Preoperative cognitive dysfunction in older patients at a central hospital

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Declaration

I, Leandra Anastasia Amado declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

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Abstract

Background

Cognitive decline following surgery includes delirium and postoperative cognitive dysfunction. Important risk factors for these include increased age and pre-existing cognitive dysfunction. This study describes preoperative cognitive dysfunction and its associated factors in patients ≥ 60 years old awaiting elective non-cardiac surgery at Chris Hani Baragwanath Academic Hospital.

Methods

A prospective, contextual, descriptive study design with consecutive convenience sampling was used. Assessment of cognition was subjective (through casual conversation) and objective (using the Mini-Cog test).

Results

A total of 194 outpatients (median age: 65 years) were assessed. A score ≤ 3 was obtained by 111 patients (57.2%). The subjective assessment of cognition was shown to be poor in comparison (sensitivity 47.8%; specificity 70%). Univariate analyses demonstrated significant associations between low Mini-Cog scores and increasing age ($r_s = -0.1901$; $p = 0.0079$), unskilled occupation ($p = 0.0033$), low functional status ($r_s = -0.1831$; $p = 0.0106$), low level of education ($p = 0.0005$) and frailty ($r_s = -0.3010$; $p < 0.0001$). Logistic regression showed level of education and frailty to be significant. Patients with grade 11 to tertiary education are 71.8% less likely to obtain a score ≤ 3 (OR: 0.2820; $p = 0.0034$), and frail patients are 7.54 times more likely to obtain a score ≤ 3 than a robust patient ($p = 0.0026$).

Conclusion

This study found undiagnosed pre-existing cognitive dysfunction to be common in older patients awaiting surgery at Chris Hani Baragwanath Academic Hospital. These “brains at risk” should be identified through brief preoperative screening.

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List of abbreviations

CAGE	Cut down, annoyed, guilty, eye-opener
CD4	Cluster of differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
COPD	Chronic obstructive pulmonary disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
FRAIL	Fatigue, resistance, ambulation, illness, weight loss
GLUT1	Glucose transporter 1
GOPD	Gynaecology Outpatients Department
Gp120	Glycoprotein 120
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
Il-2 / Il-6	Interleukin-2 / interleukin-6
LA	Leandra Amado
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
OPD	Outpatients Department
PHQ-2	Patient health questionnaire-2
PLWH	People living with HIV
POCD	Postoperative cognitive dysfunction

RNA	Ribonucleic acid
SOPD	Surgical Outpatients Department
Tat	Trans-Activator of Transcription

Section 1: Literature review

1.1 Introduction

The normal aging process is accompanied by a decline in a number of cognitive abilities. Older adults who present for surgery may exhibit further postoperative cognitive decline relative to their preoperative level of functioning. This cognitive morbidity may include delirium and postoperative cognitive dysfunction, both the incidence and the associated consequences of which are significant (1, 2). In addition to increasing age, pre-existing cognitive impairment is a risk factor for these complications (3). The high prevalence of undiagnosed pre-existing cognitive deficits shown in other studies suggests that routine preoperative cognitive screening should be done (4-6). This would impact on the process of informed consent, allow for more accurate risk assessment, and catalyse interventions both intraoperatively and postoperatively to reduce the negative impact of surgery on this vulnerable population. Strategies may include the use of fewer opioids and hypnotics, less invasive surgery (3), and the use of anti-inflammatory drugs such as meloxicam, which inhibits surgery-induced neuroinflammation and preserves object recognition postoperatively (7). This review will explore the mechanisms of normal cognitive aging, describe factors which influence the trajectory of this decline, discuss cognitive testing, critically examine other studies which have looked at the prevalence of pre-existing cognitive dysfunction in older adults, and finally discuss the anaesthetic relevance of preoperative cognitive dysfunction.

1.2 Mechanisms of normal cognitive aging

Jan Baars reflected that the effect of aging on the brain has inspired writing since the time of Solon, a sixth century BC poet who described the stages of life as periods of seven years: “… in the ninth, though he’s still capable, his tongue and expertise have lost some of their force” (8).

The normal aging brain undergoes changes at both a structural and functional level, some of which are difficult to distinguish from the pathological changes of neurodegenerative disease (9). Loss of grey matter (10, 11), not as a result of cell

death but rather due to a decrease in synapse density (12) occurs. This decrease in synapse density occurs steadily between the ages of 20 and 100 years (13) and disrupts major neural circuits (9). Similarly, there is also a loss of white matter, which has been implicated in deficits of executive function (14).

The resultant volume changes of structures within the brain (a measure of both thickness and area) have been investigated. Changes associated with the normal aging process include loss of volume in the prefrontal cortex and medial temporal structures (11, 15, 16). The prefrontal cortex, particularly in the lateral regions, declines linearly at an average rate of 5% per decade over the age of 20 years (17, 18). The result of this decline is a picture similar to that of frontal lesions: failure to suppress interfering information, perseveration and poor working memory capacity (15, 19).

The striatum experiences smaller volume losses with aging – 3% per decade in one cross-sectional study (20). It has connections to the prefrontal cortex and is responsible for dopamine production (9), a neurotransmitter which itself undergoes age-related changes: concentration decreases (21), and there is diminished transporter and receptor availability (22). Dopamine has been shown to be more important than chronological age for aspects such as processing speed and episodic memory, with one animal study demonstrating a reduced rate of cognitive decline when dopamine was administered to monkeys (23). The hippocampus experiences only small changes in normal aging, which affect declarative memory (17, 24). In pathological states such as Alzheimer's disease, hippocampal changes can be greater. The "perforant path" is a key interconnection between the hippocampus and the neocortex, and is most vulnerable to pathological changes such as neurofibrillary tangles, a prominent feature of Alzheimer's disease (25). The perforant path originates in layer II of the entorhinal cortex, an area which "funnels" information into the dentate gyrus (26). Its destruction essentially "cripples" hippocampal memory.

On a functional level, there is loss of cortical excitability, reduced cerebral blood flow (a measure of neural activity) and reduced plasticity (9).

Both structural and functional changes in the aging brain result in an overall decline in certain cognitive abilities, even in the absence of pathology (9). However, there is

“variable vulnerability” with some declines occurring during the entire adult lifespan and others occurring late in life (9); still others remain relatively stable even in centenarians (27).

These life-long declines occur in processing speed, working memory, and encoding new memories. The rate of decline of these abilities becomes more rapid with time, accelerating 3 – 6 years prior to death (28, 29). Hedden and Gabrieli (9) postulate that this could be due to the influence of disease processes. Links have also been drawn between sensory function, which worsens with age, and cognition; visual impairment in the elderly is associated with impaired cognitive function (30, 31).

Other types of cognitive decline occur only later in life. These include well-practised tasks, semantic knowledge – which older adults use to form more efficient strategies during task performance (32, 33) – vocabulary (34) and short-term memory, which drops sharply at ages greater than 70 years (35).

The question of whether these age-related memory deficits may persist despite environmental support has been explored, with disparate findings (36, 37). The healthy aging brain attempts to compensate for the loss of these functions by activating brain regions that are not recruited by younger patients doing the same task (38).

Abilities which remain relatively stable throughout life include autobiographical memory, emotional processing – though changes in the amygdala result in the selective processing of positive input (39) – “theory of mind” tasks, which is the “ability to attribute independent mental states to self and others” (40), automatic memory – even when effortful recall fails (41) – and implicit memory (42).

All these changes occur in the normal aging brain; however, other factors may interact with the structural and functional changes described and alter the trajectory of these changes.

1.3 Factors influencing cognition

There are numerous factors which influence cognition. These include comorbidities, medications, alcohol use, psychological factors such as anxiety and depression, hospitalisation, frailty and functional status.

1.3.1 Comorbidities

Unfavourable associations have been shown between several chronic medical conditions and cognition. This is particularly true in multi-morbidity, or the presence of two or more chronic diseases. As this occurs in 23.2% of adults, it will be increasingly relevant in older adults, making this an important topic to examine (43).

Cerebral- and cardiovascular disease

The brain is dependent on a continuous blood supply to match the energy requirements of its cells. This is ensured by a sophisticated control of blood flow in the face of a range of blood pressures, a concept termed autoregulation (44). Autoregulation relies on an intact endothelium to release nitric oxide, endothelin and prostanoids in response to both mechanical signals (such as sheer stress) as well as chemical ones (45, 46). Excessive free radicals result in endothelial dysfunction (impaired vasorelaxation and apoptosis), causing leakage from vessels, protein extravasation and inflammation (46, 47). This eventually leads to demyelination of axons, loss of the energy-efficient mode of signal transmission called saltatory propagation, higher metabolic demands in the brain and, as blood supply has not increased, hypoxia (48). Disruption of the blood brain barrier, brain dysfunction and tissue death (infarction) may occur (46).

Cerebral infarction, or stroke, is common in older people. The risk of dementia is approximately 10% after a first stroke. Chronic macroscopic infarcts have been found in up to half of older people by clinical pathologists (49). This has been noted by Gorelick et al (46) to be significantly greater than the incidence of diagnosed clinical stroke. In the community, however, multiple microscopic infarcts are even more common (49). Atrial fibrillation is an important risk factor for cerebral infarcts, particularly in patients not on anticoagulation (50). Atrial fibrillation is also more common in older people – the incidence doubles for each decade of life (51). Studies disagree on whether atrial fibrillation is an independent risk factor for cognitive dysfunction (52, 53).

Cognition is affected by vascular pathology in areas other than the brain. Increased coronary artery calcium as seen on radiological imaging, representing atherosclerosis in the vessels supplying the heart (54), and a low ankle-brachial

index (a measure of peripheral vascular disease) are both associated with increased risk of cognitive impairment (55, 56).

Risk factors for vascular disease are themselves associated with cognitive impairment. Midlife hypertension and total cholesterol are important modifiable risk factors for late-life cognitive decline, although findings are less clear in late-life cohorts (57, 58).

Finally, low cardiac output, resulting from cardiac failure, is also associated with cognitive dysfunction, particularly in executive tasks such as sequencing and planning. This has been attributed to chronic hypoperfusion (59, 60).

Diabetes mellitus

Diabetes mellitus, characterised by either chronically low insulin secretion or insulin resistance, is a common chronic condition in older people (61). The association between diabetes and cognitive dysfunction has been shown to affect learning and memory, mental flexibility and mental speed (62). Furthermore, an accelerated rate of decline in diabetics has been highlighted. This is particularly unfortunate, given that normal cognition is paramount to self-management of diabetes (63, 64).

The pathways leading to cognitive dysfunction in older diabetics may stem directly from poor glycaemic control: both recurrent episodes of hypoglycaemia, and chronic hyperglycaemia, are implicated. Prior in-hospital diagnosis of hypoglycaemia results in a three-fold increase in the risk of dementia (65). Hyperglycaemia produces advanced glycated end products, to which the endothelium of blood vessels is particularly vulnerable (66). This results in reduced cerebral blood flow. When better glycaemic control is restored, this altered cerebral blood flow resolves (67). White matter damage (68), inefficient glucose utilisation during cognitive tasks (69), and comorbidities associated with diabetes (70) have also been implicated in cognitive dysfunction in the diabetic population.

Independent associations are shown between cognitive dysfunction and onset of diabetes at ages below 65 years, longer duration of diabetes, presence of micro- and macro-vascular complications, and treatment with insulin (71). Treatment with insulin may worsen cognition as it inhibits synaptic activity in the brain, promotes the

development of amyloid plaques, causes decreased production of enzymes which degrade insulin, and contribute to episodes of recurrent hypoglycaemia (72, 73).

Thyroid disease

The thyroid gland is an endocrine organ producing thyroxine and triiodothyronine under the stimulation of thyroid stimulating hormone (TSH) (74). Thyroid hormones and TSH play roles in the normal development and functioning of both the foetal and adult brain (75). Abnormalities in thyroid hormone production may alter cognition (76).

An increased risk for dementia has been shown both in patients with hyperthyroidism and hypothyroidism: in hyperthyroidism, it is postulated that high levels of thyroid hormone induce amyloid deposition, neuritic plaques and result in smaller hippocampal volume (77-80); in hypothyroidism, concentration and perception are altered (81). A slight rise in TSH occurs as part of normal aging (82); however, further increases in excess of these norms herald the presence of hypothyroidism. Hypothyroidism is prevalent in older patients – and may even occur subclinically, where TSH is raised but free thyroid hormone levels are still within normal range (83), in as many as 20% of this age group (84).

Shrestha et al. (75) showed that cognitive dysfunction in thyroid disease predominantly affects visuospatial function.

Hypoxia

Hypoxia, or reduced oxygen supply at a tissue level, is responsible for the activation of the hypoxia-inducible factor transcription system (85). This system results in transcription of hundreds of genes, the activities of which are geared toward cell survival in the face of hypoxia. These include regulators of glucose transport such as GLUT1, glycolysis, oxygen transport and angiogenesis (85). Cell survival is diminished in aging cells in the face of hypoxia (86).

