Original Article

Perioperative utility of goal-directed therapy in high-risk cardiac patients undergoing coronary artery bypass grafting: "A clinical outcome and biomarker-based study"

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ABSTRACT

Goal-directed therapy (GDT) encompasses guidance of intravenous (IV) fluid and vasopressor/inotropic therapy by cardiac output or similar parameters to help in early recognition and management of high-risk cardiac surgical patients. With the aim of establishing the utility of perioperative GDT using robust clinical and biochemical outcomes, we conducted the present study. This multicenter randomized controlled study included 130 patients of either sex, with European system for cardiac operative risk evaluation ≥3 undergoing coronary artery bypass grafting on cardiopulmonary bypass. The patients were randomly divided into the control and GDT group. All the participants received standardized care; arterial pressure monitored through radial artery, central venous pressure (CVP) through a triple lumen in the right internal jugular vein, electrocardiogram, oxygen saturation, temperature, urine output per hour, and frequent arterial blood gas (ABG) analysis. In addition, cardiac index (CI) monitoring using FloTrac™ and continuous central venous oxygen saturation ($ScVO_2$) using PreSep™ were used in patients in the GDT group. Our aim was to maintain the CI at 2.5–4.2 L/min/m^2, stroke volume index 30–65 ml/beat/m^2, systemic vascular resistance index 1500–2500 dynes/s/cm^5/m^2, oxygen delivery index 450–600 ml/min/m^2, continuous $ScVO_2$ >70%, and stroke volume variation <10%; in addition to the control group parameters such as CVP 6–8 mmHg, mean arterial pressure 90–105 mmHg, normal ABG values, oxygen saturation, hematocrit value >30%, and urine output >1 ml/kg/h. The aims were achieved by altering the administration of IV fluids and doses of inotropes or vasodilators. The data of sixty patients in each group were analyzed in view of ten exclusions. The average duration of ventilation (19.89 ± 3.96 vs. 18.05 ± 4.53 h, P = 0.025), hospital stay (7.94 ± 1.64 vs. 7.17 ± 1.93 days, P = 0.025), and Intensive Care Unit (ICU) stay (3.74 ± 0.59 vs. 3.41 ± 0.75 days, P = 0.012) was significantly less in the GDT group, compared to the control group. The extra volume added and the number of inotropic dose adjustments were significantly more in the GDT group. The two groups did not differ in duration of inotropic use, mortality, and other complications. The perioperative continuation of GDT affected the early decline in the lactate levels after 6 h in ICU, whereas the control group demonstrated a settling lactate only after 12 h. Similarly, the GDT group had significantly lower levels of brain natriuretic peptide, neutrophil gelatinase-associated lipocalin levels as compared to the control. The study clearly depicts the advantage of GDT for a favorable postoperative outcome in high-risk cardiac surgical patients.

Key words: Biomarker; Cardiac surgery; Goal-directed therapy; Outcome measures; Perioperative

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INTRODUCTION

After undergoing cardiac surgery, most patients have a short Intensive Care Unit (ICU) and hospital stay. However, up to 10% of patients have a complicated postoperative course because of organ dysfunction or multiple organ failure resulting in increased burden on the hospital resources and costs.[1] Limited cardiovascular reserve and an inadequate hemodynamic response to postoperative surgical stress have been shown to be independent predictors of a prolonged ICU stay.[2,3]

Cardiac surgery, at present, is being conducted in an increasingly high-risk population as it is backed by continually improving surgical strategy and technology.[4] Shoemaker *et al*. showed that high-risk cardiac surgical patients had increased morbidity and mortality and the survivors had consistently higher postoperative cardiac output and oxygen delivery than those who died.[5] An understanding emerged that the high mortality rate might be reduced, if the flow-related cardiovascular values become additional goals for perioperative management. An indicator of low cardiac output, global tissue hypoxia is a key development proceeding to multiorgan failure and death.[6] It is in the immediate postcardiopulmonary bypass (CPB) period when the recognition and treatment produce maximal benefit in outcome.[7]

