ORIGINAL ARTICLE

Early Post Operative Cognitive Dysfunction (POCD) in middle aged hypertensive patients: A pilot study

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Abstract

Background: Nowadays, hypertension is prevalent in middle aged persons. Patients with hypertension are known to have cognitive dysfunction and, therefore, may be vulnerable for post-operative cognitive dysfunction (POCD) also. Intra-operative hypotension is documented to be associated with cognitive decline in hypertensive patients. **Materials and Methods**: A prospective pilot study was conducted in 30 hypertensive (Group H) and 30 non-hypertensive (Group N) patients, aged 40-59 years, undergoing elective surgery under general anaesthesia to estimate the incidence of early POCD in known hypertensive patients and compared with non-hypertensive patients. All patients underwent a "Neuro-psychological Test Battery" to assess cognitive function on preoperative day and on 7th postoperative day. A standard anaesthesia protocol was followed. Vasopressor boluses were used to maintain mean arterial pressure (MAP) within 20% of the baseline value in both groups. **Results**: The incidence of POCD was 23.3% in hypertensive patients and 20% in non-hypertensive patients. The vasopressor boluses used to maintain blood pressure was more in hypertensive patients (P = 0.041). Consequently, hypertensive patients had a significantly higher minimal MAP (P = 0.001) and a lower fractional minimal MAP (P = 0.011) compared to non-hypertensive patients. No significant correlation was observed between fractional minimal MAP and occurrence of POCD. **Conclusion:** This pilot trial shows that the incidence of early POCD in middle aged hypertensive and non-hypertensive patients are similar after general anaesthesia.

Key words: Early Post Operative Cognitive Dysfunction, fractional mean arterial pressure, middle aged hypertensive patients, Neuropshychiatric test battery, Z score

INTRODUCTION

Derangement of higher mental functions is known to occur in the postoperative period. It could manifest immediately after surgery in the form of Post-operative delirium characterised by disturbance of attention and reduced clarity of awareness of the environment. When the derangement of cognition develops 72 hours to 1 week after surgery, it is known as Early Post Operative Cognitive Dysfunction (Early POCD).[1] When it develops after weeks and lasts for month or persists permanently, it is known as delayed Post operative cognitive dysfunction (Delayed POCD).[1] Assessment for early POCD is usually done 72 hours after anaesthesia and preferably at the end of one week after surgery.

Hypertensive patients are at a greater risk of decreased cerebral perfusion during episodes of hypotension in peri-operative period due to altered cerebrovascular auto-regulation.[2] They are also known to have cognitive dysfunction.[3-6] Schmidt *et al.* found increased peripheral blood levels of s-100b-a marker of cerebral injury, in hypertensive patients in the post-operative period.[3,7] Though the relationship between hypotension and cognitive dysfunction has been studied in elderly patients undergoing surgery, the results are inconsistent.[8-11] An analysis of neuro-cognitive performance in hypertensive patients, who underwent spine surgery under general anaesthesia

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suggested a significant relationship between minimum intra-operative mean arterial pressure (MAP) and decline in cognitive functions one day after and one month after the anaesthesia exposure.[11]

Hypertension is a common finding in middle-aged population, the prevalence among urban population varies from 15-25%.[12,13] Though studies in the elderly hypertensive patients have assessed incidence of POCD, no study till date has estimated incidence of POCD in middle aged hypertensive patients. Middle-aged population comprises critical resource both at work places as well as in the domestic front. Therefore, it is essential to know the incidence of POCD in middle aged hypertensive patients, probable aetiological factors and preventive measures. Therefore, this pilot study was intended to evaluate the effect of general anaesthesia on early POCD in hypertensive middle aged patients.

