

Incidence of myocardial injury after non-cardiac surgery: Experience at Groote Schuur Hospital, Cape Town, South Africa

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Background. Myocardial injury after non-cardiac surgery (MINS) is a newly recognised entity identified as an independent risk factor associated with increased 30-day all-cause mortality. MINS increases the risk of death in the perioperative period by ~10-fold. More than 80% of patients with MINS are asymptomatic, so the majority of diagnoses are missed. Awareness of MINS is therefore important for perioperative physicians.

Objectives. To investigate the incidence of MINS after elective elevated-risk non-cardiac surgery at Groote Schuur Hospital, Cape Town, South Africa (SA).

Methods. Patients aged ≥ 45 years undergoing elective elevated-risk non-cardiac surgery were enrolled via convenience sampling. The new fifth-generation high-sensitivity cardiac troponin T blood test was used postoperatively to identify MINS. Preoperative troponin levels were not measured.

Results. Among 244 patients included in the study, the incidence of MINS was 4.9% (95% confidence interval (CI) 2.8 - 8.5), which was not significantly different from that in a major international prospective observational study (VISION) (8.0% (95% CI 7.5 - 8.4)); $p=0.080$.

Conclusions. Our SA cohort had a lower cardiovascular risk profile but a similar incidence of MINS to that described in international literature. The impact of MINS on morbidity and mortality is therefore likely to be proportionally higher in SA than in published international studies. The limited sample size and lower event rate weaken our conclusions. Larger studies are required to establish patient and surgical risk factors for MINS, allowing for revision of cardiovascular risk prediction models in SA.

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Recent reports estimate global annual perioperative morbidity and mortality rates to be ~3% and 0.5%, respectively.^[1] One-third of deaths in patients undergoing non-cardiac surgery are cardiovascular in origin.^[2] Myocardial ischaemia with subsequent injury is strongly associated with perioperative mortality.^[3,4] A large multicentre international study in 2012 investigated the mortality associated with perioperative elevated troponin levels in >15 000 patients from North and South America, Australia, Europe and Asia (Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation (VISION) study).^[3] The 30-day mortality was found to be independently associated with myocardial injury after non-cardiac surgery (MINS) in a subsequent analysis of the data.^[5] Ten percent of patients with myocardial injury died within 30 days of surgery.^[5] Eighty-four percent of perioperative patients with myocardial injury were asymptomatic, resulting in missed diagnosis in the vast majority of patients with MINS.^[5] Thirty-day mortality was found to be independently associated with an elevated cardiac biomarker, specifically cardiac troponin T (cTnT).

The VISION study utilised the previous fourth-generation cTnT test.^[3] MINS has been defined as an isolated fourth-generation cTnT level of ≥ 30 ng/L (0.03 $\mu\text{g/mL}$) due to myocardial ischaemia, which predicted mortality with an odds ratio of 10.07 (95% confidence

interval (CI) 7.84 - 12.94).^[5] A substudy of the VISION investigation suggested that a suitable cut-off level for the more sensitive fifth-generation cTnT (hs-cTnT) for a diagnosis of MINS is >33 ng/L.^[6]

With regard to MINS, only a single vascular surgical cohort has been studied in South Africa (SA).^[7-9] Because of differing patient characteristics and risk profiles, extrapolation of the incidence of MINS from international data to SA surgical patients may be inappropriate.

Objectives

The primary objective of this study was to determine the incidence of MINS after non-cardiac surgery in an elective elevated-risk surgical population in SA. The null hypothesis for this study was that the incidence of MINS would be similar in the SA study population to that described in peer-reviewed international reports. Secondary outcomes were the prevalence of risk factors such as patient demographics, surgical categories and comorbidities associated with MINS.

Methods

This was a prospective, single-centre observational study investigating the incidence of MINS at Groote Schuur Hospital, a tertiary referral

centre in Cape Town, SA. Patients aged ≥ 45 years presenting for elective elevated-risk non-cardiac surgery were eligible. Elevated-risk surgery was defined as all surgery with a predicted risk of major adverse cardiac events of $>1\%$.^[10] This included all intra-abdominal, non-cardiac thoracic, joint replacement, major orthopaedic and vascular surgery. Patients were selected by means of convenience sampling from November 2014 to February 2016, and only these patients were included in the study.

Enrolled patients were investigated for MINS, defined as an elevated postoperative hs-cTnT level suspected to be due to myocardial ischaemia, with no other known non-ischaemic causes of troponin elevation. Once patients were enrolled, postoperative blood samples were collected. Specimens were analysed using the Troponin T hs (highly sensitive) immunoassay (Roche Diagnostics, Germany).

After approval from the Human Research Ethics Committee of the University of Cape Town (ref. no. 818/2014), data collection was commenced. Theatre lists were interrogated and patients with appropriate inclusion criteria were identified. Informed consent was obtained postoperatively, after which appropriate blood samples were taken. In the majority of patients (90.6%), one blood sample was taken within 24 hours of surgery. In the remainder, a second sample was taken within 72 hours. If two samples were taken, the highest troponin elevation was recorded. MINS was diagnosed if the postoperative hs-cTnT level was >33 ng/L.

As sampling only commenced after surgery, we could not identify patients with pre-existing cTnT elevation. Known preoperative myocardial infarction, pulmonary embolism, sepsis and renal dysfunction were therefore also grounds for exclusion because of the direct or indirect influence of these conditions on measured postoperative cTnT. Renal impairment was defined using international guidelines.^[11,12] Further exclusion criteria included pre-existing hypotension and low-risk surgery such as ophthalmic and superficial plastic surgery. Other comorbidities were identified during the patient interview. Postoperative mortality data were not collected.

A *post hoc* decision was made to present some of the key characteristics of the Groote Schuur Hospital cohort, the SA vascular surgery cohort and the VISION cohort in order to provide further insight into the incidence of MINS in the Groote Schuur patients.^[3,8] A statistical comparison of these characteristics between the Groote Schuur cohort and the VISION cohort was conducted.

Statistical analysis

Based on previous studies, a prevalence of MINS of 10 - 15% was estimated for our study population. On this basis, a sample size of 219 - 266 would be required for a 95% CI of 10% for the estimate of the prevalence of MINS. A sample size of 300 was targeted.

Statistical analysis was done using Minitab 17 Statistical Software (Minitab, USA).^[13] Continuous variables were described using sample means and standard deviations (SDs) and categorical variables using sample medians and interquartile ranges. Where statistical comparisons were made between continuous variables, the unpaired *t*-test was used, while categorical data were compared using the χ^2 test or the χ^2 test with Yates's correction, as appropriate.

Results

During the data collection period (16 months), theatre lists were actively interrogated for only 39 weeks owing to researcher availability. For this reason, convenience sampling was our method of selection. During that time, ~ 1 100 patients underwent elective surgery, of whom 301 were eligible. The flow diagram of patient recruitment is shown in Fig. 1. The majority of initial exclusions were because

of inappropriate age and/or low-risk surgery. The final number of patients included was 244.

The patient demographic details, surgical categories and comorbidities are shown in Table 1. The majority of patients were in the younger age category, 45 - 65 years. General and gynaecological

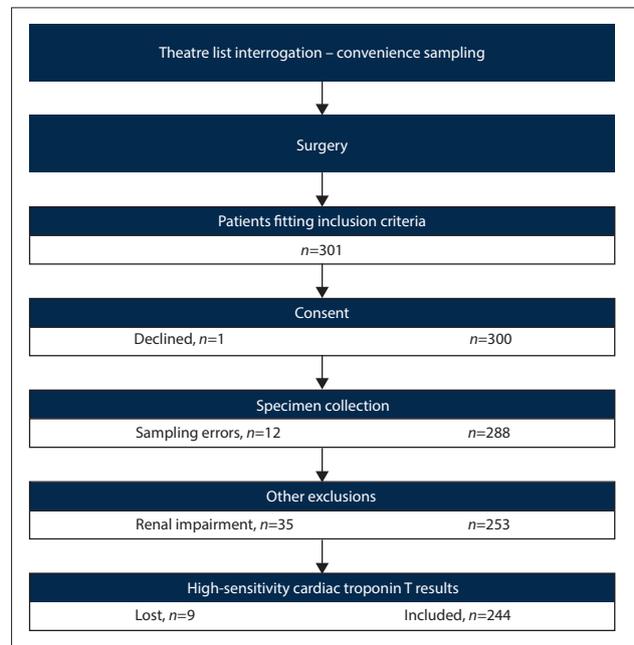


Fig. 1. Flow diagram of patient recruitment.

