV1-SIV5  | 10.14      | 11.95 | 45.5 | 0.51 |
| SIV1-SIV6  | 10.23      | 11.85 | 46.5 | 0.56 |
| SVRI       |            |     |     |
| SVRI1-SVRI2| 12.09      | 9.80  | 43.0 | 0.43 |
| SVRI1-SVRI3| 10.82      | 11.20 | 53.0 | 0.92 |
| SVRI1-SVRI4| 10.82      | 11.20 | 53.0 | 0.92 |
| SVRI1-SVRI5| 11.18      | 10.80 | 53.0 | 0.92 |
| SVRI1-SVRI6| 12.18      | 9.70  | 42.0 | 0.39 |
| VIS        |            |     |     |
| VIS1-VIS2  | 10.45      | 10.55 | 49.5 | 0.97 |
| VIS1-VIS3  | 10.40      | 10.60 | 49.0 | 0.97 |
| VIS1-VIS4  | 8.80       | 12.20 | 33.0 | 0.22 |
| VIS1-VIS5  | 8.5        | 12.25 | 32.5 | 0.19 |
| VIS1-VIS6  | 10.0       | 11.0  | 45.0 | 0.74 |
| HCT        |            |     |     |

*:* P < 0.05 statistically significant, HR: Heart rate, HCT: Hematocrit, VIS: Vasoactive index score, SVRI: Systemic vascular resistance index, SIV: Stroke volume index, CI: Cardiac index, SVV: Stroke volume variation, CVP: Central venous pressure, MAP: Mean arterial pressure
EVLWI was deemed to be a surrogate marker for tissue edema that could occur as a result of inflammatory mediator release during cardiac surgery on CPB. The beneficial effect of a low-dose dexamethasone on reducing EVLWI was explored in this study. Vascular permeability can be increased by an inflammatory reaction during CPB and result in increased EVLWI despite normal to low intravascular fluid status and hydrostatic pressure. Hence, PVPI was also studied. Factors such as fluid overload, decreased myocardial contractility could contribute to increase in EVLWI. While assessing preload, it is known that higher central venous pressure and/or a higher pulmonary capillary wedge pressure are not reliable indicators for this purpose. Therefore, a volumetric parameter like GEDVI was also measured in the current study. Global EF offers a complete picture of the overall cardiac contractility which was also obtained for all patients. Hematocrit and serum osmolality were measured in both groups to identify if they could be contributing to EVLWI values. However, these parameters were comparable in both groups.

Previous studies have shown that corticosteroids can reduce the need for postoperative inotropic support. Murphy et al. could not demonstrate any beneficial effects of low dose dexamethasone on cardiac function. In the current study, the VIS was similar between the steroid and nonsteroid groups exhibiting no beneficial effect of low-dose steroid on hemodynamic parameters.

There are several limitations to this study. First, the sample size comprises only 20 patients. Second, only low-risk patients were investigated. Third, as the sample size was small, no increased risk of steroid-related infection was observed.

Conclusions

Low-dose dexamethasone did not have any effect on EVLWI or other volumetric parameters in patients subjected to on-pump primary coronary bypass surgery. There were no beneficial effects of dexamethasone on hemodynamic parameters as well. Probably, the advanced hemodynamic monitoring aided in optimal fluid management in the nonsteroidal group impacting EVLW accumulation thereby nullifying the beneficial effects of a low-dose dexamethasone.

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Conflicts of interest

There are no conflicts of interest.

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