Goal-directed therapy (GDT) is a term used to describe the use of cardiac output or similar parameters to guide intravenous (IV) fluid and inotropic therapy.[8] In the present study, GDT was used to optimize the various hemodynamic variables in the post-CPB period in high-risk patients with European system for cardiac operative risk evaluation (EuROSCORE)[9] ≥3 undergoing coronary artery bypass grafting (CABG) in the study group, whereas the control group comprised patients managed without using GDT. In the patients receiving GDT, the additional aims were to maintain the cardiac index (CI) between 2.5 and 4.2 L/min/m^2, stroke volume index (SVI) 30–65 ml/beat/m^2, systemic vascular resistance index (SVRI) 1500–2500 dynes/s/cm^5/m^2, oxygen delivery index (DO_2I) 450–600 ml/min/m^2, continuous central venous oxygen saturation ($ScVO_2$) >70%, and stroke volume variation (SVV) <10%. All data gathered in this study were derived using the FloTrac™ (a new minimally invasive cardiac output monitor) cardiac output sensor, and the PreSep™ catheter in conjunction with the Vigileo monitor (Edwards Life Sciences, Irvine, CA, USA).

Besides hemodynamic parameters, a plethora of biomarkers pertaining to myocardial, renal function, and the overall tissue perfusion have been described in recent years. The biomarkers such as brain natriuretic peptide (BNP) and neutrophil gelatinase-associated lipocalin (NGAL) correlate well with the clinical outcomes in various studies involving the use of GDT.[10,11] This study also aimed at comparing the biomarkers between the patients undergoing CABG with or without GDT for establishing the utility of GDT in the perioperative care of high-risk cardiac surgical patients.

MATERIALS AND METHODS

The study was conducted in two cardiac surgical centers after obtaining ethical clearance from the Institutional Review Board and informed consent. One hundred and thirty patients of either sex with a EuroSCORE ≥3 undergoing CABG were included in this prospective randomized controlled study. The patients were divided randomly into two groups, namely, control and GDT groups, by the sealed envelope technique. Patients with cardiac dysrhythmias and contraindication to the central venous cannulation were excluded from the study. Patients requiring the initiation of intra-aortic balloon pump (IABP) therapy were excluded from the study because the FloTrac™ is not equipped to identify the waveforms of arterial pressure waveform while using IABP.

Induction and maintenance of general anesthesia was done in accordance with the institutional protocol. Electrocardiogram (ECG), oxygen saturation (SpO_2), invasive blood pressure, central venous pressure (CVP) and arterial blood gas (ABG), urine output, and $EtCO_2$ monitoring were common to both the groups. In addition, the CI using FloTrac/volumeView set (Edwards Life Sciences Ltd.) and the $ScVO_2$ using PreSep catheter were monitored in the GDT group. A VolumeView™ cardiac output monitoring sensor was connected to the radial arterial cannula in the GDT group. PreSep™ catheter (continuous central venous oximetry) was inserted in the GDT group. The baseline readings (T_1) of heart rate (HR), mean arterial pressure (MAP), CVP, SpO_2, and ABG were recorded. The additional baseline readings (T_1) of CI, SVRI, DO_2I, SVI, SVV, and $ScVO_2$ were recorded in the patients in the GDT group. The blood samples were collected for T_1 values of BNP, NGAL, and lactate in all the patients.

The CPB was initiated after systemic heparinization and was maintained as per standard institutional protocols. The rewarming was accompanied by administering IV infusion of dobutamine at 5 μg/kg/min and 0.5 μg/kg/min nitroglycerin or any other vasoactive/vasodilator drug depending on patients' condition. After separation from CPB, protamine sulfate was administered in a dose of 1.2 mg/mg of heparin to antagonize the effects of heparin. Thereafter, the patients received 0.1 U/kg of platelet transfusion. All patients received fluids to maintain the CVP between 6 and 8 mmHg[12] and MAP was maintained between 90 and 105 mmHg using inotropic agents (dobutamine, dopamine, adrenaline, noradrenaline, and milrinone) and vasodilators. ABG and urinary output was monitored on an hourly basis, and the biochemical abnormalities corrected as necessary. Hematocrit (HCT) values were maintained at or above 30% with packed cell transfusions.