MATERIALS AND METHODS

After obtaining approval of the Institute Ethics Committee, 30 hypertensive and 30 Non-hypertensive patients, aged 40-59 years, undergoing elective surgical procedures under general anaesthesia lasting ≥2 hrs were enrolled in this prospective pilot study from July 2009 to October 2010. Patients who were diagnosed with essential hypertension and taking anti-hypertensive medication were included in Group H. Group N consisted of age matched non-hypertensive patients. Patients with other co-morbidities were not included in this study. Patients who had not completed high school education, those with significant visual, auditory or central nervous system (CNS) disease and those on tranquillisers/antidepressants were not included. Patients with mini mental state examination (MMSE)[14] score of ≤23 or Beck's depression Scale[15] ≤15 at screening were excluded. Patients unwilling to comply with the protocol or unable to understand the language used (English or Hindi) were also excluded.

A written informed consent was obtained from each patient. All the patients were interviewed twice, once on the day prior to surgery and again, seven days after the surgery. Following pre-anaesthetic assessment, patients were subjected to two neuropsychological tests to exclude pre-operative dementia (MMSE)[14] and depression (Beck's depression scale).[15,16] The enrolled patients underwent the "Neuropsychological Test Battery" comprising of four tests: Verbal learning test,[14,17] Stroop's color word test,[18-20] trail making test,[14,21,22] symbol digit modality test.[14,23] Questions were asked either in English or Hindi as chosen by the patient and were completed within 45 minutes.

A standard anaesthetic protocol was used in all the patients. Anaesthesia was induced with propofol 1.0-2.5 mg/kg and endotracheal intubation was facilitated with vecuronium 0.1 mg/kg. Hypertensive patients received intravenous lignocaine 1 mg/kg, 90 seconds prior to intubation. Intra-operative analgesia was maintained with morphine 0.1-0.2 mg/kg. Anaesthesia was maintained with propofol infusion (3-6 mg/kg/hour), intermittent doses of vecuronium along with oxygen and nitrous oxide (40:60). At the end of the surgery, neuromuscular blockade was reversed with neostigmine (50 µg/kg) and glycopyrrolate (10 µg/kg).

Blood pressure was maintained within 20% of the baseline value in all the patients. Hypertension was managed by increasing rate of propofol infusion while mephentermine (3 mg/dose) was used to treat hypotension. Mean blood pressure was recorded at 5 minute interval till the end of anaesthesia. Intra-operative hemodynamic events were recorded along with the rescue medications used. All the patients were re-assessed using the same "Neuropsychological Test Battery" on 7th postoperative day.

Assessment for POCD was done using number of correct answers from cumulative number of words recalled and the number of words at delayed recall from the Verbal learning test; time to complete and error scores from Part C of Stroop's color word test; time to complete part B and the number of errors from trail making test and number of correct answers in symbol digit modalities test. Each patient acted as his/her own control by comparing post-operative test scores against their performance in the pre-operative period. The Z scores were generated to evaluate neuropsychological performance from pre- and post-operative values for every test in each patient. They were calculated by dividing the difference of change in (pre and post operative) individual neuropsychological test score and the mean change in test score of all the patients by the standard deviation (SD) of the change in test score of all patients in that group.[8,24,25] Composite Z scores were calculated by combining Z scores of all the tests for each patient in both the groups. Early POCD was defined as the combined Z score to be less than −2 SD or the individual 2 or more Z scores with a value of less than −2 SD.[8,24,25]

Fractional MAP data was derived in each patient from the intra-operative MA*P* values. Fractional MAP was the difference between intra-operative MAP and baseline MAP measured as percentage of pre-operative baseline MAP. The duration for which the MAP was less than 20% below baseline was calculated by drawing a graph of individual MAP readings and noting the time as fraction of total anaesthesia time in which the MAP was less than 20% of the baseline MAP.

Statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS version 17.0). Normally distributed data like age, duration of anaesthesia are presented as mean ± standard deviation (SD) and analysed using unpaired Student's *t*-test. Scores of neuropsychological tests are presented as median (interquartile range) and analysed using Mann Whitney U-test as appropriate. Categorical data like sex or mephentermine boluses are presented as frequency or percentage and analysed using Chi-Square test and Fisher's exact test. *Ps* < 0.05 was considered as significant. The binary outcome of POCD was compared with fractional minimum MAP in a binary logistic regression for the two groups separately.

RESULTS

All the patients were able to complete the battery of neuropsychological tests. Both groups had similar demