Original Article

Association between frailty, cerebral oxygenation and adverse post-operative outcomes in elderly patients undergoing non-cardiac surgery: An observational pilot study

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ABSTRACT

Background and Aims: Although both frailty and low cerebral oxygen saturation increase the risk of post-operative complications, their relationship is yet to be investigated. The purpose of this observational study was to investigate the association between frailty, intraoperative cerebral oxygen saturation and post-operative complications in elderly patients undergoing non-cardiac surgery. **Methods:** After approval from the Institutional Review Board, 25 elderly patients (>65 years) undergoing non-cardiac major surgery were included in this study. Pre-operatively, all included patients were assessed for frailty and classified into frail and non-frail groups. All patients had routine intraoperative monitors, and a cerebral oximeter applied during anaesthesia. The 'intraoperative' anaesthesiologist and the post-operative study investigator were blinded to cerebral oximeter readings throughout the study. The incidence of significant intraoperative cerebral oxygen desaturation, adverse post-operative outcomes and length of hospital stay were compared. Statistical significance was defined as a value of $P < 0.05$. **Results:** We found that the frail group had more intraoperative cerebral desaturation (odds ratio [OR] [95% confidence interval [CI]]: 1.75 [1.11–2.75]) and longer median (interquartile range) length of hospital stay compared to the non-frail group (13.5 days [8.75–27.5] and 8 days [6–11], respectively). Furthermore, in patients with a low-baseline cerebral oxygen saturation (<55%), intraoperative cerebral desaturation (OR [95% CI]: 2.10 [1.00–4.42]), adverse post-operative outcomes (OR [95% CI]: 1.80 [1.00–3.23]) and median (interquartile range) length of hospital stay (15 days [9–31.5] vs. 9 days [6.25–13.75], $P = 0.04$) were significantly higher compared to subjects with higher baseline (≥55%) cerebral oxygen saturation. **Conclusions:** Frail patients have more intraoperative cerebral desaturation and longer lengths of hospital stay compared to non-frail patients.

Key words: Cerebral oxygenation, frailty, non-cardiac surgery, post-operative outcome

INTRODUCTION

As the population worldwide ages, there are tremendous implications to world healthcare. Approximately, more than 21% of the population aged >65 years undergoes surgery every year.[1] With an expected increase in this age group, more elderly patients are expected to undergo surgery and anaesthesia in the near future. Although post-operative mortality in the elderly has decreased, perioperative morbidity and complications, involving primarily the cardiovascular, neurologic and

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pulmonary systems continue to be more frequent in this age group.[2,3]

Frailty is a syndrome characterised by a decrease in physiological reserve across multiple organ systems. As a consequence, frail patients are at increased risk of disability and death from relatively minor external stresses. Frailty has been found to be predictive of post-operative complications and adverse outcomes in a number of studies.[4] Several studies have attempted to reduce the deleterious effects of frailty by modifying its associated factors such as correction of nutritional deficiencies or improvement of exercise capacity using exercise intervention protocols. Similar to frailty, low cerebral oxygen saturation (measured using non-invasive spectroscopy) has been suggested to indicate decreased physiological reserve and has been found to be associated with poor post-operative outcomes.[5]

Only a limited number of studies have investigated the effect of low intraoperative cerebral oxygenation on post-operative outcomes in non-cardiac surgery. The purpose of this observational study was to investigate the association between frailty and intraoperative cerebral oxygen saturation. The primary outcome compared between the study groups was the incidence of significant intraoperative cerebral oxygen desaturation. Secondarily, the association between intraoperative cerebral oxygenation and adverse post-operative outcomes in elderly patients undergoing non-cardiac surgery were also investigated.

METHODS

After approval from the Institutional Review Board and with written informed consent to participate in the study, 25 elderly patients (>65 years) undergoing both general and regional anaesthesia for non-cardiac major surgery (defined as operations expected to require more than 2 days of post-operative stay, and/or operative duration more than 2 h) were included in the observational study. Patients with disabling neuropsychiatric or neurological disorders such as severe dementia, Alzheimer's disease, schizophrenia, severe depression, those suffering from delirium or those patients who cannot complete the pre-operative mental tests (confusion assessment method-Intensive Care Unit [CAM-ICU] and/or mini-mental state examination [MMSE]) were excluded from the study. Pre-operatively, all included patients were administered an MMSE, CAM-ICU test and had frailty assessment [Appendix 1] performed using modified Fried criteria[6,7] by the study investigators. All patients undergoing surgery had routine intraoperative monitors, bispectral index (BIS) monitor and a cerebral oximeter at left forehead (5100C INVOS cerebral/somatic oximeter; Somanetics Corporation, Troy, MI, USA) applied before induction of anaesthesia. We also noted the pre-induction baseline cerebral oxygen saturation on room air. Further perioperative management proceeded as dictated by the attending anaesthesiologist. The intraoperative anaesthesiologist and the post-operative study investigator were blinded to cerebral oximeter readings throughout the study. All the recruited patients were assessed for delirium (using the CAM-ICU by the study investigators) for 3 days post-operatively or until hospital discharge (whichever occurred first). Patient variables including intraoperative mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO_2), BIS values (BIS®), blood loss, perioperative laboratory results, pre-operative medical status, incidence of post-operative cardiac events and incidence of post-operative hospital-acquired infections were extracted from the electronic medical records (Sunrise Clinical Manager™-Allscripts Healthcare Solutions Inc, Chicago, illinois, USA and WinChart®-WinChart Health Informatics, Sydney, NSW, Australia). Area under the curve was calculated from the extracted values to determine exposure to factors such as intraoperative hypotension (MAP <75 mmHg), deep anaesthesia (BIS <45) and peripheral oxygen desaturation as measured using a peripheral oximeter (SpO_2 <90%) which could affect study outcomes.[8,9]

Patients were classified into frail and non-frail groups based on the presence of frailty. Similarly, study outcomes in study subjects with a baseline cerebral oxygen saturation of <55% (low baseline cerebral oxygenation [LB] group) were compared with study subjects with cerebral oxygen saturation ≥55% (high baseline cerebral oxygenation group).

The primary outcome compared between the study groups was the incidence of significant intraoperative cerebral oxygen desaturation (defined as intraoperative cerebral oxygen saturation <25% of baseline or <50% absolute value for a >50% min area under the curve).[10]

Also compared between groups was the total length of hospital stay, post-operative length of hospital stay (defined as duration of hospital stay following an operation until discharge), and the incidence of adverse post-operative outcomes (defined as the composite of new post-operative incidence of one or more of the following: Delirium, Hospital acquired infection [occurrence of urinary tract infection, lower respiratory tract infection or wound infection in a 10 days post-operative period], or perioperative cardiac complications). Perioperative myocardial infarction was considered to be present if it occurred in the immediate perioperative period (<10 days post-operative) and was diagnosed by an attending cardiologist or critical care physician on the basis of the universal definition of perioperative myocardial infarction.[11] Perioperative cardiac arrhythmia was considered to be present if an attending cardiologist, anaesthesiologist, or critical care physician diagnosed a non-sinus rhythm in the immediate perioperative period (<10 days post-operative).

Data are presented as median (interquartile range) for continuous variables and as count (percentage) for categorical variables. Mann–Whitney U-test, Fisher's exact test, or Chi-square test were used for intergroup comparisons as appropriate. Statistical significance was defined as a value of $P < 0.05$. All analyses were performed with SPSS statistical software version 20.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Between September 2014 and March 2015, 31 patients were screened for inclusion in the study. After exclusion of 6 patients (one- operation cancelled, three- refused and two- severe dementia), 25 patients were included in the analysis. The median age of the study sample was 79 (74–83) years, with 68% of participants being females. The median baseline cerebral oxygen saturation was found to be 57% (51–66.5). Fifty-six percentage of the participants (14/25) were found to be frail on testing and 36% (9/25) study subjects had baseline cerebral oxygen saturation <55% on room air (LB group).

Table 1 illustrates the comparison of demographic and perioperative variables between the study groups. The incidence of cerebral desaturation (the primary outcome measure in our study) was significantly higher in the frail group and low baseline cerebral oxygen saturation (LB) group [Table 2]. Similarly, patients in the frail and LB group had a significantly longer duration of both total and post-operative hospital stay compared to the other study group.

DISCUSSION

We found that frail patients had a significantly longer hospital stay and more intraoperative cerebral desaturation compared to non-frail subjects. We also found that patients with a LB had significantly more cerebral desaturation intraoperatively and poorer post-operative outcomes.

Several studies have found that frailty in elderly patients is an independent risk factor for adverse post-operative outcomes including longer duration of hospital stay.[4,12,13] Fifty-six percentage of the participants (14/25) in our study were found to be frail. Other studies in older patients undergoing surgery also quote frailty prevalence rates at between 41.8 and 50.3% in contrast to a frailty prevalence rate of <10% in older community dwelling individuals.[12,13] This difference highlights the vulnerability of elderly surgical patient population. Several studies have attempted to reduce deleterious effects of frailty by modifying associated risk factors such as anaemia,[14] Vitamin D deficiency and physical activity intervention[15] with varying degrees of success. The significant time needed for these interventions reduces their applicability in the perioperative period, especially during urgent or emergency surgery. Similar to frailty, low cerebral oxygen saturation (measured using non-invasive spectroscopy) has been suggested to indicate decreased physiological reserve and has been found to be associated with poor post-operative outcomes.[5,10,16] In our study, the frail group had more intraoperative cerebral oxygen desaturation compared to non-frail patients. Similar to previous studies,[17] we also found that these cerebral oxygen desaturation episodes were not apparent on peripheral oximetry and would most likely be missed in routine clinical practice without a cerebral oximeter. Unlike other modifiable factors associated with frailty, optimisation of intraoperative cerebral oxygenation can be relatively easily and quickly achieved. Previous intervention studies[5,17] which have optimised intraoperative cerebral oxygen saturation have reported improvement in post-operative outcomes and reduction in hospital length of stay. Our results suggest such an intervention may be useful in frail subjects and could be the subject for future research.

Table 1: Comparision of demographic and perioperative characteristics in study participants based on frailty and baseline cerebral oxygenation

Characteristics	Non-frail (*n*=11)	Frail (*n*=14)	*P*	HB group (*n*=16)	LB group (*n*=9)	*P*
Baseline cerebral oxygen saturation (%)	56 (52-67)	58 (48.25-63.5)	0.85	61.5 (57.5-67.75)	49 (39.5-53)	0.001
Demographic						
Age (years)	79 (73-83)	79.5 (74-82.75)	0.89	79.50 (73-84.50)	79 (74.50-82.50)	0.93
Weight (kg)	53 (50-65)	52 (47.2-53.7)	0.37	51.3 (47.1-54.87)	53.1 (51.7-62.5)	0.17
Race (%)						
Chinese	11 (100)	13 (92.8)	1.00	15 (93.8)	9 (100)	1.00
Other	0 (0)	1 (7.1)		1 (6.2)	0 (0)	
Gender (%)						
Female	6 (54.5)	2 (14.3)	0.08	14 (87.5)	3 (33.3)	0.01
Male	5 (45.5)	12 (85.7)		2 (12.5)	6 (66.6)	
Intraoperative variables						
AUC BIS <45 (BIS.minutes)	18.79 (11.83-80.25)	6.1 (0-46.36)	0.24	14.64 (0.17-37.11)	18.79 (0.39-101.99)	0.45
AUC MAP <75 (mmHg.minutes)	72 (45.59 -92.46)	69.9 (39.05-108.1)	1.00	73.49 (41.83-89.59)	70.07 (42.86-165.81)	0.63
AUC SpO_2 <90 (%.minutes)	0 (0-0.47)	1.52 (0-7.71)	0.08	0.46 (0-4.5)	0.25 (0-1.37)	0.598
Duration of operation (minutes)	171.63 (122.5-227.6)	132.73 (95.44-213.62)	0.47	132.73 (100-198.57)	147.68 (111.13-289.61)	0.35
Blood loss (mL)	210 (150-450)	200 (150-525)	0.69	200 (112.5-575)	210 (175-475)	0.56
Type of anaesthesia (%)						
General	10 (90.9)	9 (64.3)	0.18	12 (75)	7 (77.8)	1.00
Regional	1 (9.1)	5 (35.7)		4 (25)	2 (22.2)	
Operation type (%)						
Femur fracture fixation surgery	4 (36.3)	6 (42.8)	0.18*	8 (50)	2 (22.2)	0.34*
Abdominal laparotomy	7 (63.6)	5 (35.7)		6 (37.5)	6 (66.6)	
Total knee replacement	0 (0)	3 (21.4)		2 (12.5)	1 (11.1)	
Preoperative blood results						
Haemoglobin (g/dL)	12 (10.3-13.3)	11.5 (9.35-13.1)	0.61	12.25 (10.67-13.27)	10.30 (9.30-11.90)	0.08
White cell count (×10^9/L)	7 (6.12-9.24)	8.85 (7-11.73)	0.13	8.18 (6.72-9.53)	8.84 (6.12-12.2)	0.76
Platelet count (×10^9/L)	255 (224-335)	256 (227.75-312.5)	0.94	270.50 (234.50-324.75)	249.00 (224.00-353.00)	0.59
Serum creatinine (μmol/L)	71 (57-109)	64 (43-96.5)	0.32	62.00 (46.50-85.25)	105.00 (59.00-177.50)	0.06
Preoperative medical status (%)						
MMSE	26 (20-28)	21.5 (19.75-25.5)	0.50	23 (20-27.7)	22 (19.5-26.5)	0.80
Diabetes mellitus	0 (0)	5 (35.7)	0.04	3 (18.7)	2 (22.2)	1.00
Hypertension	5 (45.4)	12 (85.7)	0.08	13 (81.2)	4 (44.4)	0.09
Ischaemic heart disease	3 (27.2)	1 (7.1)	0.29	1 (6.2)	3 (33.3)	0.11
Chronic renal failure	0 (0)	2 (14.3)	0.49	0 (0)	2 (22.2)	0.12
Stroke	1 (9.1)	2 (14.3)	1.00	3 (18.7)	0 (0)	0.28
Congestive heart failure	0 (0)	1 (7.1)	1.00	1 (6.2)	0 (0)	1.00
ASA grade (%)						
1	0 (0)	0 (0)	0.07*	0 (0)	0 (0)	0.01*
2	5 (45.4)	10 (71.4)		13 (81.2)	2 (22.2)	
3	6 (54.5)	2 (14.3)		2 (12.5)	6 (66.7)	
4	0 (0)	2 (14.3)		1 (6.3)	1 (11.1)	
Home medication (%)						
Aspirin	1 (9.1)	4 (28.6)	0.34	2 (12.5)	3 (33.3)	0.31
Clopidogrel	0 (0)	1 (7.1)	1.00	1 (6.3)	0 (0)	1.00
Statins	6 (54.5)	4 (28.6)	0.24	6 (37.5)	4 (44.4)	1.00
Β blocker	3 (27.2)	2 (14.3)	0.62	2 (12.5)	3 (33.3)	0.31