The goal-directed therapy algorithm

In accordance with the GDT, if the CI was <2.5 L/min/m^2, CVP <6 mmHg, or SVV >10%, fluids (100 ml aliquots of fluid) were given intravenously till the target CVP and SVV levels were achieved [Figure 1]. Inotropic agents and vasodilators were adjusted to maintain the parameters within the target values. The choice of inotropes was determined by MAP, SV, and SVRI. If $ScVO_2$ was <70%, packed red cells were administered to maintain HCT >30% and if $ScVO_2$ continued to be <70%, GDT was initiated to achieve the CI at 2.5–4.2 L/min/m^2, SVI at 30–65 ml/beat/m^2, SVRI at 1600–2600 dyne/s/cm^5/m^2, DO_2I at 450–600 ml/min/m^2, $ScVO_2$ >70%, and SVV <10%; in addition to the goals in the standard care such as CVP 6–8 mmHg, MAP at 90–105 mmHg, ABG analysis values (pH 7.35–45, PaO_2 >100 mmHg, and $PaCO_2$ 35–45 mmHg), SpO_2 >95%, HCT >30%,

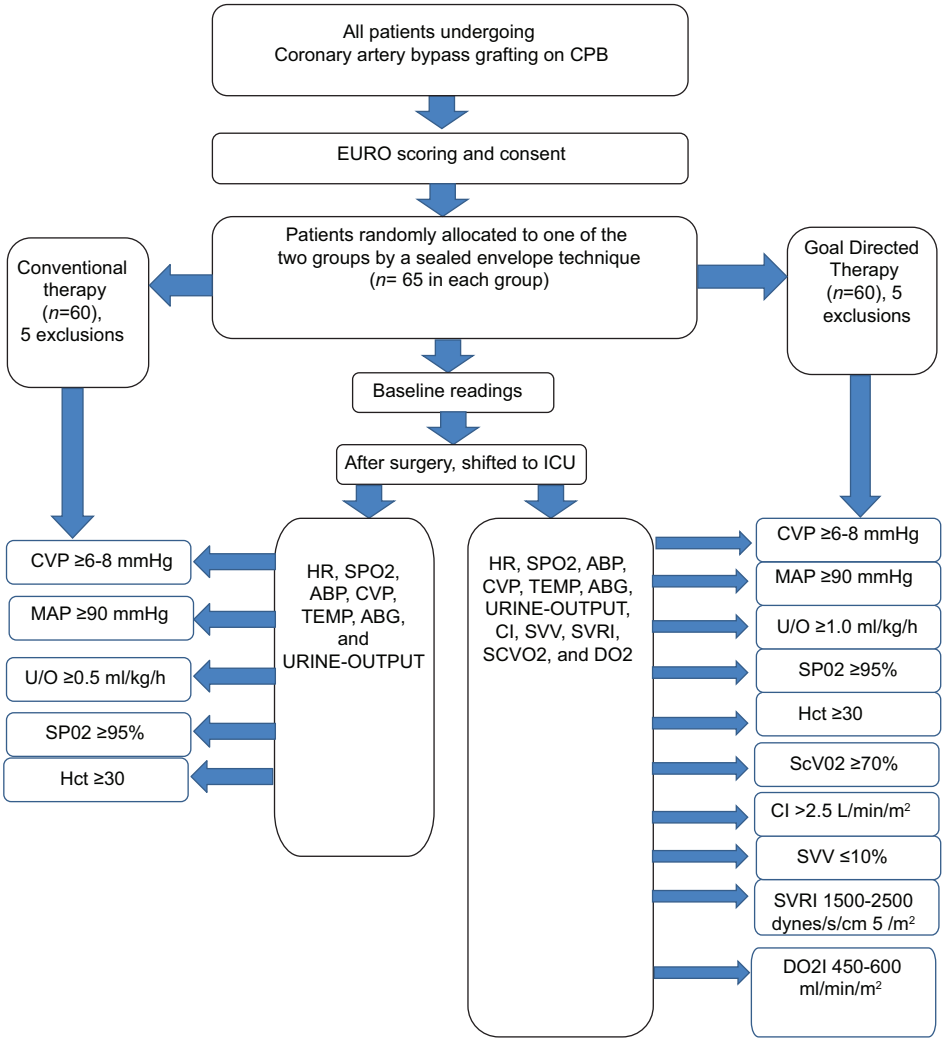

Figure 1: The step-wise algorithm followed in the study to allocate, study, and manage the patients receiving goal-directed and conventional therapy

and urine output >1 ml/kg/h. The monitoring was gradually withdrawn after 24 h.

