Clinical Communication

Impact of preoperative hypercoagulability on myocardial injury in overweight and obese patients undergoing lower limb arthroplasty: An observational study

INTRODUCTION

Myocardial injury following noncardiac surgery (MINS) is defined as troponin elevations occurring up to 30 days postoperatively in the absence of non-ischaemic causes.[1] Obesity is associated with hypercoagulability, which can be diagnosed using viscoelastic assays, such as rotational thromboelastometry (ROTEM).[2,3] Previous viscoelastic assay studies have shown a higher incidence of thromboembolic and ischaemic events in those with hypercoagulability.[4,5] In this study, we aimed to examine the association between preoperative hypercoagulability and MINS in overweight and obese patients undergoing elective primary total hip arthroplasty (THA) and total knee arthroplasty (TKA).

METHODS

This prospective observational cohort study was conducted on patients who underwent elective unilateral THA and TKA after ethical approval (Metro North Hospital and Health Service Human Research Ethics Committee number: HREC/15/QPCH/123; dated June 24, 2015) and trial registered at the Australian New Zealand Clinical Trials Registry (vide registration ID: ACTRN12615000825550; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368077&isReview=true). Patients with a history of thrombophilia, other possible causes of hypercoagulability, or disorders requiring postoperative anticoagulation were excluded. Individual written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study was conducted according to the principles expressed in the Declaration of Helsinki, 2013. In the pilot phase, perioperative hypercoagulability and its association with obesity were investigated in 50 patients of all body mass index (BMI) ranges.[3] Subsequently, a larger study was undertaken on 303 obese patients to investigate the relationship between preoperative hypercoagulability and thromboembolic complications.[6] In this exploratory study, we present the analysis of data from the participants with obesity (BMI ≥25 kg/m^2 or waist circumference ≥94 cm (male) and ≥80 cm (female)) who had perioperative troponin measurements.

Participant characteristics, surgical description, medication details, clinical history, and obesity metrics, including BMI, waist, neck, and hip circumferences, were collected. Cardiac troponins were measured immediately before surgery and on the first three postoperative days (POD), regardless of symptoms. MINS was defined as (a) cTn (Beckman Coulter) levels of ≥0.04 μg/L (99th percentile of upper reference limit (URL)) and (b) highly sensitive cardiac troponin I (hs-cTnI) (Beckman Coulter) levels with cut-offs of ≥10 ng/L (female) and ≥20 ng/L (male) in combination with five units increase from baseline levels (for hs-cTnI). Additional measures, such as the relative increase in hs-cTnI levels, C-reactive protein (CRP), and D-dimer on POD 3, were included for the hs-cTnI group. Baseline blood samples were taken before the surgery to diagnose ROTEM-hypercoagulability. ExTEM G-score was calculated as 5000 × ExMCF/(100-ExMCF), and hypercoagulability was defined as a G score of 11 K dyne/cm^2.[3,7]

The primary outcome measure for this analysis was the incidence of MINS on POD 1, 2, or 3, and the secondary outcomes included in-hospital thromboembolic complications (myocardial infarction, ischaemic stroke, cardiovascular death, nonfatal cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism (PE), and 30- and 90-day mortality following surgery.

Statistical analyses were performed using the Stata statistical software package, version 15 (StataCorp LLC, College Station, Texas, USA). Patients were categorised into those with and without MINS, and the variables of interest were compared between groups. Analyses were repeated and stratified by assay type. Continuous variables were summarised as mean (standard deviation [SD]) and tested between groups using an independent-sample *t*-test or summarised using median (interquartile range [IQR]) and tested using Wilcoxon's rank sum test as appropriate. Categorical variables were summarised using frequencies (%) and tested using Pearson's Chi-square or Fisher's exact test. The analysis was performed on consecutive samples of patients with perioperative troponin measurements,

and a formal sample size was not calculated as it was an exploratory analysis.

RESULTS

The analysis included 172 participants with a mean (SD) age of 67 (10) years, and 96 (56%) were female. Median (IQR) BMI was 32 (29–37) kg/m^2 with 55 (32%) classified as overweight, 50 (29%) class 1 obese, 46 (27%) class II obese, and 21 (12%) class III obese (World Health Organization criteria).[8] There were 24 participants (13.9%; 3/47 pilot study participants with c- TnI and 21/125 main study participants with hs-cTnI measurements) with a diagnosis of MINS.

