Original Article

Intraoperative factors contributory to myocardial injury in high-risk patients undergoing abdominal surgery in a South Indian population

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ABSTRACT

Background and Aims: Myocardial injury after non-cardiac surgery (MINS) is associated with high postoperative mortality. We sought to examine the intraoperative variables associated with MINS among high-risk patients undergoing abdominal surgery at a South Indian Centre. **Methods:** A retrospective analysis of patients who underwent abdominal surgery, aged >45 years with one of five factors: hypertension, diabetes mellitus, previous coronary artery disease (CAD), stroke, or peripheral vascular disease or all patients >65 years of age was undertaken. Forty-six patients with raised troponin Group *P* (Trop I > 0.03 ng/d) were compared with 125 troponin-negative patients Group N (Trop I < 0.012 ng/dL) as well as 51 with intermediate levels Group I (Trop I > 0.012 and < 0.03 ng/dL). We evaluated the association of pre and intraoperative factors on MINS using logistic regression to identify the explanatory variables. **Results:** Demographics were similar among the three groups. In-hospital mortality was significantly higher in group *P* (*P* = 0.005). The use of vasopressors (OR 2.6; 95% CI 1.2–5.5), female gender, (OR 2.3; 95%CI 1.1–4.7), associated CAD (OR 2.8;95% CI 1.1–7.4), and fresh frozen plasma (FFP) transfusion (OR 12.1;95% CI 1.3–11.7) were associated with MINS in regression analysis between group *P* versus group N. Female gender (OR2.3; 95% CI 1.2–4.5), postoperative mechanical ventilation (OR 3.5; 95% CI 1.2–10.4), and perioperative hypothermia (OR 4.5; 95% CI 1.3–14.9) were significant between Group P and Group I with Group N. **Conclusions:** Female patients with CAD undergoing abdominal surgery, needing vasopressors and transfusion of plasma are at high risk for MINS with higher hospital mortality and merit vigilant monitoring postoperatively.

Key words: Anaesthesia, myocardial injury, troponins

INTRODUCTION

Postoperative myocardial injury after non-cardiac surgery (MINS) is defined as the occurrence of myocardial injury that may or may not result in necrosis within 30 days after non-cardiac surgery and that might have adverse prognostic significance.[1] MINS is increasingly being identified during non-cardiac surgery with reported increased 1-month mortality.[1,2] Incidence of unrecognised MINS appears higher among Indian patients in comparison to the Western literature;[3] however, specific intraoperative associations relating to anaesthetic management are lacking. As abdominal surgery involves a high-risk group, we sought to identify the perioperative factors that could contribute to MINS amongst at-risk patients undergoing abdominal surgery.

The primary objective of this study was to evaluate the relationship of intraoperative factors such as

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vasopressor use, blood and blood product transfusions, hypothermia (<34°C), hemodynamic fluctuations, and need for postoperative mechanical ventilation with MINS. Additionally, we sought to evaluate the impact of preoperative risk factors on postoperative MINS.

METHODS

Following approval from the Institutional Ethics Committee, data of patients who had presented for surgery in the gastro-surgical divisions at a tertiary centre in South India between 1st July 2015 and 30th June 2016 were retrospectively analysed for outcomes and myocardial injury.

The data was specifically analysed among a group that was considered at-risk for MINS. The study cohort consisted of patients >45 years with one of five risk factors namely hypertension, diabetes mellitus, previous CAD, stroke, or peripheral vascular disease and all patients >65 years of age undergoing abdominal surgery.[3] Patients with preoperative creatinine >2.0 mg/dL, preoperative sepsis, patients with pulmonary embolism, pregnancy, and those needing cardioversion were excluded from our study.

As per the institutional protocol for MINS, Troponin I was measured at 12 h, 24 h, and 48 h following surgery using ARCHITECT stat highly sensitive Troponin I (hs TnI) assay (Abbott).

Patients with troponin I levels ≥0.03 ng/dl at 12, 24, or 48 h postoperatively were considered positive and classified as Group P. The threshold values of troponin I for myocardial injury were determined by the Public Health Research Initiative Canada for the assay Architect 2000i.[3] Among the patients included, a control group with troponins <0.012 ng/dl, Group N and patients with troponins between 0.012 ng/dL and 0.029 ng/dL indeterminate group, Group I were also included for analysis.