Median (interquartile range) was reported for continuous variables and count (%) for categorical variables; The Mann–Whitney U-test was used to compare continuous variables; The Fisher exact test was used for categorical variables except for variables indicated by *Chi-square test was used. HB – High baseline cerebral oxygenation; LB – Low baseline cerebral oxygenation; AUC – Area under the curve; BIS – Bispectral index; MAP – Mean arterial pressure; SpO_2 – Peripheral oxygen saturation; ASA – American society of Anaesthesiologists; MMSE – Mini-mental state examination

Previous studies[5,10,16] have found an association between low cerebral oxygenation and adverse post-operative outcomes but not an association between baseline oxygen saturation and the incidence of intraoperative desaturation. We found that patients with a low baseline cerebral oxygen saturation (<55%) had a significantly higher incidence of cerebral desaturation episodes intraoperatively compared

Table 2: Study outcomes compared between participants based on frailty and baseline cerebral oxygen saturation

Outcome	Non-frail (*n*=11) (%)	Frail (*n*=14) (%)	Odds ratio (CI) of outcome in frail	*P*	HB group (*n*=16) (%)	LB group (*n*=9) (%)	Odds ratio (CI) of outcome in LB group	*P*
Significant cerebral oxygen desaturation	0 (0)	6 (42.8)	1.75 (1.11-2.75)	0.02	1 (6.25)	5 (55.5)	2.10 (1.00-4.42)	0.01
Composite outcome	2 (18.2)	2 (14.3)	1.27 (0.21-7.65)	1.00	0 (0)	4 (44.4)	1.80 (1.00-3.23)	0.01
Hospital acquired infection	1 (9.1)	1 (6.2)			0 (0)	2 (22.2)		
Cardiac complications	1 (9.1)	1 (6.2)			0 (0)	2 (22.2)		
Delirium	1 (9.1)	1 (6.2)			0 (0)	2 (22.2)		
TOLOS (days)	8 (6-11)	13.5 (8.75-27.50)		0.03	9 (6.25-13.75)	15 (9-31.5)		0.049
POLOS (days)	7 (5-8)	9.5 (6.75-16.25)		0.02	6.5 (5.25-10.5)	10 (7.5-15.5)		0.049