Overall, 65 (38%) of the participants were aged ≥70 years, comprising 75% (18/24) of those with MINS. Participants with MINS were older and had higher renal impairment ($P < 0.001$ and $P < 0.004$, respectively) [Table 1]. No differences were observed in the CRP or D-dimer values between the groups in the hs-cTnI subset [Table 1]. Preoperative hypercoagulability was observed in 55/172 (32%) patients, with no evidence of a difference between those with and without MINS ($P = 0.43$) [Table 1].

Among patients with MINS, elevated troponin levels were observed in three preoperatively and 8, 16, and 21 patients respectively on POD 1, 2, and 3; an additional four patients had at least one mildly elevated troponin level. In the hs-cTnI group, among the 21 patients who experienced MINS, nine patients experienced peak values on POD 3 and seven on POD 2 [Figure 1]. The median (IQR) peak value of hs-cTnI was 33 (15–71) ng/L, and the increase from baseline was 25 (11–66) ng/L. A cardiologist was referred to three patients in the pilot study with MINS and one of them was commenced on aspirin prophylaxis. The other two had negative repeat troponin results. The investigatory team was blinded to troponin results for the main study, and the participants were managed according to clinician preference.

Of the secondary outcomes, two female participants (82 and 77 years of age) developed confirmed PE on POD 3. Four participants developed postoperative atrial fibrillation, including one of those diagnosed with PE. Another patient demonstrated sustained troponin elevations POD 2 and 3 along with electrocardiographic changes of posterior ischaemia. There was one case of a type 2 myocardial infarction. There was no mortality before discharge or at 30-9- days.

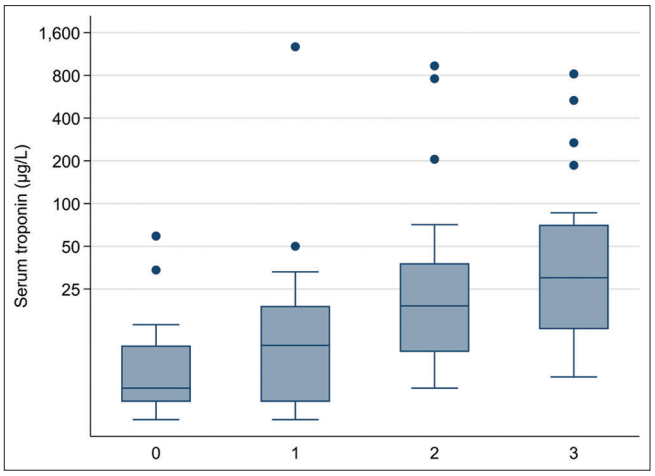

Figure 1: Boxplots showing distribution of serum troponin levels (hs-cTnI; logarithmic scale) following surgery among the participants who experienced elevated troponin levels (n = 21/125); 0 = preoperative baseline measurement, 1–3 postoperative days

DISCUSSION

A third of overweight and obese patients undergoing THA and TKA were identified as hypercoagulable, and MINS was observed in around 14% of our study participants. The occurrence of MINS did not differ based on preoperative hypercoagulability or individual obesity measures. There were two patients with PE, two with myocardial ischaemia/infarction and no reported mortality.

Hypercoagulability is one of the possible contributors to type 1 myocardial injury. In the VISION sub-study on vascular patients, those with myocardial injury were observed to have increased levels of individual clotting and fibrinolytic factors.[9] Our contrasting observations may have resulted from methodological differences, such as using different troponin assays, ROTEM rather than blood biomarkers, and differences in the patient cohort.[10] We observed significantly higher renal impairment in those with MINS. We also included a relative increase of 5 ng/L as a requisite in the hs-cTnI subset to differentiate from chronic troponin elevations in patients with chronic kidney injury. With no differences in CRP or D-dimer levels, our troponin elevations likely resulted from ischaemic causes.[10] In 12.5% of those with MINS, higher preoperative troponin levels were observed, probably related to pre-existing coronary artery disease.

