PRE-OPERATIVE COGNITIVE TRAINING TO PREVENT POST-OPERATIVE COGNITIVE DYSFUNCTION IN OLDER PATIENTS
COGNITRAIN: A RANDOMISED CONTROLLED TRIAL

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

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ABSTRACT

The incidence of post-operative cognitive dysfunction in the elderly is increased and the subsequent impact can be devastating as patients need to retain their faculties in order to remain independent. A pilot study was carried out to determine the effectiveness of a novel home-based cognitive training on the incidence of delirium and post-operative cognitive dysfunction in patients aged 65 and above undergoing elective surgery. 18 subjects were recruited in pre-operative anaesthetic clinic and randomised into 2 groups. The intervention group was taught to perform cognitive training at home. Pre-operative and post-operative cognitive assessments were carried out and results compared. No patients developed delirium post-operatively. There was a low compliance rate (50%) among subjects leading to mixed findings on cognitive testing.

ACKNOWLEDGEMENT

To Professor Loh Pui San, thank you for your guidance

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LIST OF ABBREVIATIONS

POCD Post-operative cognitive dysfunction

MoCA Montreal cognitive assessment

TMT Trail making test

DSST Digit symbol substitution test

PAL Paired associates learning

RTI Reaction time

1.0 INTRODUCTION

As age expectancy increases with improved standards of living and advancing healthcare, the population of older patients presenting for anaesthesia and surgery becomes increasingly pertinent. This is no different in Malaysia with its ageing population increasingly mirroring trends in developed countries. This presents challenges in itself but the frequently side-lined consequence of post-operative delirium and cognitive dysfunction has the potential to greatly alter the quality of life in the long-term and even lead to increased mortality for a vulnerable age group of patients.[1] Moreover, the high incidence of post-operative cognitive dysfunction in the older population which is estimated to be in the order of 20 percent to as high as 40 percent from several studies demonstrates that our patients are at real risk of developing this complication.[2,3,4,5]

Post-operative delirium is characterised by a fluctuating state of inattention and disturbances of perception, thinking, memory and psychomotor behaviour. It has an acute onset and occurs in the first few days following surgery.[6] The disorder exhibits hypoactive and hyperactive forms, the former of which is often missed by clinicians. Post-operative cognitive dysfunction (POCD) however, denotes a deterioration in cognition that is temporally related to surgery.[4] It is identified on neuropsychological testing before and after surgery.[3] It has the distinction from delirium of a normal conscious level.

These conditions mark the older patient in particular who are least able to adapt or recover from its effects. This insidious and persistent consequence has the capacity to rob them of their independence, creates a greater burden on healthcare services and ultimately on families. It is therefore, of great interest and a matter of prudence to not

only attempt to delineate causation and hence address risk factors but to reach towards actively intervening to prevent this feared complication from arising.

The concept of pre-conditioning is not an unfamiliar one. An example of this is the effect of exposure to volatile anaesthetic agents and ischaemic events on myocardial protection.[18] There is also great interest in pre-habilitation which is preconditioning in the physical sense prior to surgery. Patients undergo strength training, breathing exercises and entire body aerobic exercise in an attempt to improve postoperative recovery.[7] A systematic review has shown translations into clinical effect with patients showing improved quality of life scores and shorter hospital and intensive care stays.[8] The initial insult of surgery reduces physical fitness post-operatively and after reaching a nadir, recovery ensues ideally attaining baseline levels. Pre-habilitation aims to increase a patient's baseline state or initial physical reserves and thus cushions the impact of surgery on physical fitness.

By extension, cognitive pre-conditioning also has the potential to increase a patient's reserves, this time, in the cognitive sense and thus reduce the impact of post-operative delirium and cognitive dysfunction. Results have been promising in animal studies showing that pre-operative environment enrichment is capable of reducing memory deficits at both clinical and biochemical levels in rats.[9] Thus far human studies have also been encouraging. An RCT in patients undergoing gastrointestinal surgery and taught a memory exercise pre-operatively showed a reduction in post-operative cognitive dysfunction.[2] On-going trials in the US (Neurobics) and the UK (Cog-Train) are underway to further prove these postulations and map out a functional cognitive training regime that can be implemented on patients most at risk.[10,11]

2.0 STUDY OBJECTIVES

2.1 Primary objective

To determine if a novel, home-based, pre-operative cognitive training reduces the incidence of post-operative cognitive dysfunction in older patients.

2.2 Secondary objectives

a)To determine risk factors for POCD in our patient population.

b)To determine the association between the duration of cognitive training and POCD.

c)To determine the association between post-operative delirium and POCD.

3.0 METHODOLOGY

3.1 Sample size

Based on the incidence of 36% POCD at one week from a previous study[2] and our proposed 50% reduction to 18% incidence with intervention, a total of 232 participants (including 10% drop-out rate) are required at a 1:1 ratio between groups to achieve an 80% powered study and Type 1 error of 5%.

A pilot study of 18 patients was determined to be necessary to test out our methods and determine feasibility.

Table 3.1: Sample size calculations[19]

Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials	
Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	36
Percent of Exposed with Outcome:	18
Odds Ratio:	0.39
Risk/Prevalence Ratio:	0.5
Risk/Prevalence difference:	-18

	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size - Exposed	96	95	106
Sample Size-Nonexposed	96	95	106
Total sample size:	192	190	212

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Results from OpenEpi, Version 3, open source calculator--SSCohort
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

Patients meeting the inclusion and exclusion criteria were recruited from pre-operative anaesthetic clinic a minimum of 10 days from the operation date. Written consent was obtained. Patients were then randomised into intervention and control groups. Baseline cognitive testing was performed. Patients in the intervention groups were asked to attend a cognitive training session after which they would perform the training at home and keep a diary. The control group was asked to continue with their daily routine. Patients were seen one day preoperatively upon admission and further cognitive testing was performed. Diaries were collected from patients in the intervention group. Bispectral Index (BIS) monitoring was used intra-operatively with values kept between 40-60, mean arterial pressure within 20% of pre-anaesthetic values and normocapnoea maintained. Post-operatively, patients were assessed at POD1, POD2, POD3, POD7, POD30 (via telephone) and post-op 1 year. Anaesthetic and surgical teams involved and post-operative assessors were blinded to the arm of the study. The researcher recruiting patients at pre-operative anaesthetic clinic would also perform pre-operative assessments during admission and a different researcher would complete the post-operative assessments to ensure blinding.

Table 3.2: Study design

ANAES CLINIC	**PREOP DAY**	**SURGERY**	**POD1**	**POD2**	**POD3**	**POD7 (interview)**	**POD30 (phone)**	**1 YEAR (interview)**
1.Eligibility assessment • GDS • My4AT 2.Consent 3.Randomize 4.Demographic • Medical history • Medications • Surgical details 5.Baseline – • IADL • MOCA 6. Test contactable phone number	Baseline cognitive assessment •My4AT •MOCA •CANTAB •TMT •DSST	1. BP/ HR 2. SpO_2 3. BIS 40-60 4. Medication 5. Surgical details and events	1. BP/ HR 2. VAS-pain 3. My4AT 4. Meds 5. Events	1. BP/ HR 2. VAS-pain 3. My4AT 4. Meds 5. Events	1. BP/ HR 2. VAS- pain 3.Assessment • My4AT • MOCA • CANTAB • TMT • DSST 4. Meds 5. Events	1. Events 2.Assessment • My4AT • MOCA • CANTAB • TMT • DSST	1. Events 2. GDS 3. IADL	1. Events 2. Assessments •GDS •IADL •My4AT •MOCA •CANTAB •TMT •DSST

BIS:	Bispectral index	IADL	Instrumental activities of daily leaving scale
My4AT:	Malaysian 4AT	MOCA:	Montreal Cognitive Assessment
CANTAB:	Cambridge Neuropsychological Test Automated Battery	VAS:	Visual Analogue Score
GDS:	Geriatric Depression Score		

Randomisation was done using computer software. Subjects were randomised into intervention and control groups. Numbered envelopes according to the randomisation tables were used throughout the trial.

3.2 Inclusion criteria:

a) Aged 65 years or older, ASA I-III

b) Elective surgery undergoing general anaesthesia (excluding neurosurgery and cardiac surgery)

c) Date of surgery at least 10 days and up to one month from date of recruitment

d) Duration from induction of anaesthesia to end of anaesthesia minimum 2 hours

e) Expected post-operative hospital stay at least 48 hours

f) Able and willing to give informed consent

g) Literate

h) Willing to undergo cognitive and delirium assessments, perform daily cognitive training and able to return for follow-up assessments at 1 week, 1 month (phone call) and 1 year.

3.3 Exclusion criteria:

a) Glasgow coma scale < 15

b) Geriatric depression score (GDS-5) ≥ 2

c) Pre-existing psychiatric disorder or delirium

d) Severe visual, hearing or speech impairment

e) General anaesthetic within the last 6 months

3.4 Cognitive training session structure

Patients in the intervention group were asked to perform 1 hour long cognitive training at home divided into 4 activities lasting 15 minutes each. Examples of exercises were memorising words, listing words beginning with an alphabet, sequential subtraction, and summarising newspaper articles. Patients were taught to gradually increase the intensity of the exercise. For example, adding on new words to remember and starting with a larger number for sequential subtraction. See appendix for detailed instructions to subjects.

Patients were scored for level of function by the Lawton Instrumental Activities of Daily Living (IADL) score. 8 aspects of daily living such as the ability to use the telephone to preparing meals and managing finances was used to represent the degree of functioning of a patient. 0 represents low function and 8 high for women and 5 for men. The latter is to avoid gender bias in daily tasks such as doing the laundry and food preparation.