The parameters recorded at the closure of sternum were designated as T_2 and blood lactate (T_2) was estimated. All patients were mechanically ventilated in the ICU and monitored with FlowTrac for 24 h. HR, MAP, SpO_2, CVP, and peripheral temperature were monitored continuously and recorded at 0 (T_3), 6 (T_4), 12 (T_5), and 24 (T_6) h after transfer to the ICU. Blood samples were collected postoperatively at 6 and 24 h for T_4 and T_6 values of BNP and NGAL and 0, 6, 12, and 24 h for T_3, T_4, T_5, and T_6 values of lactate.

Early postoperative care in the ICU was jointly determined by the cardiac surgical and ICU staff, as per standard practice. Patients were weaned off when they were fully awake and adequately rewarmed (core temperature ≥36°) with normal skeletal muscle power, hemodynamically stable with normal chest radiograph and ABG, chest-tube drainage <100 ml/h, and urine output >1 ml/kg/h. All extubated patients were transferred from the ICU on the 2nd day unless inotropes or vasodilator drugs were necessary. A 12-lead ECG was performed on the day 3. The criteria for discharge from hospital comprised a stable cardiac rhythm, oral temperature <99°F, HCT ≥25%, oral intake of a minimum of 1000 calories/day, and successful completion of exercise testing that included independent ambulation, no significant wound-related complications, and an adequate home support system. Patients were contacted by phone at 30 days and their medical records reviewed to ascertain if they experienced any adverse outcomes.

Statistical analysis

Discrete categorical data were presented as number or percentage. The normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. Continuous data were written either in the form of its mean and standard deviation or in the form of its median and interquartile range, as per the requirement. For normally distributed data, *t*-test was applied for statistical analysis of two groups. For skewed data, nonparametric Mann–Whitney U-test was used for statistical analysis of two groups. For time-related variable, Wilcoxon signed-rank test was applied. For categorical data, comparisons were made by Pearson's Chi-square test or Fisher's exact test as appropriate. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Analysis was conducted using IBM SPSS Statistics (version 22.0, IBM corporation, USA).

RESULTS

To begin with, there were a total of 130 patients. Five patients from both the groups were excluded from the study since three patients in the control and one in the GDT group required IABP and postoperative atrial or ventricular fibrillation resulted in two and four patients in the control and the study group, respectively. The results of the remaining sixty patients in each group were analyzed. Demographic data and EuroSCORE, duration of CPB, duration of aortic cross-clamping (AOXCL), and an average number of grafts/patient were comparable [Table 1]. HR, MAP, CVP, SpO_2, and ABG at various time intervals were comparable between the groups [Table 2]. The patients in the GDT group produced more urine during the study period, which was not statistically significant from the result of the control. $ScVO_2$, CI, SVV, SVRI, SVI, and DO_2I were maintained within the physiological values in the GDT group.

There was statistically significant difference in the extra volume used (343.33 ± 62.02 and 376.33 ± 55.23, $P = 0.003$) and the number of times the inotropic agent was changed (2.77 ± 0.91 and 3.12 ± 0.80, $P = 0.029$) in the control and GDT groups, respectively [Table 3]. The average duration of ventilation (19.89 ± 3.96 vs. 18.05 ± 4.53 h, $P = 0.025$), hospital stay (7.94 ± 1.64 vs. 7.17 ± 1.93d, $P = 0.025$), and ICU stay (3.74 ± 0.59 vs. 3.41 ± 0.75 d, $P = 0.012$) was significantly less in the GDT group, compared to those in the control group [Table 3]. The duration of inotropic support was less in the GDT group though not significant as compared to the control. One patient in GDT group and three patients in the control group had renal dysfunction, which improved by administering