Regarding patient-specific factors, the impact of age in our study was consistent with the literature.[11] A previous study on patients who underwent non-cardiac surgery reported the lowest risk of cardiac injury

Table 1: Characteristics of the study participants undergoing lower limb total joint arthroplasty. The table compares those with/without myocardial injury after noncardiac surgery (MINS) diagnosed based on their hs-cTnI and cTnI levels in the postoperative period

Variable	Complete cohort				hs-cTnI subset				cTnI subset		
	No MINS (*n*=148)	MINS (*n*=24)	Total (*n*=172)	*P*	No MINS (*n*=104)	MINS (*n*=21)	Total (*n*=125)	*P*	No MINS (*n*=44)	MINS (*n*=3)	Total (*n*=47)
BMI*; kg/m^2	32 (29–37) [31–34]	31 (29–36) [29–36]	32 (29–37) [31–34]	0.41	32 (29–37) [31–35]	32 (29–36) [29–36]	32 (29–37) [31–34]	0.86	32 (29–38)	29 (26–30)	31 (29–38)
Age**; years	65.8 (9.1) [64.3–67.3]	74.4 (9.6) [70.4–78.5]	67.0 (9.6) [65.5–68.4]	<0.001	65.2 (8.9) [63.5–67]	76.1 (8.1) [72.4–79.8]	67.0 (9.7) [65.3–68.8]	<0.001	67.1 (9.4)	62.7 (13.1)	66.9 (9.5)
Gender; female†	79 (53.3) [45.2–61.3]	17 (70.8) [49.5–85.7]	96 (55.8) [48.2–63.1]	0.11	52 (50.0) [40.4–59.6]	17 (81.0) [57.9–92.9]	69 (55.2) [46.3–63.8]	0.009	27 (61.4)	0 (0.0)	27 (42.6)
Neck**; cm	40 (4) [39.6–41.1]	39 (3) [37.6–40.4]	40 (4) [39.5–40.8]	0.16	40 (4) [39.6–41.1]	39 (3) [37.3–40.4]	40 (4) [39.4–40.8]	0.13	40 (5)	40 (2)	40 (5)
WHR**	1 (1) [0.9–1.1]	1 (0) [0.9–1]	1 (1) [0.9–1.1]	0.67	1 (0) [0.9–1.2]	1 (0) [0.9–1]	1 (0) [0.9–1.1]	0.64	1 (0)	1 (0)	1 (0)
Hypertension†	88 (59.5) [51.3–67.1]	13 (54.2) [34.1–73]	101 (58.7) [51.1–65.9]	0.63	58 (55.8) [46–65.1]	11 (52.4) [31.2–72.7]	69 (55.2) [46.3–63.8]	0.78	30 (68.2)	2 (66.7)	32 (68.1)
COPD†	12 (8.1) [4.6-13.8]	3 (12.5) [4–33.2]	15 (8.7) [5.3–14]	0.48	7 (6.7) 3.2–13.6]	3 (14.3) [4.5–37.1]	10 (8.0) [4.3–14.3]	0.24	5 (11.4)	0 (0.0)	5 (10.6)
Diabetes†	33 (22.3) [16.3–29.8]	7 (29.2) [14.3–50.5]	40 (23.3) [17.5–30.2]	0.46	25 (24.0) [16.7–33.3]	7 (33.3) [16.4–56.1]	32 (25.6) [18.6–34.1]	0.37	8 (18.2)	0 (0.0)	8 (17.0)
eGFR <60 ml/min/1.73 m^2	13 (8.8) [5.1–14.6]	7 (29.2) [14.3–50.5]	20 (11.6) [7.6–17.4]	0.004	9 (8.7) [4.5–15.9]	7 (33.3) [16.4–56.1]	16 (12.8) [7.9–20]	0.002	4 (9.1)	0 (0.0)	4 (8.5)
Current Smoker‡	7 (5)	0 (0)	7 (4)	0.60	5 (5)	0 (0)	5 (4)	0.59	2 (5.0)	0 (0.0)	2 (4.0)
IHD†	9 (6.1) [3.2–11.3]	4 (16.7) [6.2–37.6]	13 (7.6) [4.4–12.6]	0.069	7 (6.7) [3.2–13.6]	3 (14.3) [4.5–37.1]	10 (8.0) [4.3–14.3]	0.24	2 (4.5)	1 (33.3)	3 (6.4)
Type of surgery: TKA†	100 (68) [59.5-74.7]	14 (58) [37.8–76.3]	114 (66) [58.8–73]	0.49	69 (66) [56.6–74.9]	13 (62) [39.5–80.2]	82 (66) [56.7–73.5]	0.80	31 (70)	1 (33)	32 (68)
Duration of surgery (h)**	1.9 (0.6) [1.8–2]	1.7 (0.3) [1.5–1.8]	1.9 (0.6) [1.8–2]	0.028	2.0 (0.6) [1.9–2.1]	1.7 (0.3) [1.5–1.8]	2.0 (0.6) [1.9–2.1]	0.012	1.7 (0.5)	1.5 (0.3)	1.7 (0.5)
Preop CRP; mg/L* (*n*=120)	2.8 (1.5–8.0) [2.3–4.4]	2.8 (1.5–5.6) [1.5–5.4]	2.8 (1.5–7.1) [2.3–4.3]	0.60	2.8 (1.5–8.0) [2.3–4.4]	2.8 (1.5–5.6) [1.5–5.4]	2.8 (1.5–7.1) [2.3–4.3]	0.60	NA	NA	NA
POD3 D-dimer; mg/L*	1.6 (1.3–2.1) [1.4–1.8]	1.5 (1.1–1.9) [1.1–1.9]	1.5 (1.2–2.1) [1.4–1.7]	0.28	1.6 (1.3–2.1) [1.4–1.8]	1.6 (1.3–2.1) [1.1–1.9]	1.5 (1.2–2.1) [1.4–1.7]	0.28	NA	NA	NA
ExMCF G score >11 K.dynes/cm^{2}†	49 (33.1) [25.9–41.2]	6 (25.0) [11.4–46.3]	55 (32.0) [25.4–39.4]	0.43	36 (34.6) [26–44.4]	6 (28.6) [13.1–51.6]	42 (33.6) [25.8–42.4]	0.59	13 (29.5)	0 (0.0)	13 (27.7)
MetS‡	63 (42.6) [34.8–50.7]	12 (50.0) [30.5–69.5]	75 (43.6) [36.3–51.2]	0.50	46 (44.2) [34.9–54]	12 (57.1) [35.3–76.5]	58 (46.4) [37.7–55.3]	0.28	17 (39)	0 (0)	17 (36)