Patients in Group P (n = 46) with MINS were compared to 125 negative patients in Group N and with 51 patients with intermediate values in Group I. Preoperative factors including demographics, and associated comorbidities, diabetes, hypertension, CAD, peripheral vascular occlusive disease (PVOD), cerebrovascular accident (CVA), and chronic kidney disease were compared. Intraoperatively, the variations of >20% from the baseline blood pressure was noted. The type of anaesthesia, regional, general or a combination, duration of surgery, emergent surgery, use of blood and blood products, need for vasopressors, hypothermia (<34°C) perioperatively and need for postoperative mechanical ventilation were compared among the groups and analysed for correlation with occurrence of MINS. Duration of intensive care unit (ICU) stay, and in-hospital mortality were also obtained from hospital records and compared among the three groups.

Statistical analysis

Continuous variables between the three groups were analysed using analysis of variance (ANOVA) followed by post-hoc Bonferroni correction. Categorical variables were analysed using Chi-square test. Univariant analysis was done among positives versus negatives as well as positive versus non-positives (negative and intermediates). Multiple binary logistic (forward conditional) regression analysis was used for $P < 0.2$ to determine the prediction factors and estimate the odds ratio with 95% CI. Statistical analysis was done using International Business Machine Statistical Package for Social Sciences version 20 Windows (IBM SPSS Inc .,Chicago, USA).

RESULTS

Two hundred and twenty-two patients with comorbid cardiovascular conditions undergoing major abdominal surgery and consenting to undergo testing for MINS were included in the study [Figures 1 and 2]. Demographic variables among the three groups were similar. Preoperative laboratory investigations were also comparable. The prevalence of associated comorbidities among the three groups was similar [Table 1]. American Society of

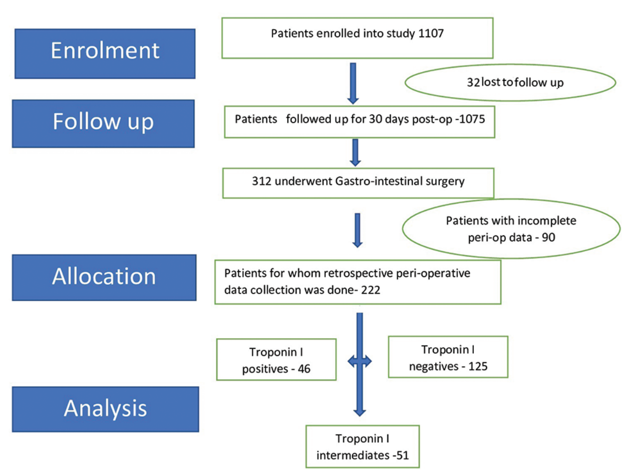

Figure 1: Flow chart

Anesthesiologists (ASA) physical status III patients were higher in Group *P* (*P* = 0.003, Table 1).

Perioperative use of vasopressors was identified as significant association for MINS (*P* = 0.019). The need for blood transfusion was higher in Group P (*P* = 0.04) and also the need for FFP transfusion (*P* = 0.005) [Table 2]. The need for postoperative mechanical ventilation was higher in Group P (8/46) versus Group N (8/125) and Group I (1/51) (*P* = 0.018). Duration of surgery was not significantly different among the three groups. Hypothermia was defined as a temperature <34°C despite the use of warming measures and incidence was significantly higher in Group P [Table 2].