Anaemia

The red blood cell is responsible for delivery of bound oxygen. Critical oxygen delivery is that amount below which oxygen supply is inadequate for demand; this

can be detected by systemic measures. Van Woerkens et al. (87) found critical oxygen delivery in an 84-year old male under general anaesthesia to be 4.9 ml/kg/min, the equivalent of a haemoglobin concentration of 4g/dl. Central nervous system dysfunction, however, occurs at much higher haemoglobin concentrations than this and acute isovolaemic anaemia may result in cognitive impairment in even healthy non-surgical patients (88); effects may be greater in the elderly. In patients undergoing major surgery where blood loss is inevitable, a low preoperative haemoglobin concentration is associated with potential postoperative cognitive dysfunction (89).

Obstructive sleep apnoea

Obstructive sleep apnoea is a breathing disorder of sleep (90). Its prevalence increases to more than 60% in the obese and the elderly populations (91). Despite this higher prevalence in older patients, sleepiness is reported less frequently in this group as a flagging symptom (91).

The hallmark of obstructive sleep apnoea is intermittent hypoxia and is analogous to repeated ischaemia and reperfusion, which results in the generation of excessive reactive oxygen species (90, 92). The resultant cognitive deficits – impaired attention, memory and executive function – are partially reversed with the application of continuous positive airway pressure (93).

Respiratory pathology

Hypoxia is similarly linked with cognitive impairment in patients with severe asthma and chronic obstructive pulmonary disease. A longitudinal study by Chyou et al. (94) found that a low forced expiratory volume at one second is an independent predictor of cognitive dysfunction, and Schou et al. (95) further showed that the severity of the COPD is associated with worsening cognition (95). Arterial oxygen tensions normally range between 80 and 100 mmHg. Hypoxaemia need not be severe for cognition to be affected; cognitive impairment may result from low but still normal arterial oxygen tensions (96).

Human immunodeficiency virus

Cognitive dysfunction is associated with human immunodeficiency virus (HIV). With increased availability of highly active antiretroviral therapy (HAART), people living with HIV (PLWH) can expect a near-average life-expectancy (97) and will progressively cross into the realm of geriatric medicine (98). It has been postulated that HIV, as well as HAART, may hasten the aging process via mechanisms that increase oxidative stress and promote telomere shortening and mitochondrial dysfunction (99, 100).

Between 30 and 50% of treated PLWH have HIV-associated neurocognitive disorders (101). Deficits include those of memory, verbal fluency, processing speed and executive function (102). Furthermore, people with HIV-associated neurocognitive disorders have reduced compensatory mechanisms and are less able to recruit alternative brain networks (103).

It has been postulated that PLWH have decreased cognitive reserve (103). Chang et al. (104) suggest that genes associated with increased risk of cognitive deficit (such as ApoE4) might cause more severe deficits in PLWH; while other authors have investigated structural changes. Such changes include increased white matter hyperdensities (105), nigrostriatal dopaminergic structural alterations, including neuronal loss in the substantia nigra (106) and apoptosis of striatal neurons caused by HIV neurotoxic proteins Tat and Gp120 (107), and white matter loss with subcortical atrophy (108).

There is conflicting data as to whether these alterations might be explained by high viral loads. Guha et al. (109) demonstrated loss in resting state functional connectivity, a non-invasive means to measure brain function, in PLWH who had detectable plasma HIV RNA loads. Cole et al. (110), however, showed increased brain aging in PLWH despite viral suppression. Cerebrospinal fluid loads may, in fact, be more important than plasma RNA loads in cognition (111); however, evidence does not support HAART regimens with greater central nervous system penetrance (112).

Nadir CD4 count has also been examined and lower nadir counts are associated with worse cognitive function (113). Despite this, there is equivocal evidence for the effect of current CD4 count on cognition (101).

Tightly interwoven with cognition in PLWH, are other factors including inflammation and stress. These three entities are described by Valdez et al. (114) as a “Gordian knot”. Chronic inflammation in HIV results from the production of numerous cytokines including Il-2 and Il-6. This state eventually leads to glucocorticoid resistance and higher levels of basal cortisol (114). Cortisol influences numerous brain regions, notably the prefrontal cortex and the hippocampus, which are important for verbal memory (115).

The resulting decline in memory and other aspects of cognitive function in this population predicts adherence to medication and has other management implications (116).

Chronic kidney disease

Both cross-sectional and longitudinal studies have associated lower glomerular filtration rate with cognitive dysfunction (117). The prevalence of cognitive dysfunction is high in patients with stage 5 chronic kidney disease – or kidney failure, where glomerular filtration rate is less than 30 ml per 1,73m² – with only 12.7% of one sample exhibiting normal cognition (118). However, a patient does not need to be in renal failure to show cognitive decline: patients with stage 3 or 4 chronic kidney disease (where glomerular filtration rate is less than 60 ml per 1,73m²) already show poorer executive function and verbal memory (119).

In patients on dialysis, the type of dialysis used is important, with patients on continuous ambulatory peritoneal dialysis showing consistently better cognitive function than those on haemodialysis (120). This may be due to selection bias (with certain patients qualifying for either modality) or may point to phenomena specific to haemodialysis such as repeated episodes of hypotension during haemodialysis, microembolisation, and cerebral oedema as part of disequilibrium syndrome (121). Timing of testing relative to haemodialysis has also been shown to be important: cognitive function was worse at 67 hours post haemodialysis compared to at 1 and

at 24 hours post dialysis. This is most likely attributable to toxic uraemic metabolite accumulation (122).

The reasons for cognitive dysfunction in kidney disease are multiple. People with chronic kidney disease have a greater risk of subclinical cerebrovascular disease, or “silent stroke”. This may be related to high levels of homocysteine, coagulation abnormalities, inflammation, oxidative stress and secondary hypertension (46, 121). Non-vascular risk factors linked to cognitive decline in people with chronic kidney disease include anaemia (123), hyperparathyroidism (124, 125), polypharmacy, uncertainty around the correct dosing of drugs in the face of uncertain renal clearance and sleep disturbances (125, 126).

1.3.2 **Medication**

Not all medication prescribed to older patients is appropriate. Inappropriate drugs are prescribed to almost half of hospitalised patients, and have attendant complications such as confusion and falls (127). The Beers List, developed in 1991 and last updated in 2015 (with a 2018 update imminent), describes medicines best avoided in patients over the age of 65 (128, 129).

The list includes drugs which have reduced clearance in older patients, drugs causing orthostatic hypotension, hypoglycaemia, increased risk of falls, and altered cognition. Drugs that impair cognition include any medications with anticholinergic properties (antihistamines, antipsychotics, antidepressants, skeletal muscle relaxants, certain antiarrhythmics, antiemetics and antimuscarinics). Benzodiazepines are also to be avoided for their effect on cognition in older people (129).

Some authors argue that the number of drugs prescribed concomitantly (polypharmacy) is a more important contributor to these adverse effects than the type of drug alone (130).

1.3.3 **Alcohol**

Chronic dependent alcohol use (which is combined with abuse into a single term, alcohol use disorders in the DSM-V) may result in Wernicke-Korsakoff syndrome, alcoholic dementia (131) and brain atrophy (the most vulnerable regions in heavy

drinking being the frontal lobes). Deficits in executive functions and memory could result, as reviewed extensively by Oscar-Berman et al. (132). Furthermore, alcohol impairs the ability of a person to accurately assess their own cognitive capability (133). These cognitive deficits may persist even with long-standing abstinence (134), and due to the dynamic course of chronic dependent alcohol use may not be demonstrable in all users at a point in time (135, 136). Potential mechanisms include direct neurotoxicity due to ethanol and its metabolite acetaldehyde (137); nutritional deficiencies associated with ethanol abuse, such as folate and thiamine deficiency (138); liver damage and events such as head trauma (139). Chronic alcohol use is a known risk factor for postoperative delirium (140), as well as postoperative cognitive dysfunction (141).

Cognitive deficits may also be caused by moderate non-dependent alcohol use, however. A decrease in total brain volume (142), increased ventricle size (143) and grey matter atrophy (144) have been found by some cross-sectional studies; while others still have found no such changes (145), or only when greater amounts of alcohol are consumed (146). Findings regarding white matter changes are equally inconsistent (143, 147).

A longitudinal study spanning 30 years found hippocampal atrophy and impaired white matter microstructure with moderate alcohol use (here defined as 14 to <21 units per week in men) that appears to be dose-dependent. As alcohol consumption increases, spelling-based fluency, a frontal function, worsens, but word recall, which is a temporal function, does not. The study found no evidence of the protective effect of light alcohol use against dementia. The sample is not representative of our population, comprising mostly educated middle-class men; some CAGE questionnaire results (a mnemonic for “cut down, annoyed, guilty, eye-opener”) are missing from the data; and as with similar studies on alcohol use, there is the potential for under-reporting. As a result of its longitudinal design, there is also a “practice effect” over time. However, the large availability of magnetic resonance imaging data and detail on confounders (such as depression and premorbid intelligence quotient) still provide insight into the relationship between moderate alcohol use and cognitive outcomes in the same individuals over time (139).

1.3.4 **Anxiety**

Anxiety is defined by Eysenck et al. (148) as “an aversive emotional and motivational state occurring in threatening circumstances”. Worrying, ruminations and impaired working memory may occur – with or without a physiological response to the anxiety-inducing situation (149). This physiological response may include increased muscle tension and activation of the sympathetic nervous system (150). Resultant changes in heart rate are partly under the influence of the dorsal lateral prefrontal cortex, a region also extensively used in tasks which are cognitively challenging (151, 152). Thus the physiological response associated with anxiety possibly acts as “competition” for resources in that brain region which would otherwise be used for normal cognition (153). With this in mind, anxiety in older patients presenting for surgery may confound poor performance in a cognitive screen.

1.3.5 **Depression**

Overall prevalence of depression in older South Africans over a 12-month period is 4% (154). Significant risk factors include female gender, disability, bereavement, disturbed sleep, and prior depression (155). The temporal relationship between cognitive decline and depression is unclear: cognitive dysfunction may precede depression, or vice versa (156).

Cognitive deficits in depression have been reviewed extensively by Austin, Mitchell and Goodwin (157); they include declines in episodic memory, executive functioning and processing, as well as speed. Verbal recall is also impaired, but verbal recognition is normal. This suggests that patients with depression find difficulty with effortful rather than automatic tasks, although this has been refuted by other studies (157).

Possible reasons for these cognitive changes have been proposed, including a deficit in motivation (157), response bias, where patients require greater certainty before responding to a task, due to a low hedonic drive (158) and negative cognitive set, where patients experience stronger negative reactions to negative feedback (159). All of these affect performance. Improvement of mood may result in better cognitive ability (160), though deficits in certain domains may still be present even three months after recovery (161). This is confounded by medication and other

treatment modalities such as electroconvulsive therapy (162) as well as inadequate definitions of recovery (163).

Differentiating major depression from cognitive impairment may be difficult. People with major depressive disorder tend to underestimate their memory and may also report more subjective complaints of memory problems; whereas people with objective cognitive decline overestimate their cognitive performance (164, 165).

The 2-item Patient Health Questionnaire (PHQ-2) is a short screening tool for depression, which enquires after depressed mood and anhedonia, either by asking about frequency of symptoms (166, 167) or as yes/no questions spanning a 12-month period (168). Several studies have validated its use (166-168), finding high sensitivity (1.0 in one study comparing results to DSM-IV criteria for depression) and modest specificity (0.77) (168). While not validated for extremely frail patients, severe concurrent medical illness or side effects due to medication (169), the questionnaire may help detect patients who require further evaluation in a busy setting.

1.3.6 **The context of hospitalisation**

Admission to hospital has itself been linked to higher rates of incident dementia (170) and a greater rate of decline in people with prior cognitive dysfunction (171). Multiple factors are responsible, including immobility, lack of sensory aids, room changes, the use of Foley catheters, physical restraints, the absence of family members and contact precautions (172). Unfortunately the recognition of resultant cognitive impairment is poor by all members of the healthcare team (173).

1.3.7 **Frailty**

Frailty is described as a “pre-disability state” (174) in which patients possess decreased physiological reserve and resilience (175). Physical frailty is associated with incident cognitive impairment and a more rapid decline of cognitive function in older people (176). Instrumental activities of daily living, a short physical performance battery, gait speed, grip strength and a one-leg stand have been used to assess frailty. A short questionnaire called the FRAIL scale, however, correlates

significantly with these parameters and its predictive validity has been demonstrated in an African-American population (177).

The questionnaire, which does not require a physical exam, comprises five questions – one each on fatigue, resistance, ambulation, illness and loss of weight. Fatigue is assessed by the amount of time in the previous four weeks the patient felt tired, resistance by difficulty climbing 10 steps without aids or resting, and ambulation by difficulty walking a few hundred yards. It is noted if more than five medical conditions are present and if unintentional weight loss of at least 5% total body weight has occurred in the last 12 months. Each affirmative response scores one point. A patient is considered “robust” with no points, “pre-frail” with 1 – 2 points and “frail” with 3 – 5 (177).

1.3.8 **Functional status**

Similarly, functional status affects cognition in older people. Functional dependence not only predicts six-month mortality (178) but may be a more important factor than age (179). Functional dependence also predicts immobility and consequently increased risk of cognitive changes such as delirium (180). This can be rapidly assessed by the modified Rankin score (0 – 6 points) which ranges from a patient with no symptoms, through patients without disability despite symptoms, patients with slight disability, those who walk unassisted but require assistance with other tasks, those who walk with aids, to bedridden and incontinent patients who require full-time nursing care. The final score of six points characterises a patient who is deceased. Inter-rater variability for this score may be significant, but this is minimised by a structured interview or the use of a single rater (181).

1.4 Cognitive reserve

Factors which worsen cognitive function in older people have been discussed; however, there are also protective factors at play.

Cognitive performance may be retained to a degree, despite brain aging. The extent of this sparing may be attributed to the protective effect of cognitive reserve, which may explain how patients with similar structural brain changes (both extent and brain regions involved) exhibit such significant differences in cognitive change (182, 183).

Stern (182) describes possible subdivisions for reserve for convenience: passive and active reserve.

Passive reserve is defined as the “amount of damage that can be sustained before reaching a threshold for clinical expression” (182). As reserve is a hypothetical construct, a potential “proxy” for, or more tangible example of, passive reserve is brain size, with the implication that a larger intracranial volume would allow for greater volume loss before cognitive deficits may appear. Synapse count and head circumference have also been described to represent passive reserve (182). Passive reserve is supported by some studies (184, 185), but not others (183, 186). It is likely insufficient on its own to explain all aspects of reserve (182).

Active reserve, on the other hand, involves “differences in how a task is processed” (182). This includes the ability to use more efficient brain networks (normal in the healthy brain carrying out a task) and to recruit alternate neuronal structures as compensation (182). Proxies for this include education, occupation and premorbid intelligence quotient. A study examining cognitive reserve by assessing changes on magnetic resonance imaging in the same patients at 11 years of age and 78 – 80 years of age supports the active hypothesis by showing that more education and more cognitively complex occupations predict greater cognitive ability in older patients than foretold by the patients’ childhood abilities. The study shows a relationship between memory and education, memory and occupation, reasoning and occupation, but not reasoning and education (183).

The two divisions of reserve do not preclude one another; education, for example, may dynamically influence brain matter (182). New, functioning neurons are developed continuously even in the adult brain (187), and this is increased by an enriched environment (188).

Socio-economic status confounds these interactions, as does neighbourhood context. This was explored by Wight et al. (189), who suggest that those living in lower-income or lower-education areas may be exposed to more hazards, have fewer safe physical resources, such as well-lit pavements and parks, and have fewer social and stimulating resources, such as libraries (189). Both physical activity (190) and social support (191) have been shown to affect cognition.

1.5 **Tests of cognition**

Identification of patients with cognitive dysfunction is possible through a variety of different screening tests. The ideal cognitive screening tests should be quick to administer (which makes it more acceptable in busy clinics or wards), tolerated by patients, have a simple scoring system, be both high in sensitivity and specificity, should have good inter-rater reliability and be relatively independent of language, culture and education (192). The Mini-Cog test meets these criteria. The Mini-Cog test was developed by Borson et al. (193) in 2000, and combines a delayed recall test of three words and a clock-drawing test.

The clock-drawing component is conducted by asking the patient to set time on a circle, representing a clock face. This circle may be pre-drawn, though there may be value in observing the patient draw their own free-form circle, according to some authors (194). The time set varies but the most frequently used time (11:10) is useful in that it assesses for an error found in subtle impairment: inhibition of “frontal pull” towards 10. The original “ideal” scoring algorithm would first look at recall of three words given to the patient prior to the clock-drawing test: patients recalling none of the words are classified of demented, those recalling all three words are classified as non-demented, and those recalling 1 – 2 words are classified based on their clock-drawing test (either normal or abnormal) (193). A subsequent description of scoring allocated 0 – 3 points for words recalled and either two points, for a normal clock, or no points, for an abnormal one, for a total score out of five (195). Abnormalities include omissions, perseveration, rotations, and substitutions (192).

The clock-drawing test assesses a variety of functions despite its brevity: comprehension, planning, visual memory and reconstruction, visuospatial abilities, motor programming and execution, numerical knowledge, abstract thinking, concentration and frustration tolerance (192).

The clock-drawing test alone has a sensitivity of 79% (196). While this has been described as acceptable for a first-level screening test, it lacks the ability to assess new learning, which is pivotal for the diagnosis of dementia (193). The effectiveness of the clock-drawing test is increased in the Mini-Cog, when tested by Borson et al. (193), by the addition of a memory task, resulting in greater diagnostic value (96%),

high sensitivity (99%) and a specificity of 93%. These values were supported by subsequent post hoc diagnoses (193).

The Mini-Cog avoids many of the pitfalls presented by other available cognitive screens such as the Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination. It is not affected by age, education level, or language bias; it requires neither specialised equipment nor training to administer (197); and has a short administration time (193) of 3.7 ± 2 minutes for demented patients and 2.5 ± 1 minutes for non-demented patients. This shorter administration time has significant cost implications (193). Borson et al. (193) notes that the test offers a "visible performance indicator" in the clock face.

Importantly, however, the Mini-Cog serves as a screen only; further criteria-based diagnoses need to be made for management purposes and to prevent unnecessary distress for the patient (193). An additional consideration is that there may be varying interpretations of the Mini-Cog score based on the examiner's judgement of whether a clock is normal or abnormal; despite this concern, inter-rater agreement (when researchers were compared to test-naïve assessors) was found to be 90% (193).

1.6 **Prevalence of pre-existing cognitive dysfunction**

Several other studies have investigated the prevalence of pre-existing cognitive dysfunction in older surgical patients and have found it to be wide-ranging.

The highest prevalence (68.0%) was found in a study by Partridge et al. (6); this is explained by the use of a study population comprising only vascular patients presenting for either elective or emergency aortic or lower limb arterial interventions. The risk factors for peripheral vascular disease (hypertension, hypercholesterolaemia and smoking) are also risk factors for cognitive dysfunction, as discussed previously (6).

Partridge et al. (6) used the MoCA as a cognitive screen, which is well validated for use in patients with vascular disease. The sample comprised 114 patients over the age of 60 years (a lower cut-off than most other studies in older patients, but with a mean age of 76.3 years) in an urban setting, with a mean length of full-time

education of 10.6 years. The majority of the sample (67.5%) was male and white (89.0%) (6) which is not representative of our own population.

While independent associations between low MoCA scores (<24) and frailty as well as diabetes were found, there was a lack of association between older age (>80 years) and low MoCA scores. Partridge et al. (6) suggest this may be due to increased mortality at younger ages as a result of vascular risk factors. The effect of aging is apparent in other studies, however. Smith and Yeow (198) demonstrate that 80% of patients in their eighth decade have cognitive dysfunction; and Robinson et al. (199) show large increases in incidence per decade of age (17% in patients in their sixties, 52% in their seventies, 63% in their eighties, and 100% of patients in their nineties).

The high prevalence demonstrated by Partridge et al. (6) may not be seen, however, in a more general surgical population. For example, Evered et al. (5) used a sample of 152 orthopaedic patients presenting for elective total hip replacement only. They have found a much lower, but still significant, prevalence of 20% for pre-existing cognitive impairment. Interestingly, Evered et al. (5) also assess for mild cognitive impairment (MCI), in which a patient has demonstrable cognitive deficits but there is also a subjective report of memory complaints (5). None of the other anaesthetic literature identified examines this subjective complaint. It is relevant, however, because amnestic MCI shows a rate of conversion to Alzheimer's disease of 10 – 15%, compared to 1 – 2% in patients without amnestic MCI (200). Evered et al. (5) found a prevalence of 22% amnestic MCI in this sample. A number of tests were performed to assess multiple domains of cognitive function. These tests were conducted by trained assessors under the supervision of a neuropsychologist (5). While this ensures sensitivity to impairment in a range of domains, such testing is impractical in our own busy setting.

Another study, by Silbert et al. (201), uses a similarly lengthy test battery, also in patients for elective hip replacement. While a larger sample of 300 patients was used, much younger patients were included (over 40 years) and contributed to a prevalence of pre-existing cognitive dysfunction of 32% (201).

One study specifically sought to determine whether the timing of cognitive testing relative to the time of surgery would affect results. Smith and Yeow (198) divided patients into two groups and did the MoCA on 113 patients on the day of surgery and on 102 patients in a preadmission clinic six weeks prior to their procedures. No significant difference was found between the two groups, with prevalence of 60% and 52% respectively (with a total of only 1.7% diagnosed previously). While this may have been an error related to sample size, it could also imply that either time frame provides an equally stressful cognitive load (198).

Not all studies found such high prevalence values; the study with the lowest prevalence (6.1%) by Silverstein et al. (202) employed the International Study of Postoperative Cognitive Dysfunction test battery in 1218 non-cardiac patients over 60 years old.

It is clear that these studies all exhibit wide differences in methodology, particularly the cognitive tests used and the various cognitive domains included, and most do not include the presence of subjective memory complaints. This makes comparisons difficult. The most important thing, it has been suggested, is not a single exact figure for pre-existing cognitive dysfunction, but rather that it is relatively common (198).

1.7 **Anaesthetic relevance**

Older patients undergo up to 30% of all surgical procedures (203). These patients face possible cognitive complications, particularly if they have pre-existing cognitive dysfunction. Awareness of this increased risk aids in the prediction of poor postoperative outcomes such as higher one-year mortality (204), increased length of hospital stay (2), increased medical costs (2), premature withdrawal from the workplace (204), and a change in long-term cognitive trajectory (205). The discussion between patients and treating physicians is also enriched: knowledge of the likelihood of these complications supports shared decision-making and informed consent (3). Finally, a positive preoperative screen for cognitive dysfunction suggests interventions to reduce the risk of delirium and postoperative cognitive dysfunction in these already-compromised brains. These interventions span the perioperative period. Preoperatively, sedative premedication should be avoided, electrolyte imbalances and dehydration corrected, polypharmacy rationalised (3),

and preoperative cognitive training, or prehabilitation, done (206). Intraoperatively, short-acting agents should be used, hypotension and hypoxia avoided, minimally invasive surgical techniques employed, the length of the procedure kept as short as possible (3), and depth of anaesthesia monitoring used to maintain as superficial an anaesthetic as possible (207). The use of drugs to reduce neuroinflammation (7, 208) as well as a xenon-based general anaesthetic (209) has been suggested. Lastly, in the postoperative period, sensory cues and prompt analgesia should be provided, and sleep disturbances as well as a haematocrit < 30% avoided (3, 210).

1.8 **Conclusion**

The aging brain and the impact on cognitive processes by surgery and anaesthesia are important considerations for the anaesthetist. To fully quantify these relationships, adequate preoperative cognitive screening must be done on older patients. To the best of our knowledge, preoperative cognition has not yet been investigated in the South African context, or indeed in any developing region, and valuable information may yet be gleaned regarding prevalence of cognitive dysfunction and risk factors in our population. A resultant change in clinical practice may serve to reduce risk in these patients.

1.9 References

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Section 2: Author guidelines and draft article

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the Research Report in order to comply with the author guidelines for the journal to which it is intended to be submitted.

In this section the author guidelines that the researcher followed with regard to formatting the article are included and followed by the draft article. It is acknowledged that the page numbering is sequential and differs from the final article format. The journal to which this article is intended to be submitted is the British Journal of Anaesthesia.

BJA author guidelines

Manuscripts

For guidance, the requested size for articles is:

Clinical investigations: up to 3000 words and 30-40 references, 4-6 tables or figures.

Submissions which ignore this guidance on word count or number of figures/tables may be returned without being assessed. Authors wishing to submit manuscripts with figures/tables in excess of the recommended number should justify this in the submission letter.

For review articles and laboratory/clinical investigations it is possible to include supplementary data (such as additional references for a review, expanded tables of results or additional images for investigations) for on-line publication only. Authors should make clear in their submission letter which files are to be considered for on-line only publication.

Preparing your manuscript

The standard layout of a manuscript is:
• Title page
• Summary, including Keywords
• Introduction (not headed)
• Methods
• Results
• Discussion
• Details of authors contributions
• Acknowledgements
• Declaration of interests
• Funding
• List of references
• Tables (including legends to tables)
• Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page one, etc. Start each section on a separate page.

Title page

A separate page which includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. This is important as some search engines use the title for searches.

Therefore, it is best to avoid enigmatic or vague titles such as 'An unusual cause of hypotension'. Titles in the form of a question, such as 'Is propofol epileptogenic?' may be acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. Details of the authors' qualifications and post (e.g., consultant, senior lecturer) are not required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ([1][2][3] etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

All authors should follow the criteria for 'authorship' as determined by International Committee of Medical Journal Editors. For details, please refer to section on *British Journal of Anaesthesia* Policies.

A short running title containing not more than 50 characters (including spaces) should be included.

Summary (abstract)

The Summary (Abstract) will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the Abstract should not be structured.

The Abstract should give a succinct account of the study or contents, in up to 250 words. The Results section should contain data. It is important that the results and conclusion given in the Abstract are the same as in the whole article, as the Abstract may be used, as it stands, by abstracting journals. References are not included in this section.