3.5 Cognitive assessments

The Montreal Cognitive Assessment (MoCA) tests subjects on 7 aspects of cognition. These are visuospatial and executive cognition, naming, attention, memory, language, abstraction and orientation.

Another cognitive test employed was the trail making test. It is a connect the dots type of exercise in a series of alternating alphabets and numbers. The time taken for the patient to complete the exercise was used as a measure of cognition. Patients who did better on the test required shorter times to complete.

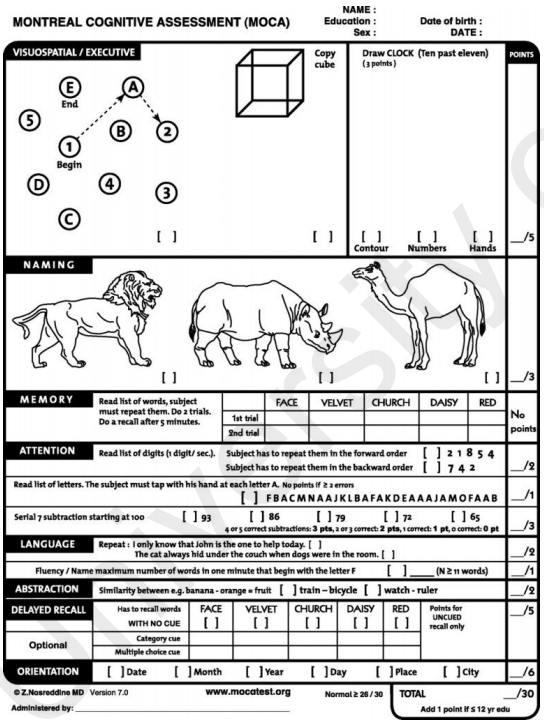


Fig 3.1: MoCA sample

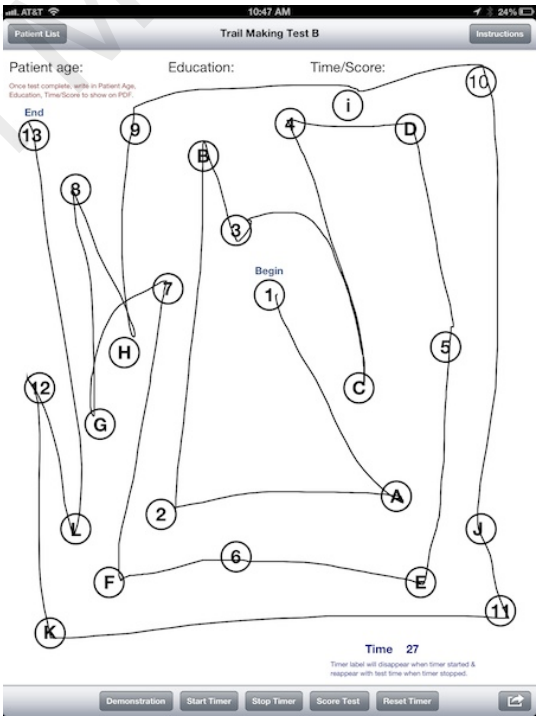


Fig 3.2: TMT sample

The Digit Symbol Substitution Test (DSST) is an exercise of substituting numbers with paired symbols following a given key. The maximum number of correct substitutions within a 2 minute period gives the score.

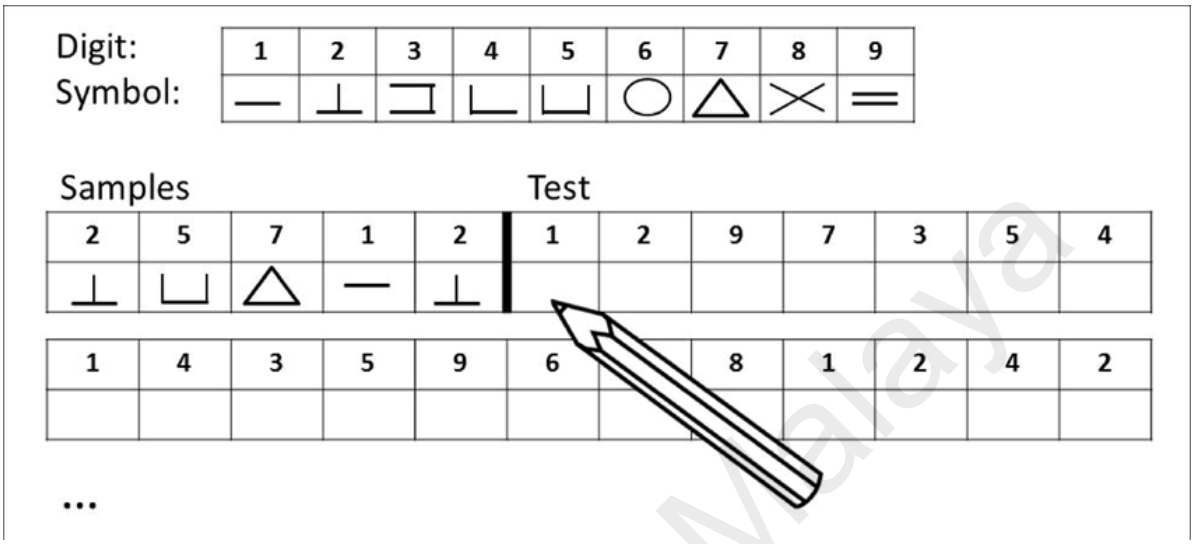


Fig 3.3 DSST sample

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is software developed by the University of Cambridge. It evaluates and measures various aspects of cognitive function and is a validated research tool. It contains a battery of tests of working memory, learning and executive function; visual, verbal and episodic memory; attention, information processing and reaction time; social and emotion recognition, decision making and response control. For this study, 2 tests were selected for use, the 'Reaction Time (RTI)' module and the 'Paired Associates Learning (PAL)' module. The software generates a raw score for each variable in each module and this allows comparison across patients and for individual patients at different testing points.

The PAL module is a test with a series of boxes which sequentially reveal and conceal various symbols in them. Patients were prompted to indicate which box contained a symbol presented to them. In the event of an error, the symbols would be again revealed and concealed and the subject is prompted again. As the subject clears a stage, the test will increase in difficulty by an increase in the number of symbols to be recalled. The test is terminated prematurely (failed attempt) if the subject is unable to clear a stage after a maximum number of attempts. Patients can elect to stop the test at any point and this is considered an aborted test.

The RTI module consists of waiting till a coloured dot appears on the screen and moving a finger across the screen to tap on said coloured dot. This is repeated. The second stage of the test has dots appearing in different locations on the screen. It essentially evaluates the accuracy and reaction time of patient responses.

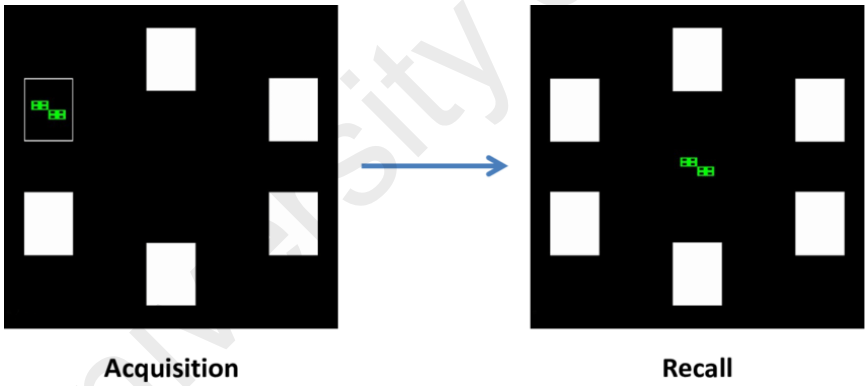


Fig 3.4: PAL screenshot

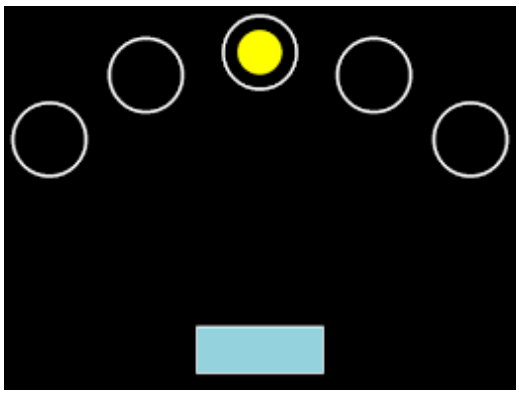


Fig 3.5: RTI screenshot

4.0 RESULTS

This study was conducted over a period of 179 days (15 January 2018 to 13 July 2018). A total of 19 patients were recruited in pre-operative anaesthetic clinic at a major teaching hospital. One patient withdrew from the study and thus, 18 patients were randomised into the trial.

4.1 Demographics

61% of patients recruited were female. Majority of patients were in the 65-69 age group represented by 8 patients and only one in the 80 and above age group.