Table 1. Patient characteristics

Included patients, N	244
Females, n (%)	139 (57.0)
Age (years)	
Mean (SD)	60.5 (9.4)
45 - 64, % (95% CI)	68.9 (62.8 - 74.3)
65 - 75, % (95% CI)	23.8 (18.8 - 29.5)
>75 , % (95% CI)	6.6 (4.0 - 10.5)
Surgical categories, n (%)	
General	63 (25.8)
Gynaecological	52 (21.3)
Orthopaedic	40 (16.4)
Urological	27 (11.1)
Vascular	18 (7.4)
Otolaryngological	16 (6.6)
Thoracic	9 (3.7)
Neurological	3 (1.2)
Comorbidities*	
Median (IQR)	1 (1 - 2)
Hypertension, n (%)	161 (66.0)
Malignancy, n (%)	78 (32.0)
Smoking, n (%)	69 (28.3)
Diabetes mellitus, n (%)	50 (20.5)
Hypercholesterolaemia, n (%)	47 (19.3)
Previous myocardial infarction, n (%)	20 (8.2)
Previous stroke, n (%)	15 (6.1)
Previous heart failure, n (%)	6 (2.5)

*Since some patients suffered from more than one comorbidity, these percentages do not add up to 100.
SD = standard deviation; CI = confidence interval; IQR = interquartile range.

surgery were the most common operations performed, which explains the higher proportion of female participants. Hypertension and malignancy were the most frequently recorded comorbidities. The hs-cTnT results are reported in Table 2.

The incidence of MINS was 4.9% (95% CI 2.8 - 8.5). There were inadequate data for multivariate regression analysis to investigate associations between patient or surgical risk factors and MINS.

Comparisons between the Groote Schuur, SA vascular and VISION cohorts are shown in Table 3. There was no significant difference in the incidence of MINS between the Groote Schuur and VISION studies. The Groote Schuur cohort had younger patients, fewer male patients and more hypertension. The Groote Schuur patients underwent more elective and vascular surgery than the VISION cohort.

Discussion

The main finding of this study was that the incidence of MINS in the elective elevated-risk surgical population in SA was comparable to reports from a large international study. It was impossible to perform a risk-adjusted analysis to compare the incidence of MINS between the Groote Schuur and VISION cohorts. A previous comparison between the South African Surgical Outcomes Study (SASOS) and the European Surgical Outcomes Study (EuSOS) suggested that SA surgical patients have a lower risk profile than surgical patients in Europe.^[14] The patients in our study probably had a lower cardiovascular risk profile, as they were younger, included fewer males and had more elective surgery than the VISION cohort, as seen in Table 3. This has important public health implications for SA, because of the major morbidity and mortality associated with MINS.

Current perioperative morbidity rates translate into major complications in ~7 million patients and 1 million deaths per

annum in the immediate perioperative period, since >200 million surgical operations are performed worldwide per year.^[1] Studies from high-income countries suggest that 50% of major adverse perioperative events could be avoided.^[1] Research on the cause and prevention of perioperative complications could therefore benefit global healthcare.

Myocardial ischaemia remains a major cause of perioperative morbidity and mortality.^[15] To provide some perspective, 7% of medical patients who are treated in hospital for an acute myocardial infarction die within 30 days.^[16] Patients may present with myocardial ischaemia either as a medical emergency or in the perioperative period. Both appear to have a significant 30-day mortality, but their clinical presentations are very different. The diagnosis of myocardial infarction in medical patients relies on clinical symptoms and signs *in addition* to positive special investigations (electrocardiogram, cardiac biomarkers, cardiac imaging studies).^[17] A recent review suggests that the high proportion of silent presentations and the lack of high-grade evidence for therapeutic interventions could explain the hesitancy of perioperative clinicians to adopt MINS as a significant perioperative event.^[18] However, it is clear that MINS results in significant morbidity and mortality and poses a significant public health burden.^[5]