Keywords

Three to five keywords should be included on the summary page under the heading Keywords. They should be in alphabetical order and must be classified according to MESH keywords. These can be found here. Please note that UK English spelling will be used for these. Please do not simply list words you think are key. For example, propofol should be listed as: anaesthetics i.v., propofol;

Introduction

The recommended structure for this section is;

- Background to the subject
- What is known / unknown about it
- What bit you are interested in / hypothesis

• Aim of your study

As a rule, the introduction to a paper should not require more than about 200 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. For example, a description and evaluation of an analgesic infusion as part of an intravenous anaesthesia regimen need not include an exhaustive account of the previous literature addressing the problems of intravenous anaesthesia and the many studies of different analgesics, etc.

The final paragraph should clearly state the primary and, if applicable, secondary aims of the study. If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

Methods

The Methods section should give a clear but concise description of the process of the study. Subjects covered in this should include:

• Ethics approval / licence
• Patient population
• Inclusion / exclusion criteria
• Conduct of the study
• Data handling
• Statistics
• (CTA)

Ethics approval / licence

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at http://www.wma.net/en/30publications/10policies/b3/. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If published research is subsequently found to be non-compliant it will be withdrawn or retracted.

On the basis of the Declaration of Helsinki, the *British Journal of Anaesthesia* requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

• The study was approved by the appropriate Ethics authority.
• Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the ethics committee.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information. Keep copies of ethics approval and written informed consents. In unusual circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

The title of this section should be 'Methods'. 'Materials and methods' or 'Patients and methods' should not be used. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). The manufacturer's town and country must be provided. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Patients

Data on the mean age (range), weight, sex, height, criteria for selection, etc. (*patient characteristics, not demographics*) should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Statistical analysis

Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value. A power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change.

Please note that a power analysis based on the primary end-point will not necessarily be applicable to any secondary measures.

It is recommended that authors seek appropriate statistical advice before starting their study, to ensure that the structure and planned recruitment is adequate to answer the question set.

Results

Guidance for this section includes;
• Must be factual
• Relate to aims
• Logical order
• State significances
• Negative findings

Description of experimental results should be concise. They should be presented in a factual manner and related to the aim of the study. It is often useful to present the results in the order described in the Methods section. Data should not be repeated unnecessarily in text, tables and figures (see below), and unwarranted numbers of digits should be avoided (Example: *the mean dose of propofol was 2.1 mg kg $^{-1}$ rather than 2.0897 mg kg $^{-1}$*). It may not be necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. Where appropriate, for example in a pharmacokinetic study, more extensive sets of data can be included as an appendix with the on-line version of the article. If authors wish to make use of this facility, they should state this in the submission letter and upload the data as a separate file. The editor has the right to request the original data collected. In the results section there should be no attempt at a discussion of the findings.

Tables and figures

Figures and Tables are often useful to present either complex or extensive data in a more easily understandable form. However, authors are cautioned against unnecessary use of tables and figures. A useful approach is to prepare the raw data in the form of tables and then decide which data are to be presented in the article. The author should then decide whether the essential data be presented succinctly in the text. If not, the essential tables/ figures should be prepared. To illustrate this with examples: *a study outcome which compares two measurements in two groups can easily be presented as text, a comparison of arterial pressure and heart rate changes at five timepoints in two*

groups would be appropriate as a table and the same measurements in comparing three groups may be better as a figure.

Tables and figures are important communications and should be accompanied by a legend which makes it self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

The use of a figure should be considered only where a figure will present the data more clearly than is possible in a table or when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

The authors should decide which form they wish to present data in. Please note the limitation given above on the number of figures/tables permissible for each article type. Duplication of data by including it as a table and as a figure is unnecessary and wasteful.

Authors are advised to note the limitation on the number of figures/tables given above (4-6 tables or figures, in total) for clinical and laboratory. The use of multiple small figures submitted as one figure (for example Figure 1 a-f) is discouraged as when reduced to printed size these may not be clear. Authors are strongly advised to be selective in their use of figures and tables.

For further guidance on the format of tables and figures, see below. It is recommended that the author refers to previous issues of the journal regarding appropriate style.

Discussion

This is an important part of the manuscript but it should not be too long, perhaps one third of the total length of the paper. This requires discipline by the author for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there.
It is suggested that the discussion should normally follow the pattern below:

• State main findings
• How do they fit in with previous studies
• Why are they different / same
• What it adds to knowledge of subject
• Weaknesses in study
• Future studies
• Conclusions

State main findings
This does not mean a repetition of all the results with their statistics. It should provide a concise

overview of the study. For example, ' *Drug X produced a greater haemodynamic change on induction of anaesthesia than occurred with drug Y, resulting in a greater fall in arterial pressure and a higher incidence of tachycardia* '.

How do they fit in with previous studies

This section should relate directly to the statements made in the Introduction and qualify you finding in relation to the previous studies of the subject. For example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.

Why are they different / same

Deductions which may explain important differences between the data of the present study, and the data of previous studies. The author should avoid excessive speculation in this section. It is quite reasonable to suggest possible explanations for your findings and any differences from previous studies but the 'missing parts' of such reasoning must be acknowledged.

What it adds to knowledge of subject

This can summarise the previous sections by pulling together the implications of your main findings, studies by other workers and their combined contribution to our knowledge of the subject. This should not be just another repetition of the results and preceding discussion but more of an expanded conclusion.

Weaknesses in study

It is appropriate to briefly acknowledge any limitations of your study at this point. Examples here could include the patient population, limitations of analytical tests, patients lost to follow-up. Authors are advised to be honest but succinct in this section.

Future studies

A logical follow on to the two previous sections is to identify future studies that would address some of the potential explanations and limitations discussed earlier. This should again be concise. An extensive list of future studies undermines you own study: i.e. has it answered anything if there are still so many questions?

Conclusions

Conclusions from the present study. The original contribution to knowledge from the present study is stated. A common fault here is to overstate the findings from a study. For example, *if you have studied the effect of a new drug in an animal model you cannot draw any conclusions at all about its effect in humans and likewise if you studied ASA 1 and 2 patients you cannot comment on its use in critically ill patients.*

It *may* be appropriate to give the implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.

Declaration of interests

It is essential to acknowledge all sources of financial assistance, and any potential material benefit expected from publication of the work. Also, please describe the role of the study sponsor, if any, in study design; collection, analysis and interpretation of data; writing the report; and the decision to submit the report for publication.

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The following rules should be followed:

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Please give initials of the names of each of the authors (i.e. R.D., I.K.M.) , and against their initials list the contributions which they individually made to the work (i.e. R.D. : Study design and data analysis; I.K.M.: Patient recruitment, data collection and writing up of the first draft of the paper).

Each author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity.

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- drafting the article or revising it critically for important intellectual content;
- final approval of the version to be published; and

- agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Acknowledgements

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References

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* and *Index Veterinarius* journals.

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It is a serious error to include in the list of references items which are not accurate. It is essential, therefore, that authors check the accuracy of all references which have been listed. It is important also to check that the references listed do indeed appear in the text and *vice versa*.

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● ○ ■ ⁜ ▼ ▲ ♦ ◊ V X +

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Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below).

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Particular problems have arisen in relation to the notation of units which was introduced at the same time as the change to the SI system. Avoid the use of the solidus (/) in favour of various units of the

expression set on one line. In the case of expressions 'below the line' superscript -1, -2, etc. as appropriate is given. Thus for drug dosage use mg kg^{-1} not mg/kg.

Spelling and grammar

Standard Oxford UK English should be used. Examples: *anaesthesia, haemorrhage, organization.*

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Draft Article

Preoperative cognitive dysfunction in older patients at a central hospital

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Running title: Preoperative cognitive dysfunction in the elderly

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Abstract

Background

Cognitive decline following surgery includes delirium and postoperative cognitive dysfunction. Important risk factors for these include increased age and pre-existing cognitive dysfunction. This study describes preoperative cognitive dysfunction and its associated factors in patients ≥ 60 years old awaiting elective non-cardiac surgery at Chris Hani Baragwanath Academic Hospital.

Methods

A prospective, contextual, descriptive study design with consecutive convenience sampling was used. Assessment of cognition was subjective (through casual conversation) and objective (using the Mini-Cog test).

Results

A total of 194 outpatients (median age: 65 years) was assessed. A score ≤ 3 was obtained by 111 patients (57.2%). The subjective assessment of cognition was shown to be poor in comparison (sensitivity 47.8%; specificity 70%). Univariate analyses demonstrated significant associations between low Mini-Cog scores and increasing age ($r_s = -0.1901$; $p = 0.0079$), unskilled occupation ($p = 0.0033$), low functional status ($r_s = -0.1831$; $p = 0.0106$), low level of education ($p = 0.0005$) and frailty ($r_s = -0.3010$; $p < 0.0001$). Logistic regression showed level of education and frailty to be significant. Patients with grade 11 to tertiary education are 71.8% less likely to obtain a score ≤ 3 (OR: 0.2820; $p = 0.0034$), and frail patients are 7.54 times more likely to obtain a score ≤ 3 than a robust patient ($p = 0.0026$).

Conclusion

This study found undiagnosed pre-existing cognitive dysfunction to be common in older patients awaiting surgery at Chris Hani Baragwanath Academic Hospital. These “brains at risk” should be identified through brief preoperative screening.

Keywords

Aged; cognitive dysfunction; Mini-Cog; preoperative period

Introduction

The normal aging brain experiences a decline in cognitive abilities.[1] Myriad possible factors responsible for altering the trajectory of this decline have been described. Previous studies have pointed to pain,[2] depression,[2-3] polypharmacy,[4] previous myocardial infarction,[5] stroke,[6] living alone,[4] certain comorbid conditions such as diabetes,[4] and low intelligence quotient[5] as significant factors.

Postoperative cognitive changes, which may include delirium and postoperative cognitive dysfunction, have been demonstrated as early as 1887, when it was written that “the use of anaesthetics, in predisposed subjects, has been followed by insanity”.[7]

These “predisposed subjects” comprise older patients and those with pre-existing cognitive dysfunction.[8] The associated consequences of this cognitive dysfunction include higher one-year mortality,[9] increased length of hospital stay,[10] increased medical costs,[10] premature withdrawal from the workplace,[9] and a change in long-term cognitive trajectory.[11]

Various interventions exist which could improve these outcomes.[8] In order to enact these interventions, the baseline cognitive status of older patients must be known. Despite the high prevalence of pre-existing cognitive dysfunction seen in developed countries (6.1 – 68%),[2-6 12-13] and the fact that the brain is the target of general anaesthetic agents, cognition is not always formally assessed by anaesthetists during the preoperative visit.[14] In a resource-constrained environment, a brief “brain stress test”[15] could simultaneously improve patient care and reduce cost.

The prevalence of undiagnosed preoperative cognitive dysfunction in developing countries, where education levels and disease profiles differ, is unknown. The objectives of this study were to describe and compare the subjective and objective assessment of cognitive functioning of patients ≥ 60 years old at Chris Hani Baragwanath Academic Hospital, South Africa; and to describe factors associated with cognitive dysfunction in these patients, including the effect of increasing age and the presence of risk factors for vascular disease.

Methods

This study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (clearance certificate M171030). The patient population included patients ≥ 60 years of age presenting for elective non-cardiac surgery at Chris Hani Baragwanath Academic Hospital's gynaecological, orthopaedic and surgical outpatients' departments. All patients provided written consent. Patients with previously diagnosed dementia, patients who had had surgery in the previous six months, and patients unable to communicate in English were excluded. A sample size of 190 was calculated in consultation with a biostatistician (level of significance 0.05; 80% power). Consecutive convenience sampling was used.

A data collection sheet was compiled following an extensive literature review and in consultation with a geriatrician. Casual conversation with the participant resulted in a subjective assessment of their cognitive function (normal or abnormal). A Mini-Cog test[16] was then performed as an objective measure, in a private consultation room free from noise and distraction. The Mini-Cog test, analogous to a "cognitive vital sign", is a quick and simple test to perform.[16] The test comprises the registration and recollection of three unrelated words, as well as a clock-drawing test, scored out of five. A normal clock has all 12 numbers, written only once each, in a clockwise direction, with anchoring numbers (12, 3, 6 and 9) in the correct position. A time of 11:10 must be shown, with one hand pointing at the number 11 and the other at the number 2. Length of hands is unimportant. While Borson and colleagues[16] used scores of ≤ 2 out of 5 to represent possible cognitive dysfunction, this study, like McCarten and colleagues[17] used a score of ≤ 3 in order to detect even incipient cognitive dysfunction.