Fig 4.1: Patient age distribution

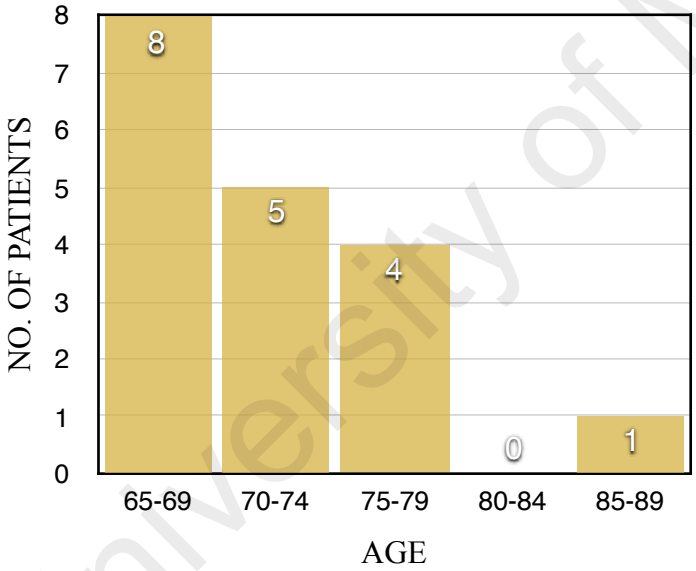
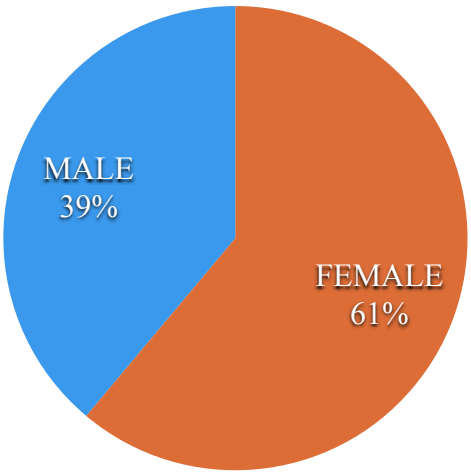


Fig 4.2: Gender distribution



4.2 Intervention and control groups

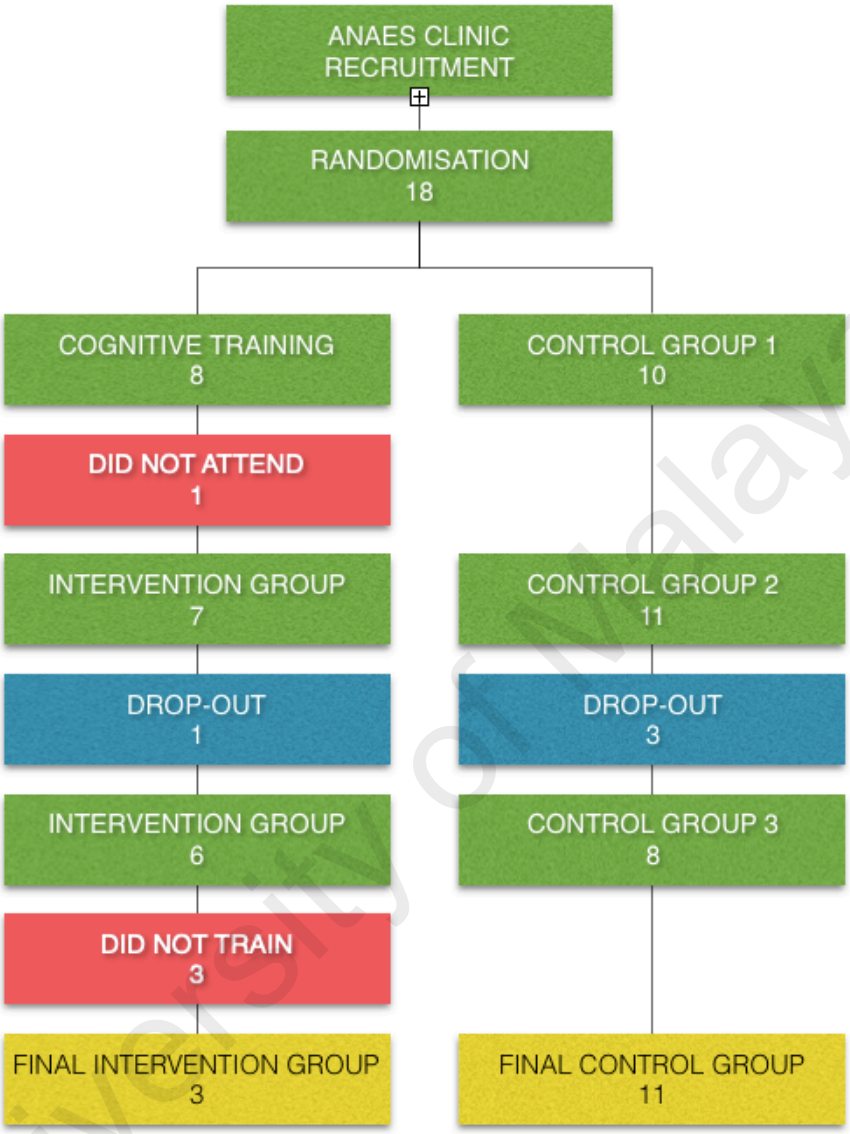


Fig 4.3: Flow chart of intervention and control groups

8 patients were randomised into the intervention group and 10 into the control group. 1 patient however could not attend due to transportation issues and was thus added to the control group. There was 1 and 3 drop-outs in the intervention and control groups respectively. 3 patients had their original operation date deferred indefinitely due to unavailability of operating time. 1 patient had a regional anaesthetic technique instead of a general anaesthetic as discussed at pre-operative anaesthetic clinic recruitment.

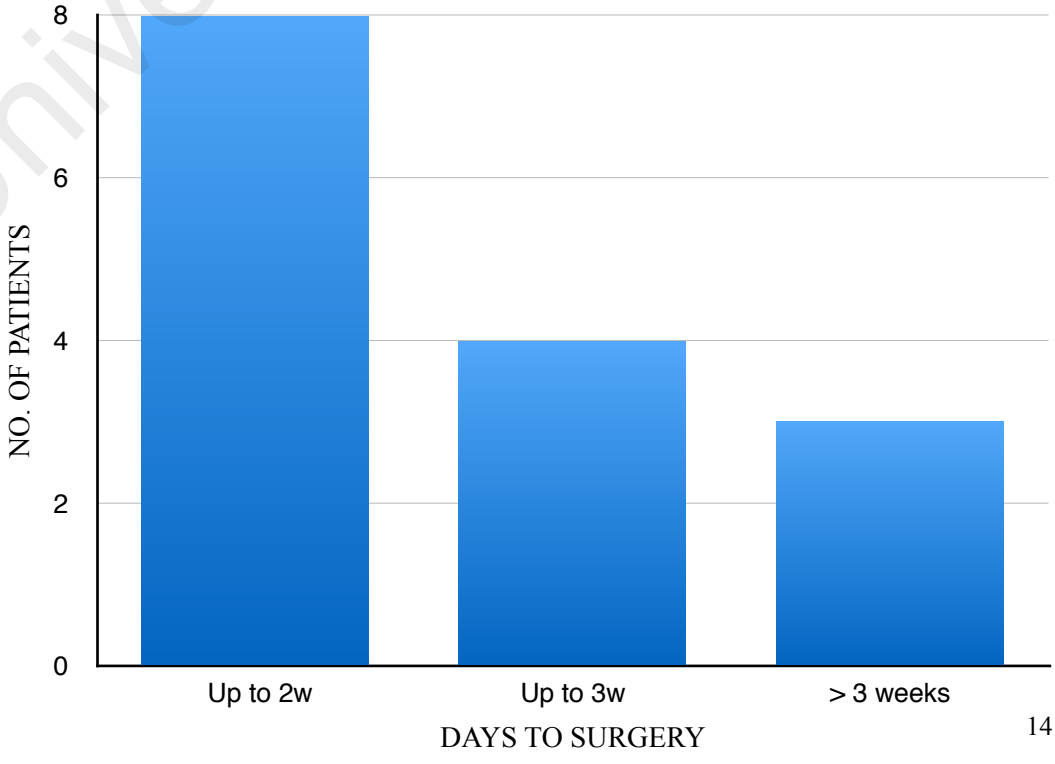
Within the intervention group, 3 patients did not perform any cognitive training at home despite having attended sessions. Reasons given were busy schedules, feeling unwell, and one patient had stopped smoking for surgery and was preoccupied with various breathing exercises in order to prepare for major surgery. Of the remaining 3 patients who had performed cognitive training at home, one completed 3 out of 13 pre-operative days, one completed 2 out of 12 and another 2 out of 14. Compliance to cognitive training rates in patients who attempted to were 23%, 17% and 14% respectively with 50% of subjects not attempting at all.

Patients who made no attempts at cognitive training were subsequently placed in the control group. The final intervention group consisted of 3 patients and the final control group, 11 patients.

4.3 Time from recruitment to surgery

Most patients had a time interval of approximately 2 weeks to the date of surgery with a small number waiting for more than 3 weeks from the time of anaesthetic clinic review.