Table 1: Demographic characteristics of the two groups

Parameter	Control group (*n*=60)	GDT group (*n*=60)	*P*
Age (years)	61.30±5.60*	61.17±5.09*	0.892
Male:female	42:18	40:20	0.695
Height (cm)	160.70±5.18*	159.98±3.30*	0.448
Weight (kg)	72.90±8.79*	72.97±9.39*	0.968
EuroSCORE	4.15±0.84*	4.13±0.81*	0.955
CPB (min)	99.22±6.66*	99.08±7.63*	0.919
AOXCL (min)	57.57±4.00*	57.50±5.20*	0.937
Number of grafts	3.43±0.64*	3.53±0.79*	0.695

*Standard deviation, *P*<0.05 is considered significant.
GDT: Goal-directed therapy, CPB: Cardiopulmonary bypass, AOXCL: Aortic cross clamping, EuroSCORE: European system for cardiac operative risk evaluation

Table 2: Heart rate, mean arterial pressure, and central venous pressure in the two groups

Parameter	Time	Control group (*n*=60)	GDT group (*n*=60)	*P*
Heart rate	T_1	69.42±5.02*	68.17±6.85*	0.257
	T_2	92.18±7.24*	93.75±6.51	0.215
	T_3	99.75±8.29*	100.45±7.69*	0.633
	T_4	99.95±8.30*	102.37±6.13*	0.072
	T_5	101.95±8.60*	103.33±6.10*	0.312
	T_6	100.00±6.81*	100.92±7.11*	0.473
MAP	T_1	89.33±6.98*	91.57±7.17*	0.087
	T_2	94.20±6.54*	94.78±6.85*	0.634
	T_3	96.07±6.06*	97.82±4.16*	0.068
	T_4	94.73±6.37*	96.78±5.65*	0.065
	T_5	94.98±5.39*	97.02±5.91*	0.052
	T_6	98.30±6.38*	100.45±5.59*	0.052
CVP	T_1	6.50±0.93*	6.08±1.09*	0.117
	T_2	6.42±0.56*	6.45±0.77*	0.753
	T_3	6.22±0.49*	6.35±0.58*	0.175
	T_4	6.17±0.46*	6.3±0.80*	0.182
	T_5	6.37±0.48*	6.4±0.58*	0.736
	T_6	6.28±0.52*	6.53±0.87*	0.059

*Standard deviation, *P*<0.05 is considered significant. T_1 (baseline), T_2 (sternal closure), T_3 (0), T_4 (6), T_5 (12), T_6 (24) h in ICU. ICU: Intensive Care Unit, MAP: Mean arterial pressure, CVP: Central venous pressure, GDT: Goal-directed therapy

Table 3: Comparison of the outcomes between the control and the goal-directed therapy group

Parameter	Control group	GDT group	*P*
Average extra volume added	343.33±62.02*	376.33±55.23*	0.003
Number of times inotropes adjusted	2.77±0.91*	3.12±0.80*	0.029
Duration of ventilation (h)	19.89±3.96*	18.05±4.53*	0.025
Duration of inotrope usage (days)	3.09±0.59*	2.81±0.94*	0.063
Length of ICU stay (days)	3.74±0.59*	3.41±0.75*	0.012
Length of hospital stay (days)	7.94±1.64*	7.17±1.93*	0.025
Mortality	6/60	2/60	0.272

*Standard deviation, *P*<0.05 is considered significant. Apart from the first two parameters, the *n* for the outcome measures for the control group was 54 and 58 for the GDT group in view of the mortality. GDT: Goal-directed therapy, ICU: Intensive Care Unit

diuretics. Total four patients (one in GDT and three in control) required IABP support. There were two mortalities in the study group and six mortalities in the control group during the study period. The causes ranged from malignant arrhythmias to refractory hemodynamic instability.

With regard to the biomarkers, the continuation of GDT in the ICU helped reduction in the lactate levels at T_4 onward, whereas the control group recorded maximum lactate levels at T_5 [Table 4]. At the same time, BNP and NGAL were significantly higher in the control group at T_6 compared to the GDT group [Table 4].