Despite its brevity, the Mini-Cog tests a variety of functions: the word recall component tests memory and attention, and the clock-drawing component tests comprehension, planning, visual memory and reconstruction, visuospatial abilities, motor programming and execution, numerical knowledge, abstract thinking, concentration and frustration tolerance.[18] The Mini-Cog has a sensitivity of 99% and specificity of 93%,[16] and avoids many of the pitfalls presented by other available cognitive screens such as the Montreal Cognitive Assessment (MoCA) and Mini-

Mental State examination (MMSE). A so-called “culture-free” test, the Mini-Cog is less affected by language, literacy and education level.[19]

Patient characteristics as well as a checklist for medical comorbidities known to increase the risk of cognitive dysfunction were then documented. The patient’s current prescribed medication was then reviewed for polypharmacy as well as drugs deemed inappropriate for older patients as per Beer’s List.[20] Weekly alcohol consumption was recorded, in units. Depression was briefly screened for in the form of a Patient Health Questionnaire-2 (PHQ-2) assessment.[21]

Frailty, a “pre-disability” state, was assessed using a FRAIL scale, which classified patients as robust, pre-frail or frail.[22] Functional status, and the patient’s degree of dependence, was assessed using a Modified Rankin Scale.[23] Both scales were administered verbally and did not require that the patient leave the room.

Data were collected by one author (LA) and analysed in consultation with a biostatistician using STATA version 14.1. Data were non-parametric. Categorical variables were summarised using frequencies and percentages. Numerical variables were analysed using medians and interquartile ranges. Comparison between subjective and objective cognitive assessments was done using a chi-squared test. Univariate analyses between Mini-Cog scores and factors influencing cognition were done using Mann-Whitney or Kruskall-Wallis tests. Spearman’s rank-order correlation was used to measure the strength and direction of the association between certain variables. Where a difference was found between groups, a post hoc test (Bonferroni correction) was done. P values < 0.05 were considered statistically significant. Factors with p values < 0.2 were included in a logistic regression analysis.

Results

A total of 205 patients were approached to participate in this study. Eleven patients did not meet the selection criteria, resulting in a sample size of 194 participants. Patient characteristics are presented in Table 1.

Cognitive function was subjectively assessed through casual conversation as normal for 116 (59.8%) participants and abnormal for 78 (40.2%) participants. The objective assessment of cognitive function, using Mini-Cog scores, is presented in Table 2. The median score (IQR) was 3 (2 – 4). A score ≤ 3 was obtained by 111 (57.2%) participants. Examples of abnormal clocks drawn by study participants are shown in Fig. 1. When subjective assessment was compared to the objective test (Mini-Cog score), poor sensitivity of 47.8% (95% CI: 38.1 – 57.4%) and modest specificity of 70.0% (95% CI: 58.9 – 79.4%) was shown (p = 0.0198). The positive predictive value of a subjective cognitive assessment is 68.0% (95% CI: 56.4 – 78.0%) and the negative predictive value is 50.0% (95% CI: 40.6 – 59.5%).

When the Mini-Cog score was compared with gender (p = 0.3804), marital status (p = 0.4408), and other social support (p = 0.6038), no significant differences were found.

The minimum age in the sample was 60 years, while the maximum was 80 years. The median (IQR) age was 65 (62 – 72). There was a weak but significant correlation between age and Mini-Cog scores ($r_s = -0.1901$; p = 0.0079).

A significant difference was found between level of education and Mini-Cog score (p = 0.0005). Participants who attained primary school education (median Mini-Cog score: 3.0), grades 8 to 10 (median score: 3.0) and grade 11 to tertiary education (median score: 4.0) were compared. No significant difference existed between primary school and grades 8 – 10 (p = 0.2621). A significant difference existed between primary school and grade 11 – tertiary education (p = 0.0002), and between grades 8 – 10 and grade 11 – tertiary education (p = 0.0137).

When the Mini-Cog score was compared with occupation, a significant difference was found between skilled workers and unskilled workers (p = 0.0033), with skilled

workers achieving higher median (IQR) Mini-Cog scores of 4 (3 – 5), whereas unskilled workers achieved median (IQR) scores of 3 (2 – 4).

Comorbidities associated with cognitive dysfunction are presented in Table 3. No significant difference in Mini-Cog score was found for any one comorbid condition. There is also no significant difference in Mini-Cog score for participants without comorbidities or with multi-morbidity ($p = 0.7976$). Participants with two or more risk factors for vascular disease (n = 67; 34.5%) showed no significant difference in Mini-Cog scores compared to patients with no or only one risk factor ($p = 0.8596$).

There was no significant difference in Mini-Cog score between smokers and non-smokers ($p = 0.6581$), and no correlation between Mini-Cog score and number of pack years ($r_s = −0.0101$; $p = 0.9600$).

There was also no significant difference between Mini-Cog scores of participants who consumed alcohol and those who did not ($p = 0.5852$), and no correlation between Mini-Cog score and the number of units of alcohol consumed weekly by the former group ($r_s = 0.0322$; $p = 0.6562$).

Of the participants, 148 (76.3%) participants had no symptoms of depression, 30 (15.5%) had one symptom, and 16 (8.2%) had two symptoms. No significant difference was found between median Mini-Cog scores in these participant groups ($p = 0.9646$).

There was no significant difference between polypharmacy and Mini-Cog score ($p = 0.9119$) or between inappropriate medications taken and Mini-Cog score ($p = 0.7419$).

The FRAIL scale scores and Modified Rankin scores of the participants are presented in Table 4. There is a weak but significant correlation between frailty and Mini-Cog scores ($r_s = −0.3010$; $p < 0.0001$), and a weak but significant correlation between functional status and Mini-Cog scores ($r_s = −0.1831$; $p = 0.0106$).

Subjective memory loss was reported by 124 (63.9%) participants. A significant difference was demonstrated between Mini-Cog scores and subjective memory complaints, with lower scores in those participants who reported memory loss ($p = 0.0264$).

A stepwise logistic regression demonstrates that the best predictors of Mini-Cog score are education and frailty. Participants with higher levels of education (grade 11 – tertiary) are 71.8% less likely to obtain a Mini-Cog score ≤ 3 than participants with primary school education only ($p = 0.0034$; odds ratio [95% CI]: 0.2820 [0.1211 – 0.6570]). Frail participants are 7.54 times more likely than robust participants to obtain a Mini-Cog score ≤ 3 ($p = 0.0026$; odds ratio [95% CI]: 7.5433 [2.0244 – 28.1077]).

Discussion

This study of 194 older patients demonstrated a high prevalence of undiagnosed cognitive dysfunction (57.2%) using the Mini-Cog test. The subjective assessment of cognitive function through casual conversation was shown to be unreliable at detecting subtle deficits, a factor not examined by other studies.

The prevalence of pre-existing cognitive dysfunction in other studies ranges between 6.1 and 68%.[2-6 12-13] The use of different cognitive assessment tools as well as heterogeneous patient populations may account for this range. None of the studies reviewed approximate our own study population of mostly black females in a developing country. Previous studies have described a predominantly white[3-4] or male population[4-6] in developed countries.[2-6 12-13]

Few other studies used the Mini-Cog,[16] the brevity of which lends itself to a busy and resource-constrained clinical environment. Only one other study,[6] conducted in the United States of America in 2012, used a cut-off score of ≤ 3 to indicate possible cognitive dysfunction. A lower prevalence of 44% was found, in a comparable population size (n = 186), albeit in a much older population (mean age 73 years) who were all planned for ICU admissions postoperatively.

The majority of the sample reported subjective memory loss (63.9%), an important factor mentioned by few other studies. Subjective memory loss suggests amnestic mild cognitive impairment.[2] The rate of conversion of patients with amnestic mild cognitive impairment to Alzheimer's disease is 10 – 15% (compared to 1 – 2% in patients without).[24]

While the influence of increasing age on worsening cognition found in this study is echoed by other studies,[3 6 13] other important factors such as polypharmacy and inappropriate medications were not found to be significant in this study (despite high preponderances of both). These, however, are still potential targets for intervention.

It is interesting that no particular comorbidity or the coexistence of multiple vascular risk factors significantly affect cognition in this study. Another study, by Partridge and colleagues,[4] which utilised an urban United Kingdom sample comprising entirely of vascular patients, found a higher prevalence of cognitive dysfunction (68%) using the

Montreal Cognitive Assessment (MoCA). This may be expected given that the risk factors for atherosclerosis, such as hypertension, hypercholesterolaemia and diabetes mellitus, are also independent risk factors for cognitive dysfunction.[4] Despite a high preponderance of the same risk factors in this study, the risk factors may not have culminated in vascular disease severe enough to warrant intervention. The patients in this study were ambulatory outpatients, whereas those in the study by Partridge and colleagues[4] were hospitalised for either elective or emergency vascular surgery. This may reflect greater disease severity or increased cognitive stress in the setting of hospitalisation; however, a study comparing admitted patients and those presenting to a clinic six weeks prior to surgery found no difference in cognitive test scores as a result of location and timing.[13] Finally, Partridge and colleagues[4] did not exclude patients known to have cognitive dysfunction or dementia, as was done in this study. The fact that patients presenting for cardiac surgery have a comparable prevalence[5] of cognitive dysfunction to their non-cardiac surgery counterparts, suggests that the relationship between vascular risk factors and cognition is complex.

The influence of education supports the effect of cognitive reserve on counteracting damaging influences.[25] The older South African black population was schooled during the Apartheid era under the Bantu Education Act of 1953,[26] which, until educational reform in the 1980s, resulted in less spending and lower-quality instruction in black schools.[27] The study by Trowbridge and colleagues,[3] conducted in the United States of America, also found that patients with more education were less likely to have cognitive dysfunction; however, 62.4% of that population had more than 12 years of formal instruction.

Frail patients were found, in this study, to be more than seven times more likely to have cognitive dysfunction than robust patients. Frailty was also found to be independently associated with cognitive dysfunction by Partridge (OR 12.55, $p < 0.001$).[4] While no other studies reviewed assessed frailty, this strong association is expected given that these geriatric syndromes often coexist.[28]

The identification of patients with cognitive dysfunction, particularly those with concomitant frailty and a low level of education, is clinically important. A positive

screen for cognitive dysfunction impacts on informed consent, aids in more accurate risk assessment, and could catalyse interventions to reduce the negative impact of surgery and anaesthesia on these at-risk brains. Such interventions span the perioperative period and include optimisation of electrolytes and hydration status, adequate analgesia, rationalising polypharmacy, conducting frailty assessments, avoiding certain drugs such as opioids and benzodiazepines intraoperatively, limiting the length of general anaesthesia, use of depth of anaesthesia monitoring, avoiding positions which compromise cerebral perfusion, maintaining adequate haematocrit levels and avoiding hypotension.[8] Drugs which counteract neuroinflammation such as luteolin[29] and the anti-inflammatory agent meloxicam[30] may also prove useful. Prehabilitation, or preoperative environmental enrichment, may attenuate or even negate the neuroinflammation and memory loss associated with anaesthesia.[31]

Limitations of this study include the reliance on self-reported data for aspects such as ethanol use and smoking, and the fact that the Mini-Cog is only a screening test (results were not compared with a fully neuropsychological battery). Anxiety is a possible confounder that was not controlled for. A further limitation is the relatively small sample of participants with certain comorbid conditions with which to do comparisons, however, this was a secondary objective. There is also an unknown number who remain undiagnosed. For example, in this sample, 6.7% were known with HIV, and 28.3% had never been tested. This makes it difficult to accurately comment on the true effect of HIV on cognition.

Future studies might include larger sample sizes for factors of interest, and assess the effect of a change in education policy post-Apartheid on the cognitive function of future older patients awaiting surgery.

This study found undiagnosed pre-existing cognitive dysfunction to be common in older patients awaiting surgery at Chris Hani Baragwanath Academic Hospital. These “brains at risk” should be identified through brief anaesthetic preoperative screening. This will facilitate the enactment of interventions across the perioperative period by the entire multidisciplinary team. These include drug rationalization, environmental enrichment and meticulous haemodynamic monitoring.

Declaration of interests

None declared.