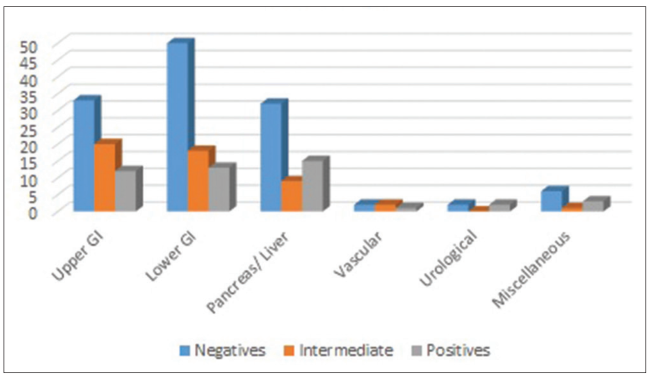

Figure 2: Types of surgeries

Fluctuations in blood pressure, colloid usage (4%hydroxyethylstarch/gelatins) and perioperative use of albumin was similar among the three groups. The type of anaesthesia and elective versus emergent surgeries was comparable. The need for postoperative dialysis and length of ICU stay were comparable among the three groups.

Postoperatively haemoglobin, total counts, and length of hospital stay were comparable among the groups. Platelets counts were lower and international normalised ratio (INR) higher on days one and two in the group P [Table 3]. There was no in-hospital mortality in Group N. One patient in the Group I died on the 9th postoperative day (POD) following a laparoscopic biopsy for intestinal tuberculosis in the background of Child B cirrhosis. Four patients in Group *P* died during the hospital stay (*P* = 0.002). One patient had peripheral vascular disease, and two were emergent surgeries for obstructed hernia and one patient had a radical surgery for a gastric malignancy [Table 3].

The use of vasopressors (OR 2.6; 95% CI 1.2–5.5), female gender (OR 2.2; 95% CI 1.1–4.7), associated CAD (OR 2.8; 95% CI 1.1–7.4), and FFP transfusion (OR 12.1;95% CI 1.3–11.7) were associated with MINS in

Table 1: Baseline parameters and Demographics

	Mean±SD			*P*
	Negatives (N) *n*=125	**Intermediate (I) *n*=51**	**Positives (P) *n*=46**	
Age y	64.76±10.46	64.94±11.08	65.00±8.62	0.988
BMI	24.15±5.20	23.60±3.84	23.76±4.50	0.756
Haemoglobin g/dL	11.62±1.97	11.51±1.99	11.65±2.15	0.932
TLC ×10³	9.12±3.28	9.76±4.19	8.52±4.57	0.274
Platelet ×10³	274.74±84.86	293.12±123.24	256.74±84.59	0.171
INR	1.07±0.18	1.14±0.39	1.06±0.13	0.169
Creatinine mg/dL	1.05±0.25	1.01±0.26	1.53±0.30	0.332
Gender				
Female	40 (32.0%)	18 (35.3%)	22 (47.8%)	
Male	85 (68.0%)	33 (64.7%)	24 (52.2%)	0.160
ASA				
I	5 (4.0%)	0	0	
II	110 (88.0%)	46 (90.2%)	33 (71.7%)	0.003
III	10 (8.0%)	5 (9.8%)	13 (28.3%)	
DM	61 (48.8%)	24 (47.1%)	21 (45.7%)	0.930
HTN	77 (61.6%)	33 (64.7%)	33 (71.7%)	0.470
CAD	16 (12.8%)	8 (15.7%)	17 (23.9%)	0.209
DLP	35 (28.0%)	7 (14.0%)	12 (26.1%)	0.144
PVOD	6 (4.8%)	4 (7.8%)	1 (2.2%)	0.442
CVA	4 (3.2%)	2 (3.9%)	1 (2.2%)	1.000
CKD	2 (1.6%)	2 (3.9%)	2 (4.3%)	0.400
CCF	-	-	1 (2.2%)	0.207

BMI=Body mass index, TLC=Total leucocyte count,INR=International normalised ratio, DM=Diabetes mellitus,HTN=Hypertension,CAD=Coronary artery disease, DLP=Dyslipidemia,PVOD=Peripheral vascular occlusive disease, CVA=Cerebrovascular accident, CKD=Chronic kidney disease,CCF=Congestive cardiac failure, SD=Standard deviation, ASA=American Society of Anesthesiologists,y=years

Table 2: Comparison of Intraoperative and post-operative characteristics

Variables	Negatives (N) *n*=125	Intermediate (I) *n*=51	Positives (P) *n*=46	*P*
SBP_0 mmHg	133.21±17.12	134.33±19.09	138.33±23.54	0.298
DBP_0 mm Hg	78.34±11.42	78.39±12.99	77.91±11.62	0.974
MBP_0 mm Hg	96.60±12.46	97.01±14.03	95.59±20.08	0.886
< 0r >20%MAP	57 (45.6%)	25 (49.0%)	27 (58.7%)	0.315
Vasopressors	33 (26.4%)	20 (40.0%)	22 (47.8%)	0.019
Colloid	21 (16.8%)	8 (15.7%)	13 (28.3%)	0.195
PRBC	22 (17.6%)	15 (29.4%)	16 (34.8%)	0.040
FFP	1 (0.8%)	3 (5.9%)	5 (10.9%)	0.005
Temp <34°C	4 (3.2%)	2 (3.9%)	7 (15.2%)	0.014
GA	49	16	12	0.212
GA + EA	74	35	34	
Emergency	10 (8%)	1 (1.96%)	3 (6.52%)	0.364

SBP_0=Systolic blood pressure, DBP_0=Diastolic blood pressure, MBP_0=Mean blood pressure, 0: at baseline/start of surgery, PRBC=Packed red blood cells, FFP=Fresh frozen plasma, GA=General anaesthesia, EA=Epidural anaesthesia, Temp=Temperature

Table 3: Postoperative parameters on days 1 and 2

	Mean±SD			*P*	Difference
	Negatives (C) *n*=125	Intermediate (I) *n*=51	Positives (P) *n*=46		
Hb g/dL Day 1	10.96±1.82	10.78±1.39	10.65±2.22	0.591	
PLT x10^3 Day 1	247.25±84.64	248.06±89.89	210.00±86.76	0.021	*P*<N *P*=0.039.
INR Day 1	1.06±0.23	1.27±0.69	1.28±0.50	0.001	*P*>N *P*=0.009, I>N *P*=0.009
Creatinine mg/dL Day 1	1.03±0.18	1.08±0.27	1.07±0.25	0.373	
Hb g/dL Day 2	10.13±1.68	9.88±1.48	9.80±1.59	0.419	
PLT x10^3 Day 2	234.33±78.43	233.57±89.14	187.11±72.43	0.002	*P*<N , *P*=0.002, *P*<I, *P*=0.015
INR Day 2	1.06±0.28	1.20±0.40	1.20±0.41	0.015	*P*>N, *P*=0.06.
Creatinine mg/dL Day 2	1.04±0.19	1.16±0.73	1.09±0.29	0.213	
Length of ICU stay (days)	13.50±7.33	12.49±6.92	13.66±8.07	0.668	
Post-op MV	8 (6.4%)	1 (2.0%)	8 (17.4%)	0.018	
Post-op Dialysis					
Yes	1 (0.8%)	1 (2.0%)	1 (2.2%)	0.405	
In-hospital Mortality					
Yes	0	1	4	0.003	

Hb=Haemoglobin, PLT=Platelets, INR=International normalised ratio, MV= Mechanical ventilation

Table 4: Regression analysis of Group P vs. Group N

	Odds ratio (95% CI)	*P*
Risk factors		
FFP	12.1 (1.3-117.0)	0.031
CAD	2.8 (1.1-7.4)	0.027
Use of inotropes	2.6 (1.2-5.5)	0.012
Female	2.2 (1.1-4.8)	0.035
Regression analysis of Group P vs. Group I + Group N		
Risk factors		
Post op mechanical ventilation	3.5 (1.2-10.4)	0.020
Female	2.1 (1.0-4.1)	0.042
Hypothermia	4.5 (1.3-14.9)	0.013

FFP=Fresh frozen plasma, CAD=Coronary artery disease, CI=Confidence interval

regression analysis between group P versus Group N, [Table 4]. We also compared the Group P with combined Group I with Group N. On logistic regression analysis, hypothermia (OR 4.5;95% CI 1.4–14.9), mechanical ventilation (OR 3.6;95% CI 1.2-10.4), and female gender (OR 2.05;95% CI 1.02–4.09) correlated with MINS.

