Myocardial injury after noncardiac surgery—incidence and predictors from a prospective observational cohort study at an Indian tertiary care centre

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Abstract
Asymptomatic myocardial injury following noncardiac surgery (MINS) is an independent predictor of 30-day mortality and may go unrecognized based on standard diagnostic definition for myocardial infarction (MI). Given lack of published research on MINS in India, our study aims to determine incidence of MINS in patients undergoing noncardiac surgery at our tertiary care hospital, and evaluate the clinical characteristics including 30-day outcome.

The prospective observational study included patients >65 years or >45 years with either hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular accident (CVA), or peripheral arterial disease undergoing noncardiac surgery. MINS was peak troponin level of ≥0.03 ng/dL at 12-hour or 24-hour postoperative. All patients were followed for 30 days postoperatively. Predictors of MINS and mortality were analyzed using multivariate logistic regression. Patients categorized based on peak troponin cut-off values determined by receiver operating characteristic curve were analyzed by Kaplan–Meir test to compare the survival of patients between the groups.

Among 1075 patients screened during 34-month period, the incidence of MINS was 17.5% (188/1075). Patients with DM, CAD, or who underwent peripheral nerve block anaesthesia were 1.5 (P < .01), 2 (P < .001), and 12 (P < .001) times, respectively, more likely to develop MINS than others. Patients with heart rates ≥96 bpm before induction of anesthesia were significantly associated with MINS (P = .005) and mortality (P = .02). The 30-day mortality in MINS cohort was 11.7% (22/188, 95% CI 7.5%–17.2%) vs 2.5% (23/887, 95% CI 1.7%–3.9%) in patients without MINS (P < .001). ECG changes (P = .002), peak troponin values >1 ng/mL (P = .01) were significantly associated with mortality. A peak troponin cut-off of >0.152 ng/mL predicted mortality among MINS patients at 72% sensitivity and 58% specificity. Lack of antithrombotic therapy following MINS was independent predictor of mortality (P < .001), with decreased mortality in patients who took post-op ASA (Aspirin) or Clopidogrel. Mortality among MINS patients with post-op ASA intake is 6.7% vs 12.1% among MINS patients without post-op ASA intake. Mortality among MINS patients with post-op Clopidogrel intake is 10.5% vs 11.8% among MINS patients without post-op Clopidogrel intake.

A higher (17.5%, 95% CI 15–19%) incidence of MINS was observed in our patient cohort with significant association with 30-day mortality. Serial postoperative monitoring of troponin following noncardiac surgery as standard of care, would identify “at risk” patients translating to improved outcomes.

Abbreviations: ACC = American College of Cardiology, AHA = American Heart Association, ASA = acetylsalicylic acid (Aspirin), CAD = coronary artery disease, CRF = case report form, CVA = cerebrovascular accident, DM = diabetes mellitus, ECG = electrocardiogram, HR = hazard ratio, hs TnI = high sensitive troponin-I, HTN = hypertension, MI = myocardial infarction, MINS = myocardial injury after noncardiac surgery, NPV = negative predictive value, POISE = PeriOperative ISchemia Evaluation, PPV = positive predictive value, VISION = Vascular Events In Noncardiac Surgery Patients Cohort Evaluation.

Keywords: myocardial injury after noncardiac surgery, perioperative care, troponin
1. Introduction