Details of authors' contributions

L.A.: study design, patient recruitment, data collection, data analysis, writing up of first draft of paper, editing of article

H.P.: study development and design, critical revision of article, final approval of version to be published

J.S.: study development and design, critical revision of article, final approval of version to be published

K-A.B-I.: study development and design, critical revision of article, final approval of version to be published

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Table 1: Patient characteristics

Characteristic		n (%)
Gender:	Male	57 (29.4)
	Female	137 (70.6)
Age:	60 – 70 years	136 (70.1)
	71 – 75 years	33 (17.0)
	> 75 years	25 (12.9)
Race:	Black	180 (92.8)
	Coloured	7 (3.6)
	Indian	4 (2.1)
	White	3 (1.5)
Department:	Gynaecology	8 (4.1)
	Orthopaedics	122 (62.9)
	Surgery	64 (33.0)
Occupation:	Skilled	50 (25.8)
	Unskilled	144 (74.2)
Marital status	Divorced	24 (12.4)
	Married	66 (34.0)
	Single	52 (26.8)
	Widowed	52 (26.8)
Social support	Yes	180 (92.8)
	No	14 (7.2)
Highest level of education	Primary school	47 (24.2)
	Grades 8 – 10	86 (44.3)
	Grade 11 – tertiary	61 (31.5)

Table 2: Mini-Cog scores

Words recalled	**n (%)**	**Mini-Cog score**	**n (%)**
0	13 (6.7)	0	13 (6.7)
1	31 (16.0)	1	19 (9.8)
2	79 (40.7)	2	38 (19.6)
3	71 (36.6)	3	41 (21.1)
Clock-drawing test	**n (%)**	4	41 (21.1)
0	99 (51.0)	5	42 (21.7)
2	95 (49.0)		

Table 3: Comparison of comorbidities and Mini-Cog scores

Comorbidity	Total n (%)	Mini-Cog score		p-value
		≤ 3 (n = 111) n (%)	> 3 (n = 83) n (%)	
Anaemia	11 (5.7)	7 (6.3)	4 (4.8)	0.8591
Asthma	14 (7.2)	9 (8.1)	5 (6.0)	0.6091
Atrial fibrillation	5 (2.6)	3 (2.7)	2 (2.4)	0.6748
Chronic kidney disease	5 (2.6)	2 (1.8)	3 (3.6)	0.9606
Chronic obstructive pulmonary disease	10 (5.2)	6 (5.4)	4 (4.8)	0.7704
Diabetes Mellitus	31 (16.0)	18 (16.2)	13 (15.7)	0.9886
HIV				0.3598
Positive	13 (6.7)	6 (5.4)	7 (8.4)	
Negative	126 (65.0)	69 (62.2)	56 (67.5)	
Unknown	55 (28.3)	36 (32.4)	20 (24.1)	
On treatment	12 (92.3)	5 (4.5)	7 (8.4)	
Hypercholesterolaemia	47 (24.2)	26 (23.4)	21 (25.3)	0.5520
Hypertension	148 (76.3)	83 (74.8)	65 (78.3)	0.6109
Obstructive sleep apnoea	69 (35.6)	39 (35.1)	30 (36.1)	0.9978
Previous myocardial infarction	7 (3.6)	4 (3.6)	3 (3.6)	0.7878
Previous stroke	9 (4.6)	5 (4.5)	4 (4.8)	0.6667
Previous tuberculosis	13 (6.7)	7 (6.3)	6 (7.2)	0.7644
Thyroid disease	6 (3.1)	4 (3.6)	2 (2.4)	0.7376
None	31 (16)	19 (17.1)	12 (14.5)	0.8061

Table 4: FRAIL scale scores and Modified Rankin scores of participants

Variable	Total	Mini-cog ≤ 3 (n = 111)	Mini-cog > 3 (n = 83)
	n (%)	n (%)	n (%)
Frailty			
Robust	23 (11.9)	7 (6.3)	16 (19.3)
Pre-frail	141 (72.7)	80 (72.1)	61 (73.5)
Frail	30 (15.4)	24 (21.6)	6 (7.2)
Functional status			
Modified Rankin score			
0	59 (30.4)	25 (22.5)	34 (41.0)
1	70 (36.1)	44 (39.6)	26 (31.3)
2	47 (24.2)	30 (27.0)	17 (20.5)
3	16 (8.3)	10 (9.0)	6 (7.2)
4	2 (1.0)	2 (1.8)	0 (0)

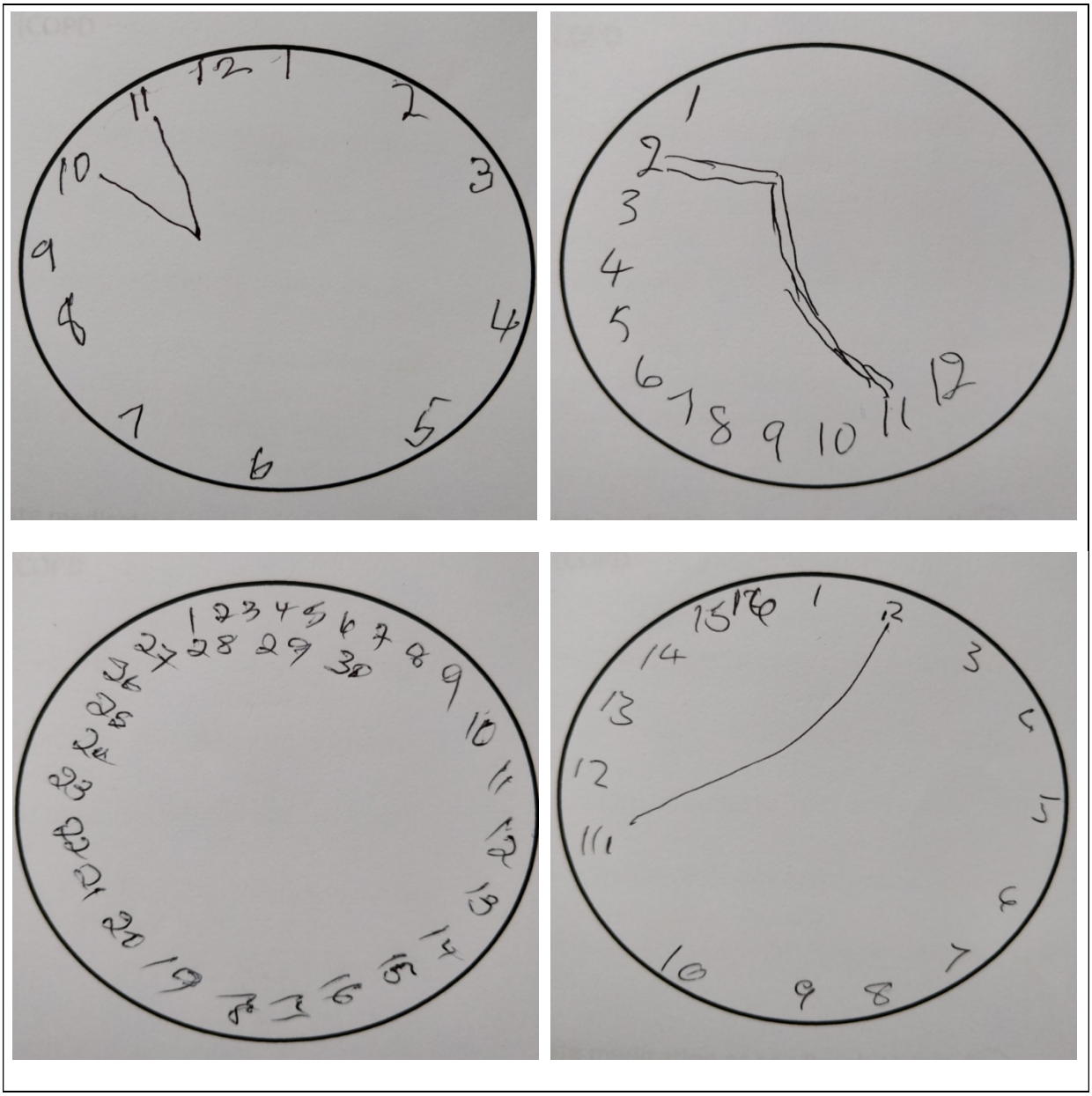


Fig.1: Examples of abnormal clocks drawn by study participants

Section 3: Appendices

Post-graduate approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

13 December 2017
Person No: 0701088K
PAG

Dr LA Amado
P O Box 751056
Gardenview
2047
South Africa

Dear Dr Amado

Master of Medicine in the Speciality of Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Preoperative cognitive dysfunction in older patients at a central hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Ethics clearance certificate

R14/48 Dr L Amado et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M171030

NAME: (Principal Investigator)	Dr L Amado et al
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Pre-operative cognitive dysfunction in older patients at a central hospital Title changed on 1 February 2018
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr H Perrie
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	16/01/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Permission to collect data at Chris Hani Baragwanath Academic Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 8 Feb 2018

TITLE OF PROJECT: Preoperative cognitive dysfunction in older patients at a central hospital

UNIVERSITY: Witwatersrand

Principal Investigator: L Amado

Department: Anaesthesiology

Supervisor (If relevant): H Perric, J Scribante, KA Ben Israel

Permission Head Department (where research conducted): will be provided

Date of start of proposed study: Feb 2018
Date of completion of data collection: Dec 2019

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 08 February 2018

.....
Approved/Not Approved
Hospital Management
Date: 13/02/18

Permission from Head of Department: Obstetrics and Gynaecology

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

OBSTETRICS AND GYNAECOLOGY
School of Clinical Medicine

Ethics Committee
School of Clinical Medicine
University of the Witwatersrand.
4th December 2017

Re: Dr L Amado – "Pre-operative cognitive dysfunction in older patients at a central hospital"

I have discussed the rationale and methods of this proposal for the study wih Dr Amado. I hereby give consent for this study to be performed in Department of Obstetrics & Gynaecology, CHBAH from January 2018.

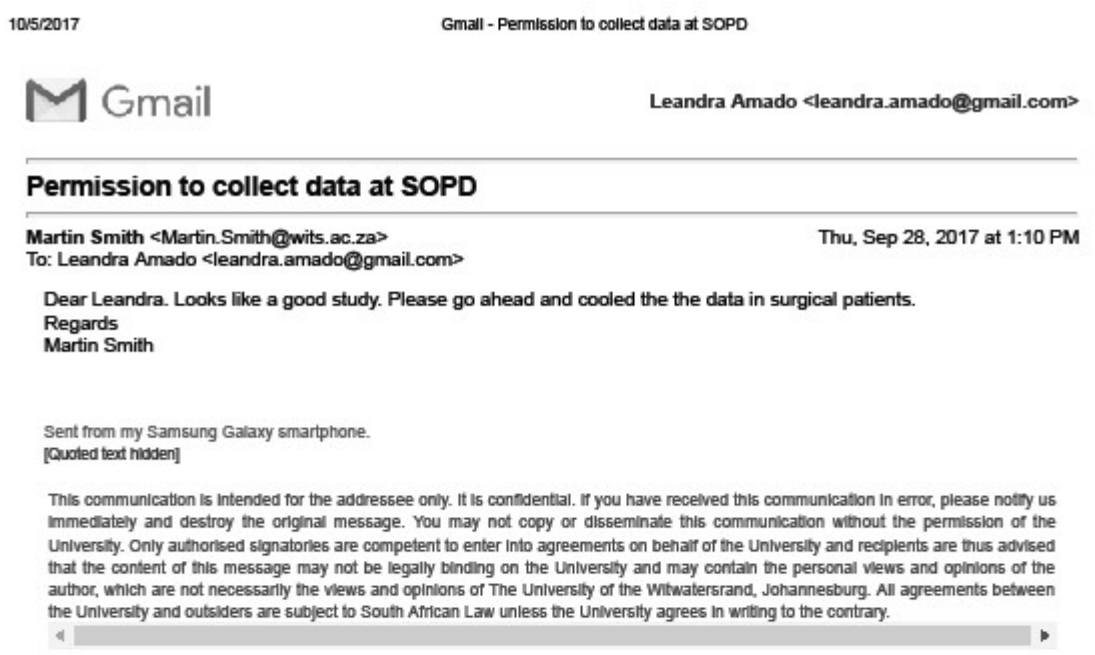
Ethics approval and approval of the CEO needs to be obtained before the study can commence.

Thank you

Yasmin Adam
Clinical Head
Chief Specialist and Adjunct Professor
Department of Obstetrics & Gynaecology
The University of the Witwatersrand

Faculty of Health Sciences
Johannesburg Hospital | Private Bag X39, Johannesburg, South Africa | T +27 11 488 3791 | F +27 11 643 2522 | www.wits.ac.za

Permission from Head of Department: General Surgery



10/5/2017 Gmail - Permission to collect data at SOPD

Gmail Leandra Amado <leandra.amado@gmail.com>

Permission to collect data at SOPD

Martin Smith <Martin.Smith@wits.ac.za> Thu, Sep 28, 2017 at 1:10 PM
To: Leandra Amado <leandra.amado@gmail.com>

Dear Leandra. Looks like a good study. Please go ahead and cooled the the data in surgical patients.
Regards
Martin Smith

Sent from my Samsung Galaxy smartphone.
[Quoted text hidden]

This communication is intended for the addressee only. It is confidential. If you have received this communication in error, please notify us immediately and destroy the original message. You may not copy or disseminate this communication without the permission of the University. Only authorised signatories are competent to enter into agreements on behalf of the University and recipients are thus advised that the content of this message may not be legally binding on the University and may contain the personal views and opinions of the author, which are not necessarily the views and opinions of The University of the Witwatersrand, Johannesburg. All agreements between the University and outsiders are subject to South African Law unless the University agrees in writing to the contrary.

https://mail.google.com/mail/u/0/?ui=2&ik=a5af232e44&jsver=khUFNOKnlXg.en.&view=pt&msg=15ec82deb7c2714a&q=martin.smith%40wits.ac.... 1/1

Permission from Head of Department: Orthopaedics

Gmail

Leandra Amado <leandra.amado@gmail.com>

Permission to collect data at Orthos OPD

Mmampapatla Ramokgopa <Mmampapatla.Ramokgopa@wits.ac.za> Tue, Nov 28, 2017 at 1:48 PM
To: Leandra Amado <leandra.amado@gmail.com>
Cc: Christeleen Ontong <Christeleen.Ontong@wits.ac.za>

Dear Dr Amado,

My apologies, I do note your previous e-mail dated the 28th September 2017. Somehow I am failing to retrieve the attachment. Please resend the protocol.