DISCUSSION

Organ dysfunction and multiple organ failure remain the main causes of prolonged hospital stay after cardiac surgery.[1] Cardiac surgery patients are at risk of inadequate oxygen delivery in view of extracorporeal circulation and limited cardiovascular reserve.[3,13]

The aim of GDT is to maintain the CI, CVP, MAP, SVRI, DO_2I, SVI, SVV, $ScVO_2$, ABG, and urine output within the physiological limits by active intervention. Pölönen *et al.* studied 403 cardiac surgery patients and concluded that maintaining mixed venous oxygen saturation (SvO2) >70%, decreases the length of stay (LOS)-ICU and LOS-hospital.[13] Patients in the high-risk group who tend to have increased morbidity and mortality may benefit from intensive monitoring and early interventions. Therefore, in this study, we wished to study the utility of GDT in patients who with EuroSCORE ≥3 points (medium and high-risk).

Mixed venous oxygen saturation is ideally measured by estimating the oxygen content of the blood drawn from the pulmonary artery through pulmonary artery catheter (PAC). Goldman *et al.* studied the importance of $ScVO_2$ in 31 patients with myocardial infarction.[14] PreSep™ central venous oximetry catheter can be used to continuously monitor the $ScVO_2$ (though not similar to SvO_2, correlates well with SvO_2). The mixed venous oxygen saturation estimated from the superior vena cava was found to be 5%–13% lower than that estimated from the PAC.[15]

In cardiac surgery, GDT was commenced using a noninvasive method such as esophageal Doppler instead of the PAC to measure the cardiac output.[16-18] Unlike the FloTrac™, Doppler probe is not readily tolerated by conscious patients, restricting its use to patients who are ventilated, and the PAC is invasive with its own set of complications.[8] Studies by Manecke *et al.*, McGee *et al.*, and Chakravarthy *et al.*, have validated the Vigileo system.[19-21] However, Opdam *et al.* showed a limited correlation for CI between FloTrac™ and PAC.[22]

Table 4: Comparison of biomarkers between the two groups

Biomarker	Time	Control group (*n*=60)	GDT group (*n*=60)	*P*
BNP (pg/mL)	T_1	152.27±11.60*	153.72±9.41*	0.454
	T_4	187.85±13.34*	184.20±10.24*	0.095
	T_6	207.70±28.44*	198.98±9.33*	0.026
NGAL (ng/mL)	T_1	77.45±12.86*	81.25±11.29*	0.088
	T_4	116.95±16.76*	112.62±9.79*	0.086
	T_6	127.45±13.52*	122.18±8.85*	0.013
Lactate (mmol/L)	T_1	1.00±0.30*	1.01±0.29*	0.752
	T_2	2.00±0.60*	2.03±0.59*	0.752
	T_3	2.52±0.40*	2.38±0.47*	0.015
	T_4	4.72±0.43*	4.51±0.53*	0.024
	T_5	5.22±0.64*	4.14±0.55*	<0.001
	T_6	3.77±0.31*	3.23±0.41*	<0.001

*Standard deviation, *P*<0.05 is considered significant). T_1 (baseline), T_2 (sternal closure), T_3 (0), T_4 (6), T_5 (12), T_6 (24) h in ICU. ICU: Intensive Care Unit, GDT: Goal-directed therapy, BNP: Brain natriuretic peptide, NGAL: Neutrophil gelatinase-associated lipocalin

A study by Smetkin *et al*. showed that a goal-directed algorithm based on continuous measurement of $ScVO_2$ could improve the course of the postoperative period after CABG on the beating heart.[23] In a 15-year follow-up, Rhodes *et al*. evaluated GDT in high-risk surgical patients, demonstrating improved long-term outcomes.[24]

The authors had previously conducted a clinical outcome comparison study between the GDT and the control groups in a small number of patients with inconclusive results.[25] Keeping in view the advent and validation of biomarkers for predicting organ dysfunction after cardiac surgery,[10,11] the authors planned a comparison between the GDT and conventional hemodynamic management with clinical and biochemical outcomes in a larger number of patients.