Fig 4.4: Time from recruitment to surgery



4.4 Montreal Cognitive Assessment (MoCA) results

Fig 4.5: MoCA score in anaesthetic clinic vs pre-op

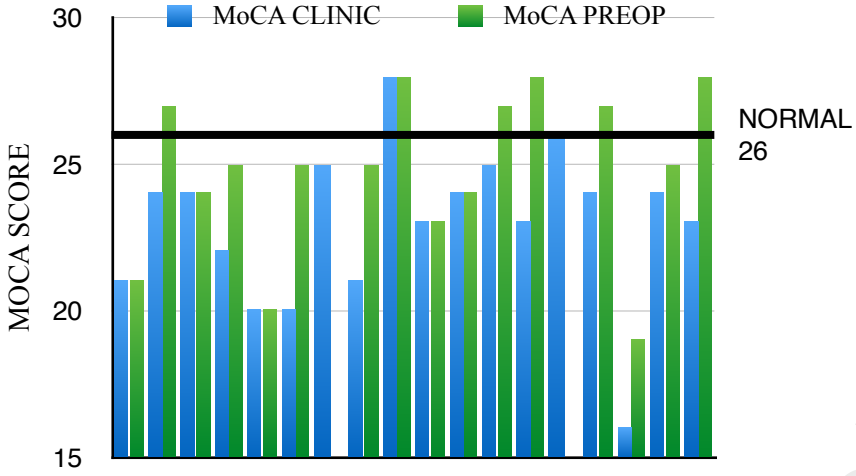
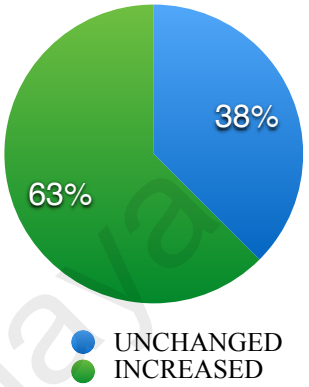
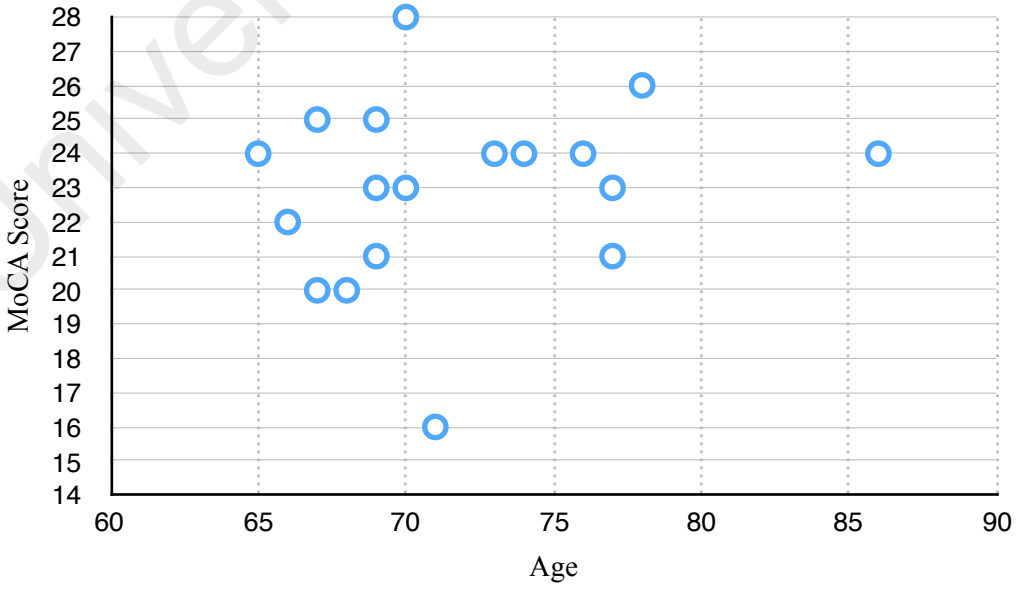


Fig 4.6: Difference in MoCA scores in anaesthetic clinic vs pre-op



The bar chart represents the distribution of MoCA scores both in clinic and pre-operatively. The majority of patients (63%) maintained their scores while the remaining demonstrated an improvement between clinic and the pre-operative day. There was no decline in scores detected. There appeared to be no association between scores and age.

Fig 4.7: MoCA score vs age



4.5 Trail making tests (TMT) results

Fig 4.8: TMT performance

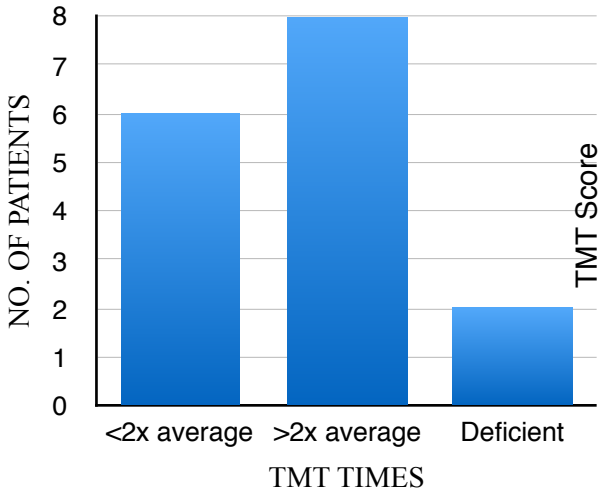


Fig 4.9: TMT score vs age

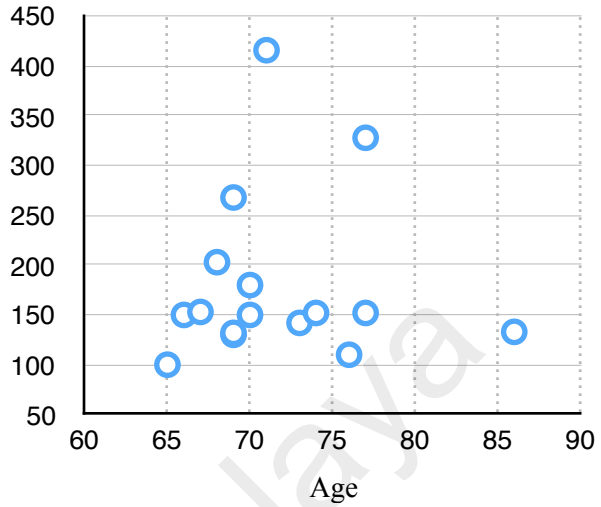
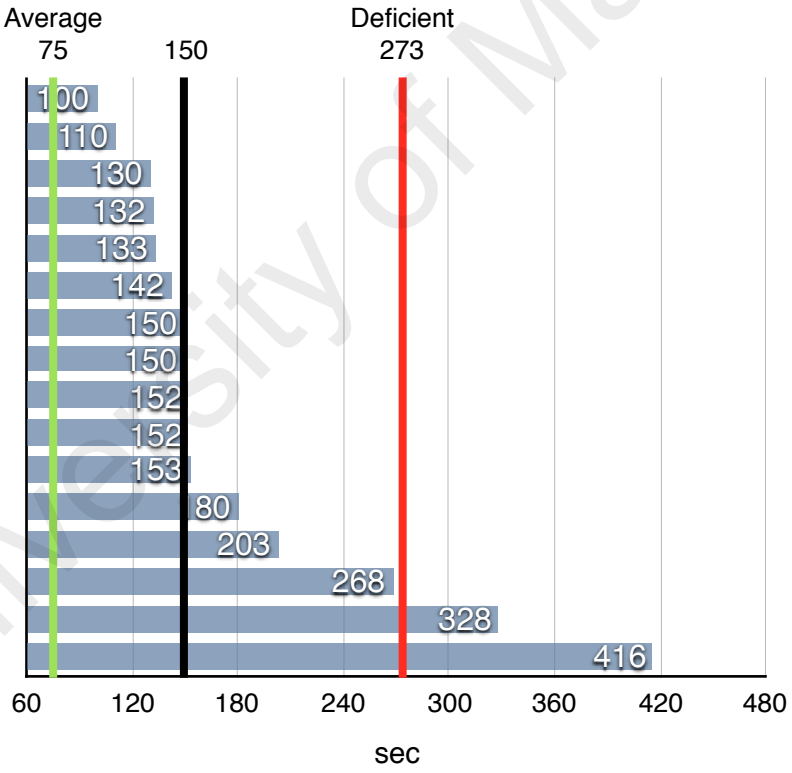


Fig 4.10: TMT score distribution

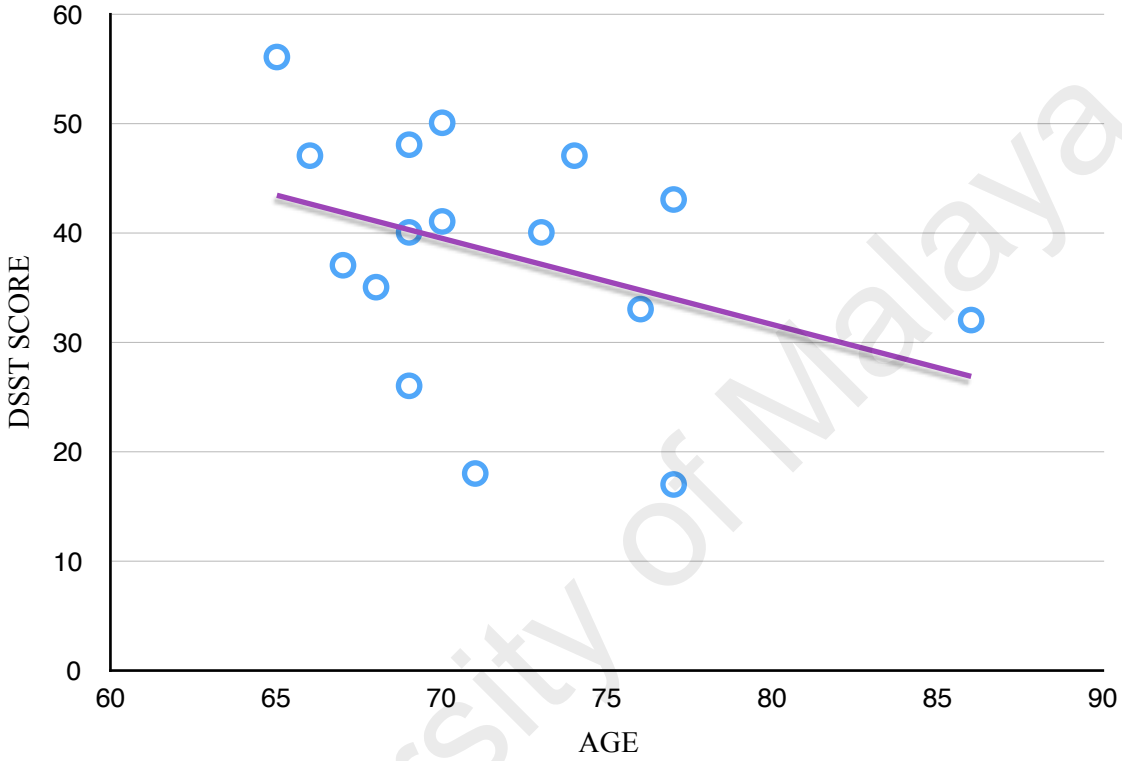


In the Trail Making Test (TMT), 273 seconds was taken as the limit beyond which a patient is deficient in this cognitive aspect. 75 was the average time taken in controlled subjects. In general, the study population required longer than 2x the average times with 2 patients particularly deficient, requiring 328 and 416 seconds to complete respectively.