Data expressed as *median (IQR) [95% confidence interval] with *P* values from Wilcoxon's rank-sum test; **mean (SD) [95% confidence interval] with *P* values from unpaired *t*-test; †*n* (%) [95% confidence interval] with *P* values from Pearson's Chi-square test or ‡*n* (%) with *P* values from Fisher's exact test. (i) Myocardial injury: defined as i) hsTnI ≥10 ng.l for females or ≥20ng.l for males with an increase >5 ng/l from baseline; ii) cTn: any value >0.04 mcg.l BMI: body mass index; hs-cTnI: highly sensitive cardiac troponin I; cTnI: cardiac troponin I; NA=no data available; WHR: waist-to-hip ratio, POD: postoperative day, CRP: C-reactive protein, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease; MetS: metabolic syndrome; eGFR: estimated glomerular filtration rate from Cockcroft–Gault equation; ExMCF: ExTEM maximum clot firmness; G score: 5000 x ExTEM MCF/(100-ExTEM MCF); TKA: Total knee arthroplasty.

in class I obese patients amongst all BMI categories, and a lower risk of 1-year mortality with higher BMI compared to normal-weight patients.[12] Despite the MINS rate in our obese cohort being around 14%, there were no deaths within 30 or 90 days. We observed a significantly higher number of females in those with MINS when assessed by hs-cTnI levels, indicating a possible sex effect. Consistent with a previous study, surgical duration influenced the occurrence of MINS.[13]

The strength of our prospective analysis is that all our patients had their anthropometric measurements performed, as well as troponins and ROTEM assays, measured on the day of the surgery and had a similar surgical risk profile. We included both absolute levels and relative troponin changes from baseline. However, our data relates specifically to arthroplasty patients with obesity.

This was an exploratory analysis of a limited sample to generate hypothesis for future studies.

CONCLUSION

In our analysis of overweight and obese patients undergoing elective THA and TKA, we observed no evidence of an association between baseline hypercoagulability and postoperative troponin elevations. We recommend further large-scale studies to validate our findings and determine the clinical value of troponin measurements in perioperative risk stratification and prognostication in patients with obesity.

Disclosure

The current submission is a sub-study analysis of the data collected for the prospective observational study. The main study results have been accepted for publication by Clinical and Applied Thrombosis/Hemostasis (manuscript doi: 10.1177/1076029 6231199737). Findings from the study were presented at the ANZCA Annual Scientific Meeting, Melbourne, Australia, on 2 May 2021.

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Conflict of interest

Prof. Harshal Nandurkar has received payments from BMS Pfizer for presentations on various haematology topics. Nil conflict of interest for other authors.

Study data availability

Deidentified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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