As for the permission to conduct the research in the orthopaedic surgery department, please do proceed and permission is thus granted.

Kind regards.

Prof MT Ramokgopa

Academic Head

Orthopaedic Surgery Department

0825646169 / 011-7172538

From: Leandra Amado [mailto:leandra.amado@gmail.com]
Sent: Monday, November 27, 2017 2:31 PM
To: Mmampapatla Ramokgopa
Subject: Re: Permission to collect data at Orthos OPD

[Quoted text hidden]

Letter from supervisor

WITS UNIVERSITY

DEPARTMENT OF ANAESTHESIOLOGY

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Tel.(011)933-9334/5 / Fax (011)933-1843

FACULTY OF HEALTH SCIENCES

11th October, 2018

The Chairperson

Graduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Dear Madam,

Re: M Med: **Preoperative cognitive dysfunction in older patients at a central hospital**

Dr Leandra Amado, student number: 0701088K, has submitted her research report to Turnitin which revealed a similarity index of 9%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

H C Perrie

Helen Perrie

Supervisor

Turnitin originality report

0701088k:L.AmadoMMed_TS.docx

ORIGINALITY REPORT

9%	6%	6%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	wiredspace.wits.ac.za Internet Source	1%
3	mobile.wiredspace.wits.ac.za Internet Source	<1%
4	www.ajol.info Internet Source	<1%
5	digital.library.unt.edu Internet Source	<1%
6	"ECR 2017 – BOOK OF ABSTRACTS", Insights into Imaging, 2017 Publication	<1%
7	Margaret A Pisani, Lynn McNicoll, Sharon K Inouye. "Cognitive impairment in the intensive care unit", Clinics in Chest Medicine, 2003 Publication	<1%
8	Larsson, Peter G., Staffan Eksborg, and Per-Arne Lönnqvist. "Incidence of bradycardia at	<1%

Section 4: Proposal

Preoperative cognitive dysfunction in older patients at a central hospital

Leandra Amado

0701088K

Supervisor:	Helen Perrie Department of Anaesthesiology
Co-supervisor:	Juan Scribante Department of Anaesthesiology
Co-supervisor:	Karin-Ann Ben Israel Department of Anaesthesiology

1. Introduction

The normal aging process is accompanied by a decline in a number of cognitive abilities. Older adults who present for surgery may exhibit further post-operative cognitive decline relative to their preoperative level of functioning. This cognitive morbidity may include delirium and post-operative cognitive dysfunction (POCD), both the incidence and the associated consequences of which are significant (1, 2). In addition to increasing age, pre-existing cognitive dysfunction is a risk factor for these complications (3).

Cognitive changes in the normal aging brain may be structural and/or functional. Structural changes include loss of grey and white matter, as reflected by volume changes (4), decreased synaptic density (5) and reduced neurotransmitter production (6). Functional derangements include loss of cortical excitability, reduced cerebral blood flow and decreased plasticity (7). Some of the cognitive abilities affected by these changes may exhibit a steady, life-long decline, while others may deteriorate sharply only late in life (7).

A variety of factors may alter the trajectory of this normal decline. These include comorbid conditions, medication, chronic alcohol use, psychological factors, such as anxiety (8) and depression (9), as well as states of reduced physiological reserve, such as frailty (10).

Comorbid conditions implicated in cognitive dysfunction are numerous. These include vascular disease, hypertension, hypercholesterolaemia, diabetes mellitus, thyroid disease, hypoxia (which may result from anaemia, obstructive sleep apnoea or respiratory pathology such as asthma or chronic obstructive airways disease) and chronic kidney disease (11). Additionally, with the increased availability of highly active antiretroviral treatment, people living with HIV are achieving a near-normal life expectancy (12); the disease as well as its treatment not only accelerate the aging process (13) but also cause neurocognitive deficits (14). The relationship between cognitive dysfunction and these comorbidities has management implications, one of which includes adherence to treatment.

Medication itself may negatively affect cognition. Up to half of all hospitalised patients have been prescribed inappropriate medication as per Beer’s list (15). This

is a list of drugs – including anticholinergic drugs and benzodiazepines – considered unsuitable for older patients based on side effects, one of which is cognitive dysfunction (16). It has been argued that polypharmacy (more than five drugs prescribed) is more detrimental to cognition than one single drug type (17).

Counteracting these damaging influences is a protective construct known as cognitive reserve. According to Stern (18), cognitive reserve has been postulated to have a passive component (represented by brain volume, synaptic count or head circumference) and an active component, where compensation for neural defects occurs via the use of more efficient networks. Active reserve may be represented by a person's education level, occupation and premorbid intelligence quotient. Higher cognitive reserve means that an aging brain may be able to withstand greater insults before cognitive dysfunction becomes apparent (18).

When cognitive reserve fails, however, such patients need to be identified. Full neuropsychological testing, while ideal, is difficult to administer in a busy clinical setting. Screening tests, which are quick to administer, have simple scoring systems and high sensitivity and specificity, are ideal (19). The validated Mini-Cog Assessment (20) is one such example. Methodology (including the type of test used) in studies assessing pre-existing cognitive dysfunction varies widely. Unsurprisingly, the prevalence of cognitive dysfunction found by these studies also ranges considerably, between 6.1% – 67.5% (21, 22). Higher prevalence occurs in the most elderly, with large increases shown for each increasing decade of age (23). More important than specific prevalence values, however, is the consistent finding that older patients presenting for surgery commonly have undiagnosed cognitive dysfunction (24).

These patients are at increased risk for post-operative cognitive morbidity (25). Between 30 – 80% of older patients experience delirium post-operatively; 30 – 40% experience early POCD; and 10 – 15% experience late POCD, at three months (26, 27). POCD may last up to six months after surgery (28). Delirium and POCD are associated with increased length of stay, increased cost, premature withdrawal from the workplace, higher one-year mortality (29), and a change in the trajectory toward dementia (25). Considering this, every effort should be made to prevent this in

susceptible patients. Patients with preoperative cognitive dysfunction are among these.

The aetiology of POCD has not yet been confirmed; however both anaesthesia and surgery itself have been implicated (3). A study by Wan et al. (30) suggests the role of cytokines released as a direct result of surgery and the neuroinflammatory effect these cytokines have in the hippocampus. The authors subjected adult rats to anaesthesia and some rats underwent splenectomies, while others received no surgery. The rats that underwent splenectomies showed cognitive dysfunction in a maze test on days one and three post-operatively, while rats that were only anaesthetised but not operated on were similar to controls. Other studies, however, implicate inhaled anaesthetic agents in causing direct neurotoxicity (31) and alterations in hormone homeostasis (32).

O'Brien et al. (3) have reviewed possible targets for intervention in susceptible patients. These span the perioperative period and include optimisation of electrolytes and hydration status, adequate analgesia, rationalising polypharmacy, conducting frailty assessments, avoiding certain drugs intraoperatively, limiting the length of general anaesthesia, conducting depth of anaesthesia monitoring, avoiding positions which compromise cerebral perfusion, maintaining adequate haematocrit levels and avoiding hypotension (30). Prehabilitation, or preoperative environmental enrichment, may attenuate or even negate the neuroinflammation and memory loss associated with anaesthesia (33). In order to enact these interventions, the baseline cognitive status of older patients must be known.

2. Problem statement

Increased age and pre-existing cognitive dysfunction are risk factors contributing to POCD, which is both common and costly (1, 3). Anaesthetists routinely evaluate surgical patients preoperatively for a range of organ system dysfunction. Despite the brain being the target of general anaesthetic agents, cognition is not always formally assessed in the same way (25). Preoperative cognition is relevant in determining long-term cognitive outcome, but these already-compromised brains are potentially missed (25). Preoperative cognitive dysfunction at Chris Hani Baragwanath Academic Hospital (CHBAH) has not previously been described.

3. Aim

The aim of this study is to describe pre-existing cognitive dysfunction in older preoperative surgical patients presenting for non-cardiac surgery at CHBAH.

4. Objectives

The primary objectives of this study are to:

- describe the subjective assessment of cognitive functioning of patients
- describe the objective cognitive function in patients using the Mini-Cog Assessment (20)
- describe factors associated with cognitive dysfunction in these patients.

The secondary objectives of the study are to:

- compare the subjective and objective assessments of cognitive function
- describe the effect of increasing age on cognitive dysfunction
- compare the difference in cognitive function between patients with and without factors associated with cognitive dysfunction
- describe and compare the difference in cognitive function between patients with vascular disease and without vascular disease.

5. Research assumptions

The following definitions will be used in the study.

Older person: any person 60 years old or older. In a recent systematic review of post-operative cognitive dysfunction at three months, 17 studies focus exclusively on patients aged 60 years or older (34). Therefore, this is the age selected.

Cognition: “the mental processes of perception, memory, and information processing, which allows the individual to acquire knowledge, solve problems, and plan for the future” (35).

Preoperative cognitive dysfunction: abnormal cognition as determined by a Mini-Cog Assessment score three or less out of a possible score of five. This cut-off, used by McCarten et al. (36) may increase detection of milder cognitive dysfunction, and

differs from original criteria for a positive screen (a score of two or less) by Borson et al (37).

POCD: a syndrome of prolonged cognitive dysfunction, lasting weeks or months post-operatively (38).

Delirium: defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a neuropsychiatric syndrome representing an acute change from baseline in attention and awareness, as well as disturbed cognition. This disturbance cannot be explained by a pre-existing diagnosis and there is evidence of an attributable cause (39). A subset of this syndrome is post-operative delirium, which may occur between 24 and 72 hours after a surgery, but is not associated with emergence (40).

Vascular disease: the presence of coronary artery disease, stroke, and peripheral vascular disease, or associated risk factors such as hypertension, diabetes mellitus, atrial fibrillation, hyperlipidamia, male gender and smoking (11).

6. Demarcation of study field

The study will be conducted in the Surgical Outpatients Department (SOPD), Gynaecology OPD (GOPD) and Orthopaedics OPD of CHBAH affiliated to the University of the Witwatersrand. CHBAH is a 2888 bed central hospital. The hospital has 25 theatres, in which, on average, 65 000 procedures are performed annually.

7. Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand.

Permission to collect data at this site will be requested from the Medical Advisory Committee of CHBAH as well as the Heads of the Department of Surgery, Department of Obstetrics and Gynaecology and the Department of Orthopaedic Surgery.

Patient consent will be obtained by approaching patients in the relevant age group at the SOPD, GOPD and Orthopaedics OPD. The study will be explained to patients and they will be invited to participate. If patients agree, an information letter (Appendix 1) will be given to them and they will be asked to sign a consent form (Appendix 2).

It will be ensured that participants do not lose their place in the queue at the outpatients department during their assessment. The assessment will be done in a private consultation room to prevent the participants from being distracted or feeling uncomfortable.

Should a patient's Mini-Cog score suggest cognitive dysfunction, the patient's primary physician will be informed; the primary physician may then refer the patient for definitive diagnosis and further management. Conducting cognitive screening tests in the outpatient setting rather than the day before surgery will ensure appropriate time for such consultations to be conducted and avoid cancellation of the patient's case.

Patient-identifying information will be omitted from data collection sheets, where only study numbers will be used. The corresponding consent forms will also be labelled with study numbers. A separate data sheet correlating the study numbers with patients' names and hospital numbers will be available to the researcher only. This will be kept on a password-protected computer.

Raw data will be available only to the researcher and supervisors, ensuring confidentiality.

The data will be stored securely in a locked cabinet for a period of six years after completion of the study. Thereafter the data will be destroyed.

The study will be conducted according to the principles of the Declaration of Helsinki (41) and the South African Guidelines for Good Clinical Practice (42).

8. Data collection

8.1 Research design

A prospective, contextual, descriptive research design will be followed in this study.

In a prospective study, “data about a presumed cause are first collected, and then the effect or outcome is measured” (43). This study is prospective as data will be collected at the time of the study.

In a contextual study, a specific population or “small-scale world” is used (44). In this study, this specific population comprises older surgical patients at CHBAH.

According to Brink et al. (43), a descriptive study is one in which characteristics of a population are described in order to answer a specific question about that population. In this study, the age, other demographic information, cognitive function and comorbidities of the population will be described in order to assess cognitive dysfunction.

8.2 Study population

The study population consists of all patients aged 60 years or older presenting for non-cardiac surgery at CHBAH SOPD, GOPD and Orthopaedics OPD.

8.3 Study sample

Sample method

In this study a consecutive convenience sampling method will be used. Convenience sampling is a technique in which participants are included because they “happened to be in the right place at the right time” (45) or are available when the researcher is available. Consecutive sampling, which is the best choice of non-random sampling is a “version of convenience sampling where every available individual or event within an accessible population is chosen” (46).

Sample size

The sample size was determined in consultation with a biostatistician. It is assumed that 6 000 patients attend these outpatient departments in a 3-month period. Should 15% of these patients have cognitive dysfunction, a sample size of 190 is required (level of significance: 0.05; 80% power).

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- patients aged 60 years or older
- presenting for elective non-cardiac surgery
- who consent to take part in the study.