4.6 Digit Symbol Substitution Test (DSST) results

When a plot of DSST score vs age was made, the observation was that pre-operative scores tended to be lower the higher the age of the patient.

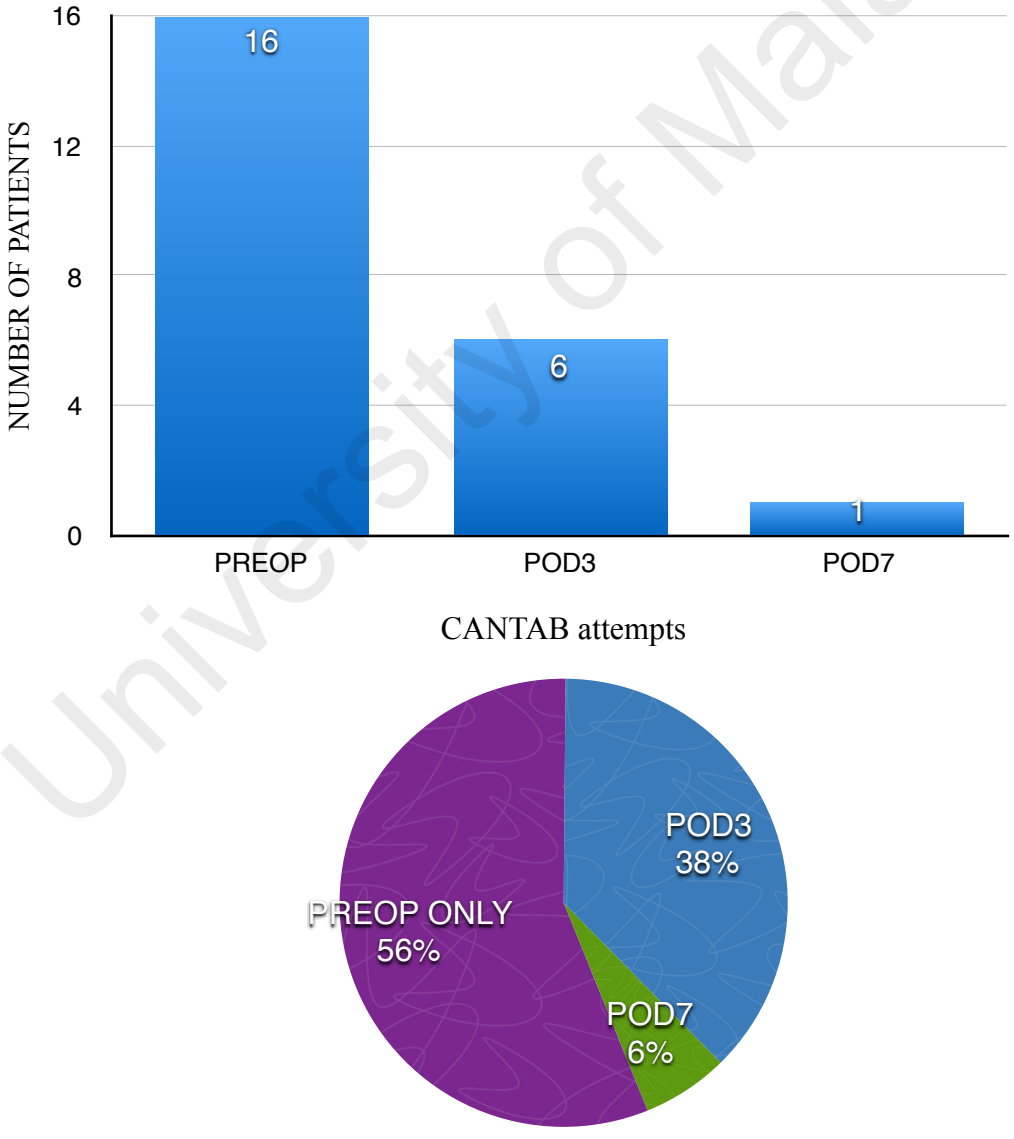
Figure 4.11: DSST scores vs age



4.7 Cambridge Neuropsychological Test Automated Battery (CANTAB) results

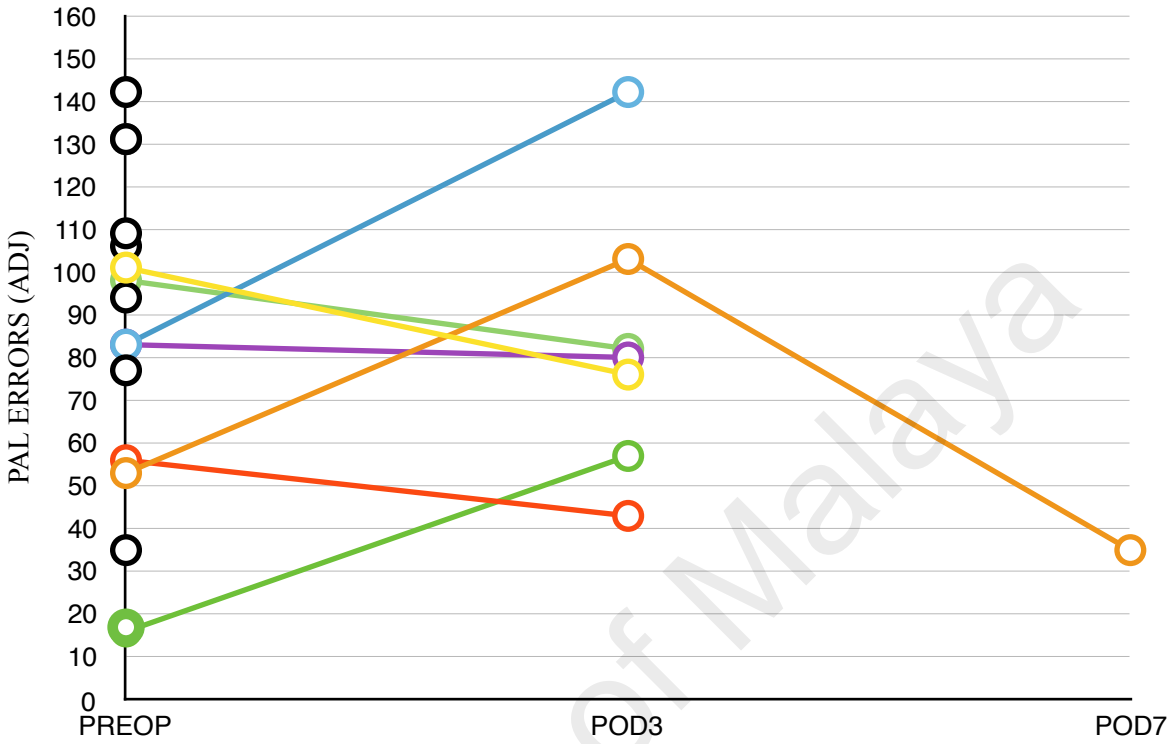
16 patients were seen pre-operatively and underwent CANTAB testing. Of the 4 drop-outs, 2 patients were tested. This occurred prior to operation date or general anaesthetic deferral. The remaining 2 did not present for hospital admission. Excluding drop-outs, 6 out of 14 patients had a CANTAB attempt at POD3 and only 1 patient was tested at POD7.

Fig 4.12: Number of CANTAB attempts at preop, POD3 and POD7 (graph and pie chart)



4.7.1 Paired Associates Learning (PAL) results

Fig 4.13: Trend of PAL errors on pre-op, POD3 and POD7



1 patient successfully completed the test only on POD7, 1 patient on 2 attempts (Pre-op and POD3) and another 2 patients on single attempts (Pre-op). 3 different patients aborted their tests. 1 during a pre-op attempt but went on to an unsuccessful attempt at POD3. The remaining 2 only had an aborted attempt preoperatively. All attempts received a corresponding raw score. Comparisons were only possible for patients who proceeded to POD3 and POD7 testing. 3 patients had an increase in PAL errors and another 3 a decrease. The only patient who was tested at POD7 had an increase at POD3 followed by a decrease at POD7.