The average duration of ventilation, hospital stay, ICU stay was significantly less in the GDT group, compared to those in the control group [Table 3]. The duration of inotropic support was less in the GDT group though not significant as compared to the control. There was statistically significant difference in the extra volume used and the number of times the inotropic agent was changed in the control and GDT groups, both being higher in the GDT group to meet the desired hemodynamic goals.

As depicted in Figure 2, the continuation of GDT in the perioperative period in the ICU helped in

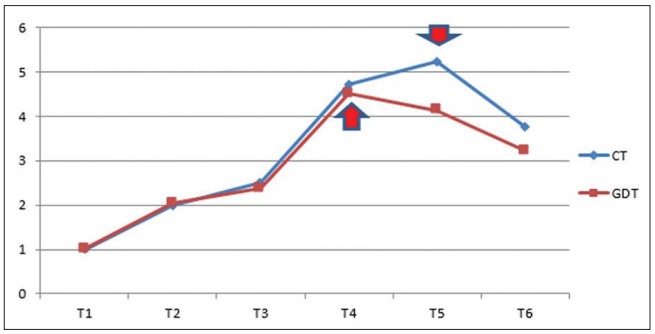

Figure 2: The lactate at T_1 (baseline), T_2 (sternal closure), T_3 (0), T_4 (6), T_5 (12), and T_6 (24) h in Intensive Care Unit. The arrow shows the peak in the groups

stabilization of the lactate levels at T_4 onward, whereas the control group recorded maximum lactate levels at T_5. It was noteworthy that NGAL levels (as well as BNP) were significantly higher in the control group after 24 h as compared to the GDT group though the urine output difference between the groups was still insignificant [Figure 3]. This highlights the importance of biomarkers in early detection of organ dysfunction after cardiac surgery. Close hemodynamic, clinical, and biomarker-based monitoring continued from the perioperative to the intensive care setting provides early mobilization in a safe manner postcardiac surgery.[26-28]

Limitations

This study had a few limitations: In spite of involving a considerable number of patients in a randomized fashion, the study could not be blinded. Second, the present study being a multicenter study, the patients enrolled in the study were operated upon by center-specific surgical teams. Preload markers of global end-diastolic volume index and extravascular lung water could not be completed in all sixty patients; hence their values were not included in the study. These markers which give more information on volume status should be part of a futuristic trial, as it substantiates adequately the efficacy of GDT.

CONCLUSION

Perioperative GDT can shorten the duration of ventilator dependency, ICU and hospital stay in high-risk cardiac surgical patients. The significantly lower levels of biomarkers in GDT group further support the importance of optimizing the hemodynamic parameters for the maintenance of tissue perfusion. This attests to the cost-effectiveness of GDT in the management of a subset of patients at higher risk of morbidity and mortality after cardiac surgery.

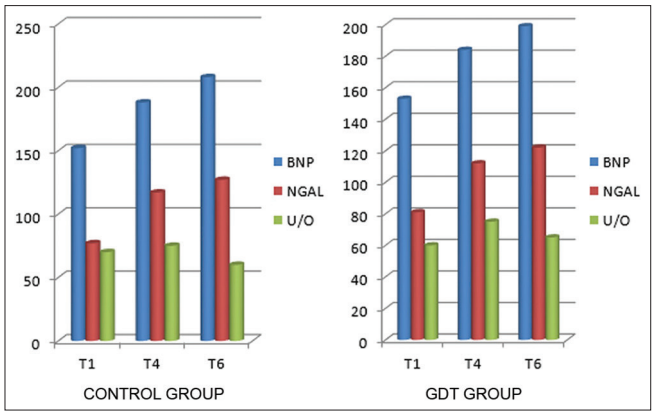

Figure 3: The brain natriuretic peptide, neutrophil gelatinase-associated lipocalin, average hourly urine output at T_1, T_4, T_6, where the rise in brain natriuretic peptide/neutrophil gelatinase-associated lipocalin is clear at T_6

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Conflicts of interest

There are no conflicts of interest.

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