Of the 200 million patients undergoing noncardiac surgery per year globally, one million adults are estimated to die within 30 days postsurgery.[1] Cardiovascular events are the major cause for perioperative complications leading to morbidity and mortality after noncardiac surgeries.[2] Acute MI (myocardial infarction) accounts for 5.7% of morbidity following noncardiac surgeries. The standard diagnostic definition of MI requires the presence of myocardial necrosis as evidenced by elevated cardiac biomarkers and supportive electrocardiographic evidence. Patients who do not fulfill the clinical criteria for MI might still sustain a myocardial injury during postoperative period without exhibiting ischemic symptoms or hallmarks ECG changes.[3,4] With advances in surgical techniques and anesthesia, elderly population with cardiovascular comorbidities undergoing noncardiac surgery continues to rise, thereby increasing the incidence of perioperative myocardial injury. Myocardial injury after noncardiac surgery (MINS) is a relatively new clinical concept, defined as “prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery.”[5] In comparison with MI, the diagnostic definition of MINS allows us to capture prognostically relevant myocardial injuries occurring during the perioperative period. MINS patients generally have elevations in cardiac biomarkers (mainly troponin) without symptoms or electrocardiographic evidence of myocardial injury.[6] Ischemic symptoms are rarely observed and transient ECG changes tend to be overlooked for patients who are under analgesics or mechanical ventilation during the perioperative period.[7] Patients with predisposing comorbidities are especially at-risk of adverse cardiac events following surgery. Mortality due to MI following noncardiac surgery, in patients with and without ischemic symptoms was reported to be similar by the POISE (PeriOperative Ischemia Evaluation) trial.[2] The study determined the proportion of patients who had elevated levels of cardiac markers comparable to patients with symptomatic or asymptomatic MI but were not MI by definition, thereby establishing need for monitoring of cardiac biomarkers postsurgery. Most troponin elevations start within 24 to 48 hours after surgery and are attributed to postoperative stress.[8]

The VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation) study was an international prospective cohort study designed to assess major vascular events in patients who had undergone noncardiac surgery.[1] The study estimated a worldwide prevalence of MINS at 8% and reported its significant association with 30-day mortality. The study established that relatively high and previously indeterminate troponin ranges to be independent predictors of 30-day mortality irrespective of their ischemic nature. As predictors of mortality, the adjusted hazard ratios for troponin ranges of 0.03 to 0.29 and > 0.3 ng/mL were estimated to be 5 (95% CI 3.7–6.7) and 10.4 (95% CI 6.2–16.1), respectively. The diagnostic threshold for MINS determined by the VISION study was at peak troponin T level of ≥0.03 ng/mL. Presence of Coronary artery disease, heart failure, renal impairment evidenced by creatinine greater than 2mg/dL, history of cerebrovascular stroke and diabetes mellitus have been identified as high risk indices for increased perioperative cardiac morbidity.[9]

Current standard of care in India do not require monitoring troponin in patients following noncardiac surgery. Conceding the knowledge gap in MINS from India, we sought to prospectively study the incidence, predictive factors, and association of MINS with 30-day mortality in a cohort of patients undergoing noncardiac surgery at our institution.

2. Materials and methods

2.1. Study design and eligibility criteria

2.1.1. Study design. A prospective observational study of patients undergoing noncardiac surgery at Amrita Institute of Medical Sciences, Kochi, India, based on previously published methodology, was done.[1] Ethical clearance was obtained from Institutional Ethics Committee prior to the study. A sample size of 1104 was estimated for the study based on the prevalence rate of 8% reported by Botto et al.[1] using nMaster with a 95% confidence and 20% allowable error. The study period during which the perioperative troponin screening was performed was from July 2015 to August 2016. The procedural flow of the study is depicted in Figure 1.

2.1.2. Patients. The study cohort consisted of patients undergoing elective noncardiac surgery who required general, spinal or peripheral nerve block anesthesia and postoperative inpatient stay of more than 24 hours.

2.1.3. Inclusion criteria. Adults above the age of 45 years with one or more of the following comorbidities diabetes mellitus, systemic hypertension, coronary artery disease, cerebral vascular accident, peripheral vascular occlusive disease, and all adults aged above 65 years with or without co-morbidities were included in the study.

2.1.4. Exclusion criteria. Patients with sepsis, cardiac drug toxicity, pulmonary embolism, or chronic renal failure were excluded from the study. Pregnant women were also excluded from the study. A process for screening of patients fulfilling the inclusion criteria with troponin I 12 and 24 hours following surgery was established in cooperation with the anesthesia and respective surgical departments to detect MINS. Following sensitization
about MINS screening, anesthetists and surgeons identified patients meeting the study criteria. Patients thus identified at preoperative anesthesia clinics, surgical wards, and surgical intensive care units were selected and screened. Informed consent was obtained prior to study enrollment.