DISCUSSION

In our analysis of high-risk cardiovascular patients undergoing abdominal surgery, the incidence of MINS was 20.72%, which is much higher than that reported in the VISION study.[2] Group P had a higher proportion of ASA III patients implying a sicker group of patients with significant perioperative risks for MINS. Female gender and associated coronary artery disease were identified as preoperative risks and the gender association was different from all other reports on MINS. [2,4] Transfusion of plasma during surgery was also significantly associated with MINS.

While there has been an understanding that MINS in high-risk patients is associated with a higher morbidity, [1-3] the intraoperative factors that predispose to elevations in troponins are poorly reported. Smilowitz *et al.*[4] in their meta-analysis of 169 studies have reported an overall incidence of 17.5% for

MINS with an increase in-hospital, 30 day and 1-year mortality. Most reports of MINS in non-cardiac surgery have included vascular surgery and few reports on abdominal surgery are available.[5]

Our incidence of MINS is higher than that of the VISION investigators who had documented an 8% incidence of MINS in a large cohort study with a predicted mortality of 10%. In a study at our centre that looked at the incidence of MINS across 1,075 multidisciplinary surgical patients,[3] 17.5% incidence was seen. We hypothesised that patients undergoing abdominal surgery could represent a high-risk group and sought to analyse factors associated with increased risk for MINS with a view to optimise or improve outcomes perioperatively.

Cardiac troponin I and T are components of the contractile apparatus of myocardial cells and are highly cardiac specific.[6] Elevations of troponins in non-cardiac surgery are due to the direct toxic effects of high endogenous or exogenous circulating catecholamine levels.[7] Patients with elevations of troponins not amounting to myocardial ischemia can be missed if biomarkers are not measured routinely.

The group at risk or vulnerable to the occurrence of MINS was identified as per the guidelines of Mauermann *et al.*[8] We followed the recommendations of the VISION workers, who had as the reference group Trop T <0.01 ng/dL and groups with a peak trop T value of 0.02 ng/dl, between 0.02and 0.029 ng/dL and ≥0.03 ng/dL documenting an adjusted hazards ratio of 1.65%, 4.81% and 10.01%, respectively. A value of Trop T ≥0.03 ng/dL was identified to be predictive of MINS in their study.[2]

We had used Troponin I as a standard for measurement in our patients as per the availability at our institution. This value was standardised with the Public Health Initiative Canada to provide the range for our study.[3]

Noradrenaline (NE) was the most commonly used agent for the management of intraoperative hypotension in accordance to the fluid restrictive strategy.[9] Prolonged infusions can have a direct toxic effect on the cardiac myocytes by inducing apoptosis on the cardiac myocytes and allowing influx of intracellular calcium.[10,11] The use of vasopressors/inotropes was associated with a higher incidence of MINS in the subgroup analysed in our study, with 47.8% patients in Group P needing vasopressors against 26.8% in Group N perhaps reflective of frail cardiovascular status in predisposed patients.

A restrictive strategy of 7.5–8.0 g/dL Hb was allowed for patients without identified cardiovascular risks but a liberal strategy was adopted for higher risk patients and postoperative haemoglobin comparable amongst the groups. Blood transfusion was needed in 34.8% patients in Group P versus 17.7% in group N ($P = 0.04$) while plasma transfusion was given for 5 patients in Group P and 1 in Group N ($P = 0.005$). Hovaguiman[12] and Doherty[13] have independently shown that in predisposed patients with features of cardiovascular disease a restrictive transfusion strategy would be harmful. Blood transfusion was not a predictor for MINS in a regression analysis but transfusion of plasma was a predictor in a comparison of Group P versus Group N (OR12.1; 95% CI 1.3–117.0). The transfusion for FFP was as per the recommended guidelines[14] and not used for the correction of prothrombin time in the absence of ongoing bleed.