Table 4.1: PAL total errors- sequential scores

ID	SURGERY	PREOP	POD3	POD7	% Δ PREOP/ POD3	% Δ POD3/ POD7	% Δ PREOP/POD7
3	MAJOR+	101	76		-25		
9	MAJOR+	16	57		250		
5	MAJOR	56	43		-23		
10	MAJOR	83	142		71		
12	MINOR	83	80		-4		
16	MINOR	98	82		-16		
4	MINOR	53	103	35	94	66	25

The table above depicts the observed sequential scores for patients. Major+ refers to major surgery with large fluid shifts (e.g. abdominoperineal resection), Major surgery refers to surgery entering body cavities (e.g. hysterectomy), and minor to breast surgery.

Both patient 3 and 9 underwent major surgery with major fluid shifts. On POD3, patient 3 had a decrease in total errors of 25% and patient 9, an increase of 250%. However, patient 9 had a very low score pre-operatively (16- lowest among all patients) and despite a large percentage of increase still had fewer errors overall compared to patient 3. Of 2 patients with similar pre-operative scores (10 and 12) major surgery was associated with a 71% increase in errors compared to minor surgery a 4% decrease in errors. In the minor surgery category, the patient with the lowest score pre-operatively experienced a 94% increase in errors on POD3, compared to patients with higher baselines. Patient 4 who was followed up to POD7 experienced an initial increase on POD3 followed by a decrease on POD7. There was an overall increase of 25% compared to pre-operatively at POD7 for this patient.

4.7.2 Reaction Time (RTI) results

Fig 4.14: RTI simple accuracy score pre-op distribution

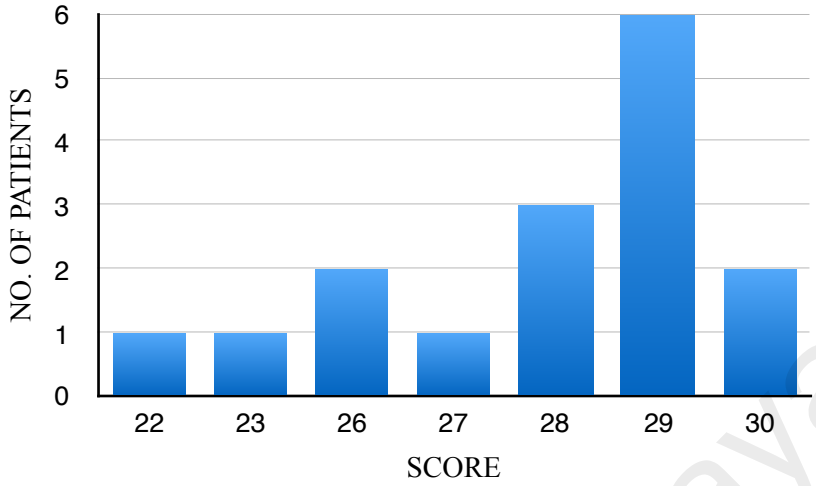
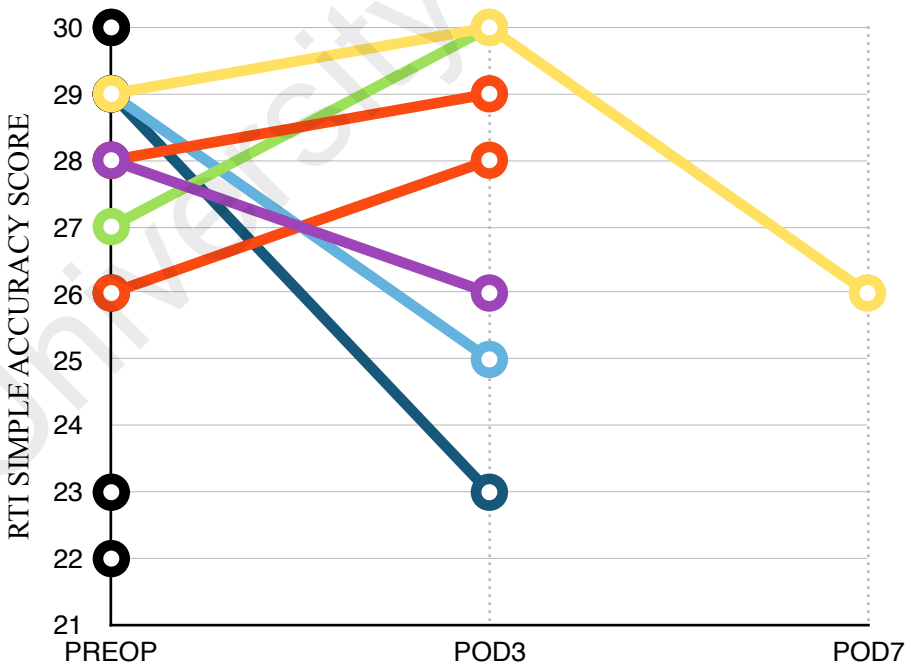


Table of distribution of patient scores for the reaction time interval (RTI) at preoperative anaesthetic clinic. 50% of patients scored near maximal scores in accuracy (29 to 30).

Fig 4.15: RTI simple accuracy score at pre-op, POD3 and POD7



Accuracy scores increased for 4 patients and decreased for 3 at POD3. 1 patient had an increase followed by a decrease in accuracy at POD7.

Table 4.2: RTI Simple accuracy score- sequential scores

ID	SURGERY	PREOP	POD3	POD7	% PREOP/ POD3	% POD3/ POD7	% PREOP/ POD7
3	MAJOR+	28	26		-7		
9	MAJOR+	27	30		11		
5	MAJOR	28	29		4		
10	MAJOR	29	25		-14		
12	MINOR	26	28		8		
16	MINOR	29	23		-21		
4	MINOR	29	30	26	3	-13	-10

There were minimal changes in either direction for this score. The most significant was patient 16 who had a 21% decrease in accuracy scores on POD3. Patient 4 had an increase in accuracy on POD3 by 3% followed by a decrease by 13% culminating in an overall decrease of 10% at POD7 compared to pre-operative scores.

Fig 4.16: RTI mean simple reaction time pre-op, POD3 and POD7

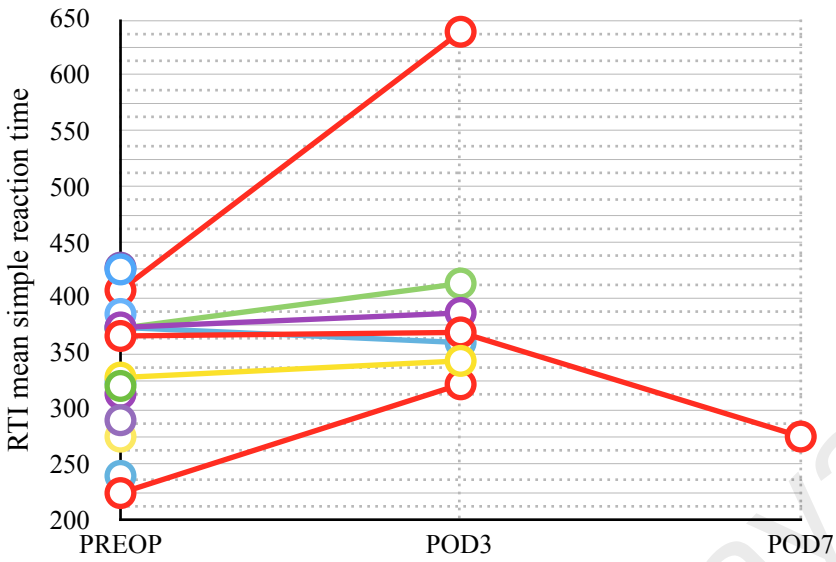
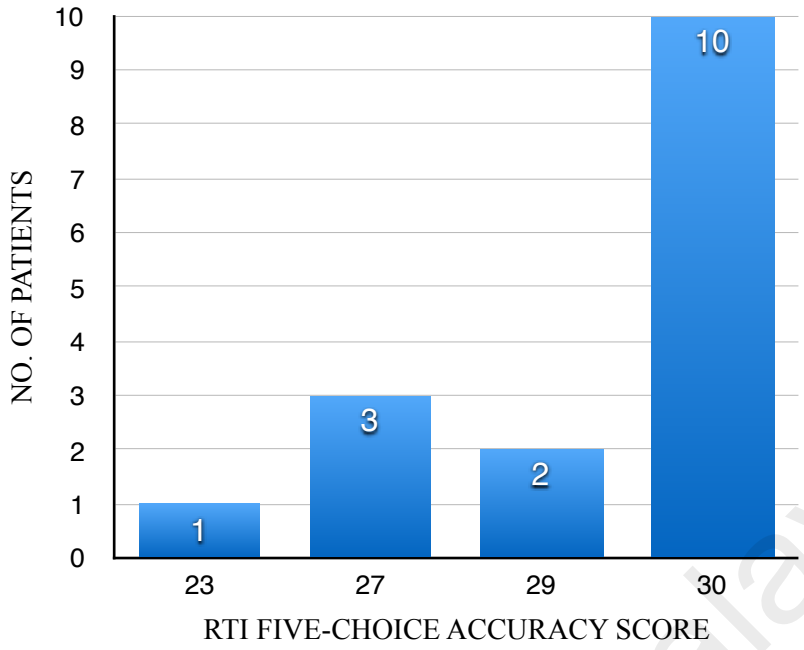


Table 4.3: RTI Mean simple reaction time- sequential trends

ID	SURGERY	PREOP	POD3	POD7	% PREOP/ POD3	% POD3/ POD7	% PREOP/POD7
3	MAJOR+	328	343		5		
9	MAJOR+	225	322		44		
5	MAJOR	373	386		3		
10	MAJOR	407	639		57		
12	MINOR	374	360		-4		
16	MINOR	373	413		11		
4	MINOR	366	369	275	1	-25	-25

Raw scores for simple reaction time ranged from 224 to 427. On this test, longer reaction times represented cognitive impairment and vice versa. On POD3, only 1 patient had a small decrease in score (-4%). 2 patients had significantly higher scores, between 44 to 57%. Patient 4 had a 1% increase in score on POD3 followed by a decrease in score of 25% on POD7. Of the 2 patients who underwent major surgery with major fluid shifts, 1 patient had only a 5% increase and the other a 44% although overall scores were lower in the latter. There were no major increases in the reaction time scores in patients who underwent minor surgery.