The exclusion criteria for this study are:

- patients with previously diagnosed dementia
- patients who have had surgery in the previous 6 months
- patients unable to communicate in English.

8.4 Collection of data

8.4.1 The data collection sheet

The literature was reviewed by the researcher. Based on this review, a data collection sheet was devised, ensuring content validity. This was then further validated (face and content validity) in consultation with a gerontologist. The final data collection sheet (Appendix 3) will comprise:

- patient demographic information
- the Mini-Cog assessment
- clinical information including comorbidities, medication, weekly alcohol consumption, depression screen, frailty score (the FRAIL scale) as well as functional status assessment (modified Rankin score).

The Mini-Cog test, analogous to a “cognitive vital sign”, is a quick and simple test to perform (20). First, the participant’s attention is ensured. The participant is instructed

to listen carefully as three unrelated words are said aloud by the researcher. The participant is given three attempts to repeat the three words. The participant is then asked to draw a clock. For this task, a circle will already be provided. The participant will be instructed to fill all numbers in on the clock face and then to set the time to show “ten past eleven”. Three minutes are allowed for the drawing of the clock. Finally, the participant will be asked to recall the three words they were given at the beginning of the assessment (37).

The Mini-Cog is then scored. One point is given for each word recalled without a clue. A further two points are given if a normal clock is drawn (zero points are given for an abnormal clock). A normal clock must include all the numbers (one to twelve), each only once, in the correct order and direction (clockwise). Two hands must be present, one pointing to 11 and one pointing to two. No points are scored for length of hands. Total score will be out of five (37). While Borson et al. (37) used scores of two or less out of five to represent possible cognitive dysfunction, this study, like McCarten et al. (36), will use a score of three or less.

A checklist for medical comorbidities known to increase the risk of cognitive dysfunction follows. The patient’s current prescribed medication is then reviewed for polypharmacy (more than five drugs) as well as drugs deemed inappropriate for older patients as per Beer’s List (16). Weekly alcohol consumption will be recorded, in units. Depression will be briefly screened for.

Two additional factors which might influence cognition in the elderly are then assessed: frailty and functional status.

Frailty, which can be considered a “pre-disability” state (47), is one in which a patient has reduced physiological reserve (48). Assessment of fatigue, resistance, ambulation, number of illnesses and loss of weight (in a FRAIL scale, scored out of five) will indicate whether a patient is robust (score of zero), pre-frail (score of 1 – 2) or frail (score of three or more) (49). This scale is administered verbally and does not require that the patient leave the room.

Similarly, functional status will be assessed in the private consultation room by the performance of a Modified Rankin Scale (0 – 6). This scale verbally assesses the

patient's degree of dependence and allows comparisons to be made between patients with different neurological deficits (50).

8.4.2 Data collection

The researcher will approach patients in the queue at the SOPD, GOPD and Orthopaedics OPD. Patients who meet the inclusion criteria will be provided with information regarding the study and invited to take part. Those who are interested will receive an information letter (Appendix 1) and will be removed from the queue to a private consultation room, as free from noise and distraction as possible. This room will have been secured at the beginning of the day from the nursing staff running the clinic. The participant's place in the queue will be reserved and the cooperation of other queuing patients secured. In the private consultation room the researcher will converse with the participant in order to subjectively assess the participant's cognitive function. The subjective assessment is simply an impression formed by casual conversation of the patient's cognitive function. This will be done in order to compare the subjective assessment with the Mini-Cog assessment. This will be recorded. Then results of the objective cognitive screen as well as further demographic and clinical information will be recorded on a data collection sheet (Appendix 3). Data collection sheets will be completed by the one researcher, unless, should the need arise, a trained research assistant will be asked to assist with data collection.

8.5 Data analysis

Data will be analysed in consultation with a biostatistician using STATA version 14.1. Descriptive and inferential statistics will be used. Subjective and objective cognitive assessments will be summarised using means and standard deviations if the data is normally distributed. Categorical variables will be summarised using frequencies and percentages. Numerical variables will be analysed using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. Comparison between subjective and objective assessments will be done using a Fisher's exact test or chi square test. In comparing the scores of patients with vascular disease and without vascular disease, a t-test or Mann-Whitney test will be used. P values < 0.05 will be considered statistically significant.

Factors influencing cognition such as demographic information, comorbidities, medication, frailty scores and functional dependence will be analysed in two steps. First, a chi squared test or Fisher's exact test will be used to determine whether there is an association between each factor and cognitive dysfunction. Then, only significant factors will be included in a logistic regression analysis to determine the magnitude of that particular association. P values < 0.2 will be considered significant for this purpose.

9. Significance of the study

Post-operative delirium and POCD have both considerable incidence and associated consequences (1). Pre-existing cognitive dysfunction is an important risk factor for both of these (3).

Undiagnosed pre-existing cognitive dysfunction has been demonstrated in other studies and varies between 6.1% – 67.5% (21, 22, 25, 51); however, to the best of the researcher's knowledge, this has not previously been described in older people in South Africa.

Describing cognitive dysfunction in this population will have an impact on informed consent, result in more accurate risk assessment, and possibly catalyse interventions to reduce the negative impact of surgery and anaesthesia on these at-risk brains. Such interventions might include the use of fewer opioids and hypnotics, less invasive surgery (3) and the use of non-steroidal drugs such as meloxicam to counteract neuroinflammation (52).

10. Validity and reliability of the study

Validity is an indication of "whether the conclusions of the study are justified based on the design and interpretation" and reliability refers to the consistency with which a measure is achieved (53).

In this study validity and reliability will be maintained by the following:

- applying the appropriate research design
- review of the literature ensures content validity of the data collection sheet

- expert evaluation of the data collection sheet by a gerontologist ensures face and content validity
- sample size calculated in consultation with a biostatistician
- ensuring consistency by the researcher and possible a trained assistant being the only data collectors and using a standardised data collection sheet
- checking every tenth data entry point for accuracy
- data analysis done in consultation with a biostatistician.

11. Potential limitations of the study

The contextual design of the study implies that results may not be generalised to older patients in other hospitals or other geographical areas.

A convenience sample may also not adequately represent all older surgical patients at CHBAH but rather only those present on a particular day.

A further potential limitation is the exclusion of people who are not proficient in English.

12. Project outline

Activity	Sept 2017	Oct 2017	Nov 2017	Dec 2017	Jan 2018	June 2018	July 2018	Aug 2018	Sept 2018	Oct 2018	Nov 2018
Proposal preparation											
Literature review											
Proposal submission											
Ethics approval											
Postgraduate approval											
Data collection											
Data analysis											
Article preparation											
Submission											

13. Financial plan

Budget

Item	Number	Cost	Total
Printing	1 600	R1/page	R1 600
Binding	4	R200	R 800
Total			R2 400

The Department of Anaesthesiology will bear the cost of printing and paper for the proposal, ethics and post-graduate approvals.

14. References

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4. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. J Neurosci. 2003; 23(8): 3295-301. doi:10.1523/JNEUROSCI.23-08-03295.2003.
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Appendix 1

Information sheet

Preoperative cognitive dysfunction in older patients at a central hospital

Dear Sir/Madam

My name is Leandra Amado and I am a doctor who puts people to sleep when they have an operation. As part of my studies at the University of the Witwatersrand, I am conducting a research project. Research is just the process of learning the answer to a question. In this study (Preoperative cognitive dysfunction in older patients at a central hospital) I want to find out if people aged 60 years or older have difficulty with remembering and thinking.

I would like to invite you to please take part in this study. As part of this study I will ask you questions and you will need to remember some words and draw something on a piece of paper. This will take approximately 15 minutes. I will write your responses on a form. This form will not have your name on it but it will have a study number. You will only need to do this once. If you agree to take part in the study, you will not lose your place in the queue. I will ask the other patients to keep your place.

You will not gain anything from taking part in this study, but it will help us to find out more information about remembering and thinking in older patients. I do not think that the questions and drawing task will hurt or upset you. You do not have to answer any questions if you do not want to and you may stop taking part at any point. Taking part in the study will not cost you any money.

If you can't remember the words or draw the picture, I will speak to your doctor. I will also refer you to a psychiatrist (a doctor who deals with health of the mind). The psychiatrist will be able to do a longer test to prove whether you definitely have problems remembering. The psychiatrist can also monitor your progress over time and assist with treatment if needed.

The information you give me will be completely confidential and only my supervisors and I will read it.

It is your choice to be part of this study. You do not have to take part if you do not want to and your doctors will continue to treat you as usual.

If you have any queries, concerns or complaints regarding this study, you are welcome to contact:

- the chairperson of the University Human Research Ethics Committee (Medical), on 011 717 1234,
- me (Leandra Amado) on 011 488 4344.

Please sign the consent form on the following page if you agree to take part in this study.

Thank you for taking the time to read this letter.

Sincerely,
Leandra Amado

Appendix 2

I, …….. agree to take part in the study of Cognitive dysfunction in older preoperative patients at Chris Hani Baragwanath Academic Hospital.

I have read and understood the information letter provided to me by Dr Leandra Amado. I understand that I may withdraw from the study if I do not wish to take part in it.

I have had an opportunity to ask questions that I may have had regarding the study and my participation in it.

……

Participant name

……

Participant signature or thumbprint

……

Witness

…… ……

Consent obtained by Date

Appendix 3

Study Number:

Date:		**Type of clinic:**	

Patient demographic data

Age:

Gender: Male ☐ Female ☐

Race: Asian ☐ Black ☐ Coloured ☐ Indian ☐ White☐

Marital status: Single ☐ Married ☐ Divorced ☐ Widowed ☐

Other social support: Y / N

Weight: Height: BMI:

Highest level of education:

Primary school	Grade 8	Grade 9	Grade 10	Grade 11	Grade 12	Tertiary

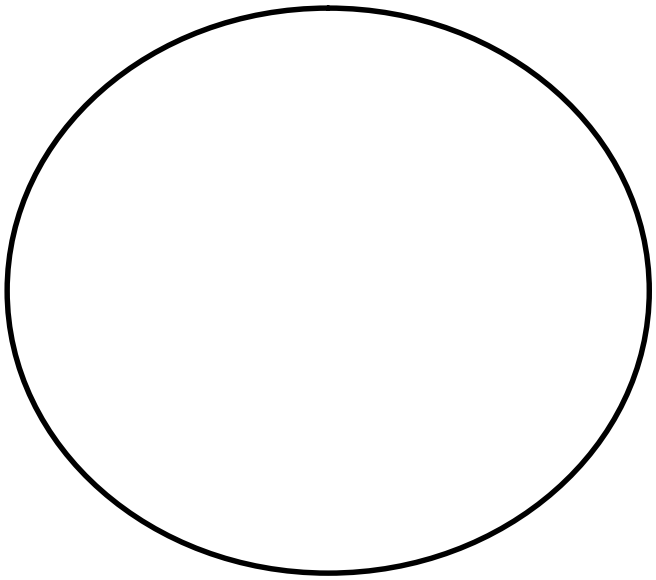
Current or previous occupation:

Professional	Clerical	Service and sales	Craft and related trades	Elementary occupation	Never employed
Manager	Technician / associate professional	Skilled agricultural, forestry and fishery workers	Plant and machine operators, assemblers	Armed forces	Other:

Researcher's subjective assessment of cognition:

Subjective memory complaints: Y / N

Previous operations: Y / N



Mini-cog test

Words used:

Words recalled: _ / 3

Clock-drawing test: _ / 2

Action taken:

Clinical information

Check all that apply:

- ☐ Previous stroke
- ☐ Previous MI
- ☐ Atrial fibrillation
- ☐ Hypertension
- ☐ Hypercholesterolaemia
- ☐ Diabetes mellitus
- ☐ Thyroid disease
- ☐ Anaemia

- ☐ OSA: Snoring / tiredness / observed apnoea / high blood pressure / BMI > 35 / age > 50 / neck circumference > 43cm [male] or > 41cm [female]
- ☐ Asthma
- ☐ Chronic obstructive airways disease (COPD)
- ☐ Previous pulmonary tuberculosis
- ☐ Cigarette smoking: ___ pack years
- ☐ HIV: treatment Y/N
- ☐ Chronic kidney disease

Medication

Polypharmacy? Y / N

Patient has been prescribed inappropriate medication as per Beer's List: Y / N

Alcohol

Number of units consumed per week:

Depression Screen: PHQ-2

1. Over the past 12 months, have you ever had a time when you felt sad / blue / depressed / down for most of the time for at least two weeks? Y / N
2. Over the past 12 months, have you ever had a time, lasting at least two weeks, where you didn't care about things you usually care about, or didn't enjoy things you usually enjoy? Y / N

FRAIL scale

	Fatigue	Tiredness	0: Robust 1 – 2: Pre-frail ≥ 3: Frail	**Patient's score:**
	Resistance	Inability to climb one flight of stairs		
	Ambulation	Inability to walk one block		
	Illnesses	>5		
	Loss of weight	>5%		

Modified Rankin Scale:

0 No symptoms at all
1 No significant disability despite symptoms; able to carry out all usual duties and activities
2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3 Moderate disability; requiring some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 Dead