Moderate hypothermia (<34°C) measured by a nasopharyngeal probe was considered as a variable as it increases myocardial stress by increasing adrenergic response. A retrospective cohort analysis of nearly 2,000 patients has shown no association between mild hypothermia between 36°C and 37°C and MINS,[15] while in another analysis of elective surgeries, hypothermia (<36°C) was associated with a higher mortality (17% vs. 4%) and morbidity[16] Hypothermia may have contributed to greater cardiovascular stress and increased myocardial oxygen consumption resulting in an imbalance between oxygen supply versus demand amongst the patients in our study. A regression analysis between Group *P* versus Group I and Group N showed an association of hypothermia with MINS (OR4.5; 95% CI 1.3–14.9) although this was not seen between Group *P* versus Group N.

The need for postoperative mechanical ventilation in abdominal surgery is commonly due to haemodynamic instability, acidosis, ongoing bleed, renal or respiratory dysfunction or inadequate neuromuscular reversal. The higher number of postoperatively ventilated patients in Group *P* (17.4%) versus 6.4% in Group N and 2% in Group I was reflective of major surgery in a high-risk patient group. Regression analysis was significant in a comparison between Group *P* versus Group N with Group I (OR12.1; 95% CI 1.3 – 117.0).

Troponins can be elevated in nearly 80% of patients with chronic renal disease (CKD) who do not have reported cardiovascular disease.[17] Patients with glomerular filtration rate (eGFR) <30 ml/min have three-fold higher troponin than those with a GFR >60 ml/min. Troponin elevation is seen in patients with acute kidney injury (AKI) also[18] and doppler evaluation of the resistive index allows early detection.[19] We had excluded all patients with CKD with a serum creatinine >2.0 mg/dL. One patient in each group needed postoperative dialysis for metabolic acidosis and volume overload.

The use of colloids was similar and included hetastarch and albumin. Incidence of kidney injury and coagulopathy with starches and gelatins are reported[20] but we did not see an association with their use.

Elderly patients and those with autonomic dysfunction tend to have fluctuations in blood pressure in non-cardiac surgery. Anaesthetic medications and surgical manipulations can produce sharp variations in the blood pressure. Intraoperative hypotension (IOH) addresses a value of <80 mm Hg systolic blood pressure or as a fall of >20% from baseline.[21] Studies have shown that a fall of more than 40% mean arterial blood pressure from baseline sustained beyond 30 min is associated with higher occurrence of MINS.[22] We had looked at a lower degree of change (< or > 20% mean arterial pressure) to institute interventions but did not find associations with either hypotension or hypertension in our study.

Female gender was a strong predictor for MINS in our study and this was different from other studies. Female gender has traditionally been considered protective for the occurrence of CAD, however the incidence of ischemic heart disease among women is on the rise and younger women are also susceptible.[23] Microvascular factors, role of inflammation, and emotional factors appear to contribute to CAD among women and its impact on mortality less understood. We feel that the belief that women are less vulnerable, lack of facilities for proper care and lesser privileges to women[24] may have resulted in undetected or under-corrected disease.

We believe that this retrospective analysis can put into perspective major associations and predictors for MINS in patients in South India undergoing abdominal surgery. Intraoperative transfusions, vasopressors, hypothermia, and need for postoperative mechanical ventilation were anticipated risks but we did not see correlations with postoperative dialysis, type of surgery, or anaesthesia. Intuitively, CAD was a predictor but strangely we found female gender as a strong associate in regression analysis among the three groups which is different from all other reports on MINS.

However, we acknowledge the limitations in our study. Our patients were part of the institutional study over that looked at the prevalence of MINS and a small subgroup of abdominal surgery was included for our study. George *et al*. have acknowledged that the study included patients and surgeons consenting for this study, hence may have excluded a population at risk who may not have consented. We had not discriminated the surgical risks that were involved and merely looked at the ASA physical status for classifying risks. Tachycardia during the study was not recorded, and this may have a role in prediction for MINS. Data on haemodynamic fluctuations were obtained from the data sheets and we did not correlate this with ongoing surgical events that might have contributed to the fall or rise.

CONCLUSIONS

From our data, female patients with CAD undergoing abdominal surgery and needing vasopressors and transfusion of plasma are at high risk for MINS with higher hospital mortality. Identification and vigilant perioperative monitoring postoperatively is indicated in this group.

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Conflicts of interest
There are no conflicts of interest.

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