Fig 4.17: RTI Five-choice accuracy score pre-op



The test progresses to its second stage where the coloured dot appears in one of 5 locations on the screen. A larger proportion of patients faired well in terms of accuracy pre-operatively (75% between 29 to 30), compared to the 1st stage.

On POD3, 4 patients had exactly the same score as pre-operatively. 2 patients had a decrease in accuracy by 20 to 22% in each the minor and major surgery category respectively. 1 patient had a slight increase in scores by 4%. Patient 4 had a 20% decrease on POD3 and returned to baseline on POD7 despite having had minor surgery.

Fig 4.18: RTI Five-choice accuracy score pre-op, POD3 and POD7

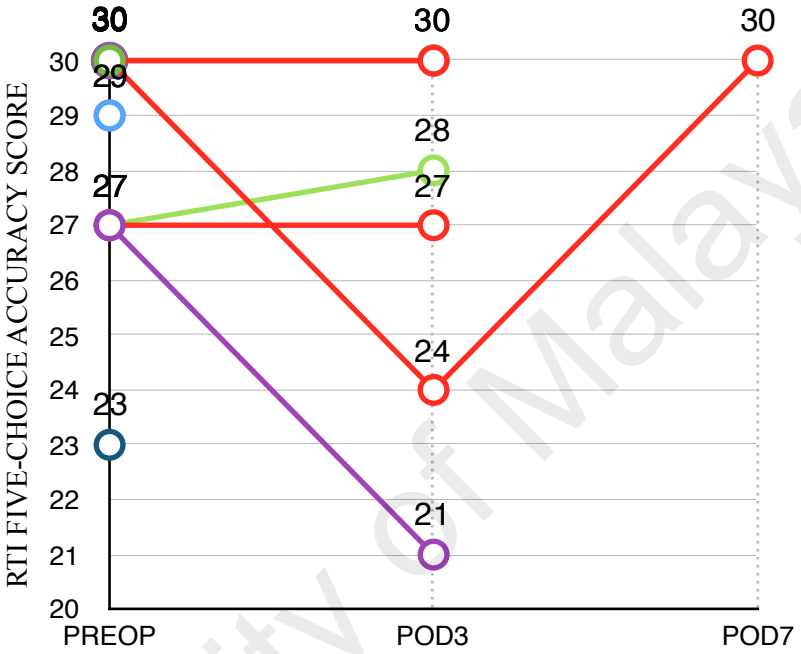


Table 4.5: RTI Five-choice accuracy score- sequential trends

ID	SURGERY	PRE OP	POD3	POD7	% PREOP/ POD3	% POD3/ POD7	% PREOP/ POD7
3	MAJOR+	30	30		0		
9	MAJOR+	30	30		0		
5	MAJOR	27	21		-22		
10	MAJOR	27	27		0		
12	MINOR	30	30		0		
16	MINOR	27	28		4		
4	MINOR	30	24	30	-20	25	0

The raw scores for reaction times for the 2nd stage of the reaction time module ranged from 258 to 544. 3 patients in the major surgery category had significant increases in reaction times ranging from 19 to 45%. The other patient in the same category experienced a decrease of 14% in reaction time. In the minor category 2 patients had a 5% and 10% decrease in scores and another a 3% increase. Patient 4 had decreases overall in this module throughout the post-operative period of up to 7 days.

Fig 4.19: RTI five-choice reaction time pre-op, POD3 and POD7

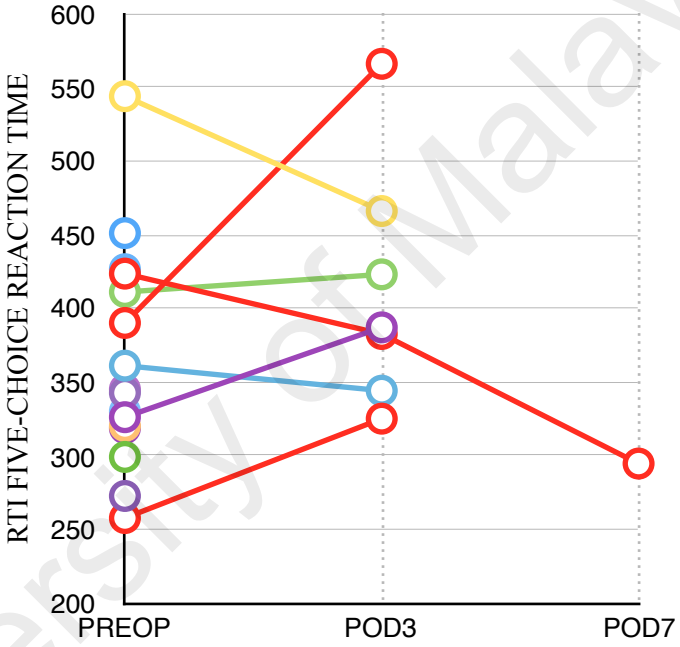


Table 4.5: RTI Five-choice reaction time- sequential trends

ID	SURGERY	PREOP	POD3	POD7	% PREOP/ POD3	% POD3/ POD7	% PREOP/ POD7
3	MAJOR+	326	387		19		
9	MAJOR+	258	325		26		
5	MAJOR	544	466		-14		
10	MAJOR	390	566		45		
12	MINOR	361	344		-5		
16	MINOR	411	423		3		
4	MINOR	424	383	295	-10	-23	-30

4.7.3 Composite trends of PAL and RTI results

Patient 3 had an improvement in the PAL (25%) and minimal changes (<10%) in the simple reaction time test. There was a longer reaction time in the 5 choice reaction time (19%) with no change in accuracy.

Patient 5 also had an improvement in the PAL (23%) and minimal changes in the simple reaction time test. However, in the 5 choice reaction time, had a less accurate response (22%) with shorter response times.

Patient 9 had a major deterioration in PAL scores (2.5x increase in errors), with general increased reaction times (26 to 44%) with little change in accuracy.

Patient 10 had a similar testing pattern to Patient 9.

Patient 12 who underwent minor surgery had minimal changes throughout.

Patient 16 who also had minor surgery had an improvement in PAL (16%). Simple reaction time and accuracy was worse (11 to 21%) but improved at the 5 choice level.

Patient 4 who had minor surgery as well had an initial deterioration and subsequent improvement in scores. This trend was marked in the PAL test (95% on POD3 and 25% on POD7).

Table 4.6: Composite trends for PAL and RTI

ID	SURGERY		PREOP/POD3 (%)	POD3/POD7 (%)	PREOP/ POD7 (%)
3	MAJOR+	PAL	-25		
		RTI-A	-7		
		RTI-RT	5		
		RTI5-A	0		
		RTI5-RT	19		
4	MINOR	PAL	94	66	25
		RTI-A	3	-13	-10
		RTI-RT	1	-25	-25
		RTI5-A	-20	25	0
		RTI5-RT	-10	-23	-30
5	MAJOR	PAL	-23		
		RTI-A	4		
		RTI-RT	3		
		RTI5-A	-22		
		RTI5-RT	-14		
9	MAJOR+	PAL	250		
		RTI-A	11		
		RTI-RT	44		
		RTI5-A	0		
		RTI5-RT	26		
10	MAJOR	PAL	71		
		RTI-A	-14		
		RTI-RT	57		
		RTI5-A	0		
		RTI5-RT	45		
12	MINOR	PAL	-4		
		RTI-A	8		
		RTI-RT	-4		
		RTI5-A	0		
		RTI5-RT	-5		
16	MINOR	PAL	-16		
		RTI-A	-21		
		RTI-RT	11		
		RTI5-A	4		
		RTI5-RT	3		

PAL- Paired Associates Learning

RTI-A- Reaction Time (Simple) Accuracy

RTI-RT- Reaction Time (Simple)

RTI5-A- Reaction Time (5-choice) Accuracy

RTI5-RT- Reaction Time (5-choice)

Yellow boxes marked unfavourable direction of scoring

5.0 DISCUSSION

Post-operative cognitive dysfunction first came to attention in patients undergoing open heart surgery in the 1950's.[13] Since then this phenomenon has received recognition in patients undergoing non-cardiac surgery. The brain appears particularly at risk at the extremes of age and increasing age has consistently been shown to increase risk of cognitive dysfunction.[13,14,15,16] We sought to include a general intact elderly population in the study in order to generate findings which could be translated to the average patient presenting for anaesthesia and surgery.

Physical training is well-established in our society and with easily measurable end-results. The field of formal cognitive training on the other hand is only recently emerging as a science and its measurement of end-results even more fraught with technicalities. The 2 on-going large randomised controlled trials employ touchpad-based commercial 'brain training' software. Although in the US and the UK, this technology may be familiar even to the older patient, in our younger society, this does not prove to be true. Commercial software is well-designed and most importantly is a standardised measure of training capable to tracking and modulation of progress. It would be useful in an ideal situation but our older patients may neither have the dexterity nor the experience to utilise these tools.