Median (interquartile range) was reported for continuous variables and count (%) for categorical variables. The Mann–Whitney U-test was used to compare continuous variables; The Fisher exact test was used for categorical variables. HB – High baseline cerebral oxygenation; LB – Low baseline cerebral oxygenation; TOLOS – Total length of hospital stay; POLOS – Postoperative length of stay; CI – Confidence interval

to patients with a higher baseline cerebral oxygen saturation and significantly poorer post-operative outcomes including longer lengths of hospital stay. Our results suggest that measurement of cerebral oxygen saturation could improve perioperative patient care in three important ways. First, pre-operative cerebral oxygen saturation can be used to risk stratify patients. Second, application of intraoperative cerebral oximetry will allow for detection of previously unrecognised cerebral desaturation episodes that can be treated intraoperatively to improve the likelihood of a successful outcome. Finally, it would allow for better planning and resource allocation by healthcare professionals to improve post-operative care.

This is the first study to explore the relationship between frailty, intraoperative cerebral oxygen desaturation and adverse post-operative outcomes in patients undergoing non-cardiac surgery. It provides new evidence regarding the effect of intraoperative cerebral oxygen saturation on post-operative outcomes after non-cardiac surgery. It also provides preliminary data that can be used to design future interventional studies.

Our study has some limitations. The study is observational and not interventional. It has a small sample size (pilot study designed to explore a previously un-investigated relationship between frailty, cerebral oxygenation and adverse post-operative outcomes). It was conducted on a relatively heterogeneous group of surgical procedures undergoing both general and regional anaesthesia. We did however, find no statistically significant difference in the surgical case mix or blood loss between the study groups. Moreover, the heterogeneity of the surgical procedures can be argued to increase the widespread applicability of the results. Since only regional cerebral oxygenation can be measured using a conventional cerebral oximeter, it can be argued that it may not reflect global cerebral oxygenation. The incidence of post-operative cognitive dysfunction was not measured in this study (the study was not designed to address this question). Patients with a LB had a significantly worse American Society of Anesthesiologists' physical status grade. This could have affected the incidence of adverse post-operative outcomes.

CONCLUSION

Our results suggest that frail elderly patients are more likely to experience intraoperative cerebral desaturation episodes and are likely to have a longer duration of hospital stay.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX 1

In our study we used the Survey of Health, Ageing and Retirement in Europe (SHARE) frailty instrument (a modification of the original fried criteria). The SHARE frailty instrument, which was developed in a large cohort of elderly individuals, has also been validated against frailty assessment based on comprehensive geriatric assessment. Similar to the Fried criteria for frailty, the share frailty index has the following parameters:

Exhaustion identified as a positive response to the question: 'In the last month, have you had too little energy to do the things you wanted to do?'. A positive answer (yes) was re-coded as 1, and no was re-coded as 0.

The weight loss criterion was fulfilled by reporting a 'Diminution in desire for food' in response to the question: 'What has your appetite been like?' or, in the case of a non-specific or uncodeable response to this question, by responding 'less' to the question: 'So, have you been eating more or less than usual?'. The presence of the criterion was coded as 1 and its absence as 0.

Weakness was assessed by handgrip strength (kg) using a dynamometer. Two consecutive measurements were taken from the left and right hands. The highest of the four was selected. This variable was kept continuous.

Slowness was defined as a positive answer to either of the following two items: 'Because of a health problem, do you have difficulty (expected to last more than 3 months) walking 100 metres?' or '. climbing one flight of stairs without resting?'. One or two positive answers received the score of 1, and two negative answers received the score of 0.

The low activity criterion was assessed by the question: 'How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or doing a walk?' This variable was kept ordinal: 1= 'more than once a week'; 2= 'once a week'; 3= '1 to 3 times a month' and 4= 'hardly ever or never'.

The results of the above questionnaire were input into two web-based frailty calculators (one for each gender) that are accessible on BioMed Central Geriatrics (http://www.biomedcentral.com/14712318/10/57/additional) to generate the presence of frailty in an individual.