2.1.5. Procedure. Troponin I or hs Troponin I are cardiac biomarkers exclusively used to detect myocardial injury. Troponin values were estimated at our hospital using ARCHITECT stat High Sensitive Troponin-I (hs TnI) assay (Abbott). Troponin I values were estimated at 12 and 24 hours after surgery for the study cohort along with the corresponding ECGs. These patients were reviewed on a daily basis to assess for symptoms of myocardial ischemia. The threshold values of Troponin I for MINS as determined by the Public Health Research Initiative (Canada) using Architect 2000i (Abbott) were followed in the study. If serial troponin values at 12 and 24 hours were elevated, then a 48-hour troponin value was estimated. All positive troponin values were reported to the primary physician or surgeon and the study team.

A peak troponin level of ≥ 0.03ng/dL after surgery was considered as MINS. The research team collected basic demographic data and clinical information relevant to the procedure and perioperative complications. (Appendix 1—CRF; http://links.lww.com/MD/C238). Data on medications including antithrombotic agents and statins taken by the patient before and after MINS were also collected. All patients with positive troponin following surgery were advised cardiology consultation.

2.2. Outcomes

All patients enrolled into the study were followed-up at 30 days postsurgery for evaluating their outcome. Any history of hospitalization or adverse event during this period was recorded. For patients who expired, an attempt was made to determine if the cause of death was cardiac or noncardiac by retrieving data from hospital information system, medical records, or through telephone calls. Patients with missing or unavailable follow-up data were excluded from the final data analysis.

2.3. Statistical analysis

Descriptive statistics were used to summarize the prevalence rate of MINS and baseline characteristics of the study cohort. Multivariate logistic regression analysis was used to identify the predictors of MINS within the entire study cohort and predictors of mortality among the patients diagnosed with MINS. The predictive value of peak troponin levels for mortality within the MINS cohort was analyzed using the area under the receiver operating characteristic curve and an optimum threshold value was determined. Kaplan–Meier plot was used to evaluate the survival of patients in each group. A log-rank test was run to determine if there were differences in the survival distribution for the 2 types of patient groups created based on the chosen peak troponin cut off values. SPSS version 20 (IBM) was used for all statistical analysis.

3. Results

3.1. Baseline characteristics of study cohort

Among the 1107 patients enrolled into the study, 32 were lost to follow-up and 1075 patients were followed till 30 days after surgery. The study cohort exhibited a male preponderance (676, 60%) and diabetes mellitus (N = 476, 43%) were the most common comorbidities. Around 29% (312) of patients underwent abdominal surgery, 23% (251) head and neck surgery, and 22% (241) neurosurgery. A total of 88% (946) of the surgeries were performed under general anesthesia and 12% (159) under regional anesthesia (Table 1). Hypertension (N = 652, 61%) and diabetes mellitus (N = 506, 47%) were the most common co-morbidities. Around 29% (312) of patients underwent abdominal surgery, 23% (251) head and neck surgery, and 22% (241) neurosurgery. A total of 88% (946) of the surgeries were performed under general anesthesia, 10% (104) under spinal anesthesia, and 2% (25) under peripheral nerve blocks.

3.2. Prevalence of MINS and its predictors

Myocardial injury after noncardiac surgery was diagnosed in 188 patients (17.5%; 95% CI 15%–19%). MINS was more pronounced in older patients as demonstrated by the increasing
incidence rates of 13%, 19%, and 23% among the age groups 45 to 59 years, 60 to 79 years, and above 80 years, respectively. Around 21% (108, 95% CI 18%–25%) of diabetic patients, 29% (46, 95% CI 22%–36%) of patients with coronary artery disease, and 39% (24, 95% CI 27%–51%) of individuals with history of CVA had an increased incidence of MINS as compared to the rest of the cohort. MINS was found to be significantly associated with patients who had diabetes mellitus (P = .001, OR 1.66, 95% CI 1.21–2.28), coronary artery disease (P < .001, OR 2.2, 95% CI 1.49–3.23) or history of stroke (P < .001, OR 3.27, 95% CI 1.91–5.6). Patients undergoing surgery under peripheral nerve block anesthesia (56%) had a significantly higher association with MINS (OR 7.55, 95% CI 2.8–19.7) compared to patients receiving spinal anesthesia (14%).

The incidence of MINS among our cohort of noncardiac surgeries was 13% in patients who underwent head and neck surgery (P = .02, OR 0.65, 95% CI 0.43–0.97). Incidence of MINS was significant among patients undergoing gastrointestinal surgery (21%, P = .05, OR 1.41, 95% CI 1.01–1.97). Patients who did not develop MINS postoperatively had inpatient stay < 7 days compared to those who developed MINS (23%, P < .05, OR 1.98, 95% CI 1.36–2.88). Around 67% of patients who developed MINS did not have any changes in serial ECG analysis. Patients with T-wave inversion (25%) and ST segment changes (7%) had a higher incidence of MINS (P < .001, OR 6.58, 95% CI 8.5–506.3). Patients with heart rates ≥96 bpm[10] before induction of anesthesia were significantly associated with MINS (P = .005).

The use of antithrombotic agents and statins as part of optimized medical therapy postoperatively was reviewed for 185 MINS positive patients for whom the data were available. Only 31 (16%) patients received antithrombotic agents postoperatively, with 15 (8%) receiving Aspirin and 19 (10%) receiving clopidogrel. Around 58 (31%) were started on statins following MINS positivity (Table 2).

A multivariate logistic regression analysis performed on all the significant variables obtained during univariate analysis to identify the predictors of MINS revealed that patients with diabetes, coronary artery disease or who received peripheral nerve block anesthesia were 1.5 (P < .01, 95% CI 1.10–2.15), 2.1 (P < .001, 95% CI 1.45–3.28), 12 (P < .001, 95% CI 4.21–34.3) times, respectively, more likely to develop MINS than individuals in the other groups (Table 3).

### 3.3. 30-day outcome

Around 11.7% (22/188) of patients diagnosed with MINS expired compared to 2.5% (23/887) of patients who did not have MINS (P < .001, HR 4.96, 95% CI 2.71–9.14).
MINS (2.7%, 22/811). In patients who received postoperative aspirin, the mortality reduced to 6.7% (1/15) in MINS patients (Table 5). Similarly among 998 patients who did not receive Clopidogrel postoperatively, 30-day mortality was significantly (P < .01) associated with MINS (12.1%, 21/173) compared to patients without MINS (2.7%, 22/811). Mortality was significantly associated with MINS irrespective of receiving statins postoperatively. A significant association was not observed between antithrombotics and outcome in the MINS cohort.

4. Discussion

The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery[11] has stated the usefulness of postoperative screening for MI, with serial troponin levels in high-risk individuals without symptoms or signs of myocardial ischemia as uncertain (Class IIb).[12] Lack of a defined management strategy for these patients has been of concern. Recent evidence, led by the VISION study[1] showed a strong association between peak troponin levels after surgery and 30-day mortality. An implementation of serial postoperative troponin evaluations in high-risk patients undergoing noncardiac surgery was done to understand the burden of “at risk” population in our setting. Prospective evaluation estimated the prevalence of MINS in our tertiary care hospital at 17.5% (188/1075). Around 11.7% (22/188) of patients who were diagnosed with MINS expired within 30 days compared to 2.5% (23/887) of patients who did not have MINS (P < .001). The mortality in our MINS cohort was higher than the 9.8% mortality reported in the VISION study. The incidence of MINS in our cohort was significantly higher than the incidence of 8% reported by the VISION study.[2] We believe that the
increased inherent cardiovascular risk in our South Indian population could have contributed to the higher incidence of MINS. Considering the fact that all of the events were asymptomatic, the number of individuals who develop MINS is definitely alarming.

With patients from all adult age groups undergoing surgery, our results were similar to the VISION trial,[2] which revealed individuals older than 75 years had a significant association with MINS. Diabetes, coronary artery disease, and cerebrovascular accidents are fast gaining the status of potential epidemics in India. Since our study reveals significant association with these noncommunicable diseases, an increase in the prevalence of MINS can be expected to parallel any rise in the incidence of these individual co-morbidities in coming years. In our cohort, the patients with high perioperative risk underwent surgery with peripheral nerve block anesthesia as compared to general or spinal anesthesia. This has contributed to higher incidence of MINS and associated mortality. The high negative predictive value of the peak troponin level cut-off of 0.152 ng/mL can be translated to screen patients with MINS who would not require close follow up within 30 days postsurgery.

Use of the standard criteria for MI alone in our cohort would have missed the diagnosis of prognostically relevant MI in 67% of our patients. We wish to highlight the importance of potential under diagnosis of this condition, as it silently emerges into a major postoperative entity. Our clinical research team overcame significant skepticism from surgeons and anesthesiologists to implement this risk based screening protocol for MINS. Based on our results, we believe we have sufficient evidence at present to standardize this protocol and integrate it into routine care.

We did not observe any significant association of MINS and 30-day mortality and type of surgery, with almost similar percentage of patients undergoing gastrointestinal, neuro- and orthopedic surgery in our cohort. This is similar to previously published data suggesting correlation with MINS and outcome in only patients undergoing major vascular surgery.[6]

The comparatively higher mortality in MINS patients in our study due to a cardiac cause and the significant association noted with lack of antithrombotic medications after MINS is of concern. At present there is no standard of care for management of MINS patients. Our observation of increased incidence and mortality in patients who did not have antithromboses is distressing. Better awareness about MINS among the surgeons and education with respect to prescription of antithrombotic medications in this patient group could improve outcomes till definitive treatment options are available.

Our study strengths include the prospective nature and wide and diverse array of surgeries done in our tertiary care hospital allowing us to screen the “at risk” patients for MINS. Another factor was the establishment of screening troponin in the high-risk population after surgery as standard process, with active participation from the anesthesia and respective surgical departments. As compared to the VISION trial, we used Troponin I instead of Troponin T, which is shown to be less influenced by renal dysfunction, hence revealing a more accurate value.[13,14]

Our study has several limitations. The study cohort included Southern Indian population; hence generalizing the observations to the Indian population at large would require broader and more widespread study to determine the true prevalence of MINS. Issues associated with physician reservations to recruit patients coupled with lack of patient consent have led to the inclusion of a random subset of screened patients, which could have potentially biased our observations. Our hospital being a tertiary care referral centre, for the state, we see high risk complex medical
cases contributing to a potential bias in the study cohort. Furthermore, Troponin I was only measured on the first 2 days’ postsurgery and hence MI occurring after 48 hours could have been missed. A third Troponin I measurement is only taken when any one of the two initial tests within 48 hours turns positive, possibly omitting any MINS positivity occurring within a window of following 24 hours.

Given the asymptomatic nature of MINS, awareness with a high index of suspicion and screening “at risk” patients will improve outcomes following noncardiac surgery. Our state being a capital for diabetes and harboring CAD at younger ages, we have a higher incidence of MINS and associated mortality compared to developed countries. Screening patients to diagnose MINS based on elevated Troponin I levels should be standard of care that could be incorporated into routine clinical practice. Due to the scarcity of published data in the Indian population, the role of MINS in influencing the outcomes of patients undergoing noncardiac surgery all over India is unknown. The results of our study emphasize the need of further research studies on MINS and identifying the various clinical variables associated with its incidence and related mortality.

5. Conclusion

We report a prospective study demonstrating a higher prevalence of MINS in our region (17.5%) when compared to the worldwide incidence of 8%, with significant association with 30-day mortality. In clinical practice, elevated troponin in the perioperative period has prognostic utility and can prepare surgical teams for adverse events so that they can be recognized, evaluated, and treated in a timely manner. We have demonstrated the feasibility of implementing a risk based screening protocol for MINS following noncardiac surgery. A greater importance must be assigned to MINS and its treatment as it has significant association with postoperative morbidity and mortality. The time interval between troponin elevation and death potentially allows physicians to modify prognosis by initiating medical treatment of myocardial ischemia. The results of our study emphasize the need of further research studies on MINS identifying the various clinical variables risk factors and ideal treatment options.

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