Another study utilised formal face-to-face sessions on memory training using the method-of-loci technique which required enrolled patients to attend regular sessions with a researcher in order to undergo training pre-operatively.[2] Along with literacy, the variety of languages spoken in Malaysia which did not always coincide with that of the researchers presented specific challenges for training design and testing options. In order to be inclusive in this context there would need to be a selection of

non-language and non-numerical based cognitive training and testing used. This requirement was possible with specialised commercial software.

There were also prominent transportation issues faced by our patients who were generally reliant on their families for transport. Public transportation is also less than accessible. In order to maximise participation, measures were taken to minimise mandatory attendances to hospital for the sole purpose of the study.

Taking all these practical issues into account, we chose to design a cognitive training module that would be primarily home-based with emphasis on straightforward exercises in order that a normal elderly patient could participate and most importantly would be least disruptive to their routine. We believed that the effort in completing the prescribed exercises would be key to achieving our goal with a secondary focus on task complexity. This was determined to be paper-based and thus would require literacy for the purposes of the study. Post-operative data collection was also timed to follow-up in surgical clinics in order to avoid additional trips.

There were more women recruited in this study which reflects the differences in age expectancies between genders. The age expectancy in Malaysia is 75 years old.[17] That is reflected in the decreasing trend with increasing age of patients presenting for surgery. Older patients also are generally not considered fit for major surgery and thus do not present for recruitment.

Patients were also intact in terms of activities of daily living with a small proportion of women dependent on their families for things like household chores and travelling.

Patients were referred to the anaesthetic clinic, majority of which would undergo surgery in less than 2 weeks. The ideal time period of implementing cognitive training is uncertain and the study also attempts to observe a correlation not only for the use of cognitive training but also its duration on post-operative effects. Repetition alone is

insufficient and may be counter productive, by increasing boredom and reducing motivation to continue exercising. It is for this reason, patients were also taught to apply simple step-wise gradations to increase the difficulty of training whenever they achieved the goal for a certain step. In fact, this is a fundamental concept of any training be it physical or cognitive.

There were significant challenges which were anticipated even with arranging for one extra visit to the hospital in order for patients randomised into the intervention group to be taught the cognitive training that they were to perform at home. Even though patients attended the training session, a large proportion did not go on to perform cognitive training despite feeding back that they understood what had been taught or had dismal compliance rates. These findings reveal that independent cognitive training without a researcher or a software monitoring progress and trouble-shooting throughout the study duration, interventions have the potential for low compliance or failure. This is an inherent flaw in our attempts to minimise inconvenience to participants, that there is poor engagement. It is also one of the main reasons that a pilot study was necessary to flesh out the potential issues. Post-operative follow-up after hospital discharge which required telephone communication was also difficult to maintain with patients saying that they could not hear an incoming call or were reluctant to answer an unknown caller ID. This is common as the mobile telephone is considered more as a tool to make calls rather than to receive them in the elderly. Therein also because patients attend primarily to consult their surgeons and study researchers attempt to intercept patients at these visits, sometimes there is a communication breakdown and patients are lost to follow-up.

This study employed 2 main modalities of cognitive assessments which were the CANTAB software which is a touchpad-based programme and more traditional paper

format testing, the MOCA, TMT and DSST. CANTAB does not require literacy as testing was based on visual cues using symbols. It did require that patients use a touchpad which some patients were not too familiar with. The gestures required were simple but for an elderly population, adequate dexterity and hand-eye coordination presented some limitation. Computer-based testing allows objective recording of results and testing across various cognitive domains. Composite scores allowed accurate scoring reflective of a patient's true abilities. The interactive nature of the testing also appeared to engage patients better although some tests were more protracted than others. Patients were better accustomed to paper format testing but it did require literacy to words and numbers. Increasing familiarity with replicated testing sessions meant patients could improve on their scores by memorising. This is in comparison to the ability of computer software to perform random presentation of any particular tests during different sessions. The CANTAB system also required a physical network key to function and this meant that only one patient could be tested at any one time leading to a practical limitation. As with any testing modality, clear, accurate and consistent instruction was key. Computer based cognitive assessments appear to have a more organised and sophisticated technique. However this modality is limited by the proprietary nature of software use and its mandated technology.

Patients in general could undertake cognitive testing presented to them. Memory components however were the only domain which posed a significant challenge to a proportion of patients to the extent that they requested to abort testing. Memory testing in itself provides on-going feedback to the patient on their abilities and may in turn be upsetting. One test in the CANTAB series, the Paired Associates Learning (PAL) in particular is programmed to repeat the memory testing until a maximum number of attempts where it determines that the patient is unable to complete the test. It is

designed to utilise repetition in order to improve memory however it has an unpleasant effect of reminding patients who were cognitively impaired in this aspect, of their short-comings.

No delirium was detected post-operatively in patients in both arms.

The incidence of post-operative delirium widely ranges from 5 to 50% but the number of recruited patients in this study could be underpowered to detect this complication.[7]

Among reasons for low compliance rates among attendees is possibly low interactive properties of training, lack of supervision and personal motivation, poor understanding or memory of training, preoccupation with impending surgery and other responsibilities (e.g. caring for grandchildren, other prescribed prehabilitation, remembering to take multiple medicines). Future studies could remedy some modifiable factors. For example, in order to minimise travelling but still maintain a degree of interaction and feedback throughout the pre-op period, daily video-conferencing could be arranged to help patients with performance of daily cognitive training. The surgical teams and surgical clinic staff could be enlisted to alert researchers of study participants in clinic in order to 'close the loop' and ensure that no patients are lost to follow-up. Patient's families could also be asked to participate in ensuring that their family members who have been recruited perform cognitive training and do not miss interviews with researchers during hospital attendances. Another possibility with family involvement is using internet-based software to run more structured and visual cognitive training which would have the added benefit of recording progress more comprehensively.

Within the limits of this study, no association was found between age and MoCA and TMT scores but there appeared to be an association between increasing age and lower DSST scores. However, this could be confounded by other factors such as previous educational attainment, previously undetected cognitive dysfunction and

lifestyle factors such as engagement in physical or cognitive exercise prior to joining the study.[7,14] The improvement in MoCA scores pre-operatively compared to at anaesthetic clinic could be attributed to familiarity with the test having done the test before and obtaining feedback from researchers. As patients are only screened for gross visual acuity problems, differences in actual visual acuity and availability of prescription visual aids (e.g. reading glasses) did have an impact on performance on visual based testing for some patients.

There was low numbers of CANTAB attempts on POD3 as majority patients were discharged before that and the ones that were still admitted were not feeling up for the long duration of cognitive testing. As discussed before, there were issues with contacting patients when they attended their clinic follow-up as well as feeling hurried to leave after their surgical reviews by their families who needed to return to their work elsewhere leading to low attempts at POD7.

The definition of POCD lies in comparing results between baseline neuro-psychological testing and post-operative testing. Therefore, test scores should be interpreted individually in order to detect POCD. Under the PAL total errors score where increasing scores reflected increasing errors in the test, there was no clear association with type of surgery. Even in major surgery involving fluid shifts patients had both decreases and increases in errors indicating that other factors were in play. Increases in errors were attributable to surgical insult and could well be early POCD. Decreasing errors however could not easily be explained for this particular test as there was no element of familiarity as testing patterns were random and difficult to predict. It could be postulated that in these patients having undergone surgery felt relief and therefore were less worried and preoccupied than they did before. They were then able to concentrate better on testing and thus achieved better scores.

The following test in CANTAB was the RTI which tested a different domain of cognition which was reaction time and accuracy of reactions. Higher times represented more sluggish responses to stimuli while lower accuracy scores meant more mistakes in responses to stimuli. The data showed that there was little changes in accuracy but marked ones in reaction times. Patients were taking longer to achieve similar accuracies post-operatively. This observation was mixed in those who underwent major surgery but was absent in those who underwent minor surgery.

If taking 20% change as the cut-off for significance in pre and postoperative scores, there was a concurrence between the 2 CANTAB tests trending. 2 patients who had undergone major surgery had both worsening of PAL and RTI scores. It is reasonable that deterioration in all domains of cognition after a common insult. However there were some patients who had contrasting observations, reflecting cognition as a multi-faceted entity. There could be varied predispositions, selective preservation of some domains, or even gradations of susceptibility affecting results.

To imagine what awaits an older patient surviving thus far intact to require even minor surgery and then becoming permanently changed cognitively and functionally after, is bleak indeed. Studies into post-operative cognitive dysfunction are fraught with multiple contending factors and truly delineating and distilling data into meaningful and applicable information is challenging to say the least. With greater numbers, enhanced screening of risk factors, standardising of testing and maximising patient engagement in the intervention of cognitive training, the picture would hopefully become clearer.

6.0 CONCLUSION

The pilot study demonstrated that improvements were needed with respect to the method of cognitive training, in order to ensure maximal engagement and compliance. Some practical solutions include involving family members during recruitment for the study. This would also enable a non-computer literate patient to be given the opportunity to participate in computer software-based cognitive training. The modality and the inherent duration of cognitive assessments must also be selected with care to be the least cumbersome as well as keeping patient sensitivities in mind. The study will also require the support of the surgical teams and trained support staff both in identifying at risk patients and follow-up during hospital admission and throughout the post-operative period.

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