Cardiac biomarkers utilised for the diagnosis of myocardial infarction require predefined reference limits. These limits or cut-off values are derived from healthy individuals.^[19-21] Analysis of data from the VISION study showed not only that elevation of the cardiac biomarker cTnT was the strongest predictor of 30-day mortality, but also that the magnitude of troponin elevation correlated with risk. The VISION study attempted to predict mortality related to increasing levels of fourth-generation cTnT, in combination with the clinical presentation. Adding positive symptomatology to the model did not change the diagnostic threshold, and the diagnosis had the same prognostic importance for mortality as a myocardial infarction diagnosed using the Universal Definition of Myocardial Infarction.^[5]

Correlations between the fourth- and fifth-generation cTnT test do exist. A fourth-generation cTnT level of 30 ng/L correlates with a fifth-generation cTnT (hs-cTnT) level of ~53 ng/L. However, a substudy of the VISION investigation found that the 95th percentile value for perioperative patients was 33 ng/L (95% CI 26 - 49 ng/L) for hs-cTnT.^[6,22] The cumulative proportion of patients with a fourth-generation cTnT level >30 ng/L was 9%, compared with 7 - 10% >33 ng/L using the hs-cTnT.

Table 2. High-sensitivity cTnT results at Groote Schuur Hospital

cTnT undetectable, n (%)	42 (17.2)
cTnT (ng/L), median (IQR)	7 (4 - 14)
cTnT (ng/L), median >33 ng/L (IQR)	60 (37 - 83)
cTnT >99th percentile*, n (%) (95% CI)	55 (22.5) (17.8 - 28.2)
cTnT >33 ng/L†, n (%) (95% CI)	12 (4.9) (2.8 - 8.5)
cTnT >53 ng/L, n (%) (95% CI)	7 (2.9) (1.3 - 5.9)

cTnT = cardiac troponin T; IQR = interquartile range; CI = confidence interval.
 * >14 ng/L.
 † Primary outcome definition.

Table 3. Comparison between the GSH cohort, the SA vascular surgical cohort and the VISION study^[3,8]

	GSH (N=244)	SA vascular cohort (N=788)	VISION (N=15 133)	p-value*
Age (years), mean (SD)	60.5 (9.4)	58.3 (14.2)	NR	
Age 45 - 64 years, n (%)	168 (68.9)	NR	7 436 (50.9)	<0.001
Males, n (%)	105 (43.0)	512 (65.0)	7 339 (49.5)	0.044
Hypertension, n (%)	161 (66.0)	540 (68.5)	7 709 (50.9)	<0.001
Diabetes mellitus, n (%)	50 (20.5)	338 (42.9)	2 952 (19.5)	0.761
History of coronary artery disease, n (%)	20 (8.2)	275 (34.9)	1 832 (12.1)	0.078
History of stroke, n (%)	15 (6.1)	159 (20.2)	696 (4.6)	0.323
History of heart failure, n (%)	6 (2.5)	37 (4.7)	703 (4.6)	0.151
Vascular surgery, n (%)	18 (7.4)	788 (100)	504 (3.3)	0.001
Elective surgery, n (%)	244 (100)	NR	12 991 (85.8)	<0.001
Incidence of MINS, n/N (%)	12/244 (4.9)	25/509 (5.0)†	1 200/15 065 (8.0)	0.080

GSH = Groote Schuur Hospital; SA = South African; VISION = Vascular Events In Non-cardiac Surgery Patients Cohort Evaluation; SD = standard deviation; NR = not recorded; MINS = myocardial injury after noncardiac surgery.
 * Comparison between GSH and VISION cohorts.
 † Reported troponin level above the 99th centile reference range.

The fifth-generation cTnT (hs-cTnT) used in the present study has improved diagnostic sensitivity to nearly 100% in patients presenting as a medical emergency; a level >14 ng/L suggests myocardial necrosis.^[21,23] The increased sensitivity has added complexity to the interpretation of perioperative changes in troponin levels, and specificity is reduced because of the many alternative causes of troponin elevation during this period.^[21] Carbon monoxide poisoning, renal failure, heart failure, acute pericarditis, acute exacerbation of chronic obstructive airway disease, chemotherapy-related myocardial damage, pulmonary hypertension, pulmonary embolism, sepsis, stroke and subarachnoid haemorrhage can all result in cTnT elevations.^[24-35] Not all of these elevations appear to affect prognosis consistently, especially in non-surgical patients. However, in the perioperative period cTnT elevation appears to be a robust marker for predicting outcome, and is independently associated with a 10% 30-day mortality.^[5,36] Preoperative hs-cTnT elevation, as well as an absolute rise of >9 ng/L hs-cTnT, have consistently been shown to have a significant short- and long-term effect on perioperative mortality.^[37]

Our study has implications for cardiovascular risk stratification in SA. Our patients have a similar incidence of MINS to that of international cohorts, despite a possible lower risk profile, which suggests that the current international cardiovascular risk prediction models may be inappropriate for SA patients and/or they may be incorrectly calibrated, resulting in an underestimation of cardiovascular risk in SA surgical patients. This finding is supported by recent literature which suggests that utilising the revised cardiac risk index in SA patients may be inappropriate, especially in vascular surgery.^[9] Another confounder may be the HIV epidemic in southern Africa, with HIV-positive patients undergoing vascular surgery having fewer of the usually cited cardiovascular risk factors than HIV-negative patients, but similar perioperative morbidity and mortality.^[7] The development of an appropriate and well-calibrated perioperative cardiovascular risk prediction model is necessary in SA. A large SA cohort is first necessary to determine calibration of cardiovascular risk factors in SA patients.

The evidence for preventive and therapeutic strategies for MINS is lacking.^[18,38] The current literature suggests implementation of simple strategies when MINS is suspected, including appropriate surveillance in the form of regular screening of troponin levels.^[18,38] Furthermore, intraoperative prevention should focus on optimising myocardial oxygen supply and demand. Once MINS is diagnosed in the postoperative setting, interdisciplinary management should be initiated. In addition, aspirin and statin therapy show potential benefit, and studies investigating specific therapeutic and preventive measures are in progress.^[18]

Study limitations

Although we screened >1 100 patients, our sample size remained relatively small, and the event rate was lower than expected, so the primary outcome had a wider than anticipated CI. The incidence of MINS in our population was lower than we expected. This may be explained in part by our methodology of single postoperative troponin sampling per patient, while the VISION study had a median of three troponin samples per patient. Furthermore, VISION included both elective and emergency surgery, and as our study only included elective surgeries, this too may have led to a lower incidence of MINS. Together with the lower event rate, our study now appears to be underpowered to achieve all our secondary objectives of establishing associations with MINS. However, as our data suggest a similar incidence of MINS to an international cohort,

we would recommend routine perioperative troponin surveillance for intermediate- to high-risk surgical patients in SA.

In addition, the intended multivariate analysis examining the association of patient factors and MINS could not be performed. The high exclusion rate was to avoid confounders for postoperative hs-cTnT elevation that may not have been secondary to myocardial ischaemia. It is possible that the incidence may be higher than reported, since we excluded many patients at high risk of cardiovascular complications who had comorbidities that may be associated with cTnT release due to causes other than ischaemia.

Conclusions

Since SA still lacks population-specific prognostic values for hs-cTnT, the present study serves as an initial indicator of the incidence of MINS, while also providing guidance for sample size calculation for future larger studies that could identify patient or surgical risk factors for poor outcomes due to MINS. This study failed to demonstrate a difference in the incidence of MINS between our SA cohort and the VISION cohort, although the study limitations weaken our conclusions. Although this study did not specifically examine the association between MINS and major perioperative morbidity and mortality in SA patients, the methodology of the VISION analysis suggests that the associated perioperative morbidity is universally applicable, and our study therefore suggests that MINS has significant implications for public health outcomes in SA. International guidelines promote the utility of troponin surveillance, and a recent study found troponin surveillance to be financially viable in SA.^[39,40] Our data suggest that postoperative troponin surveillance is necessary in elevated-risk non-cardiac surgical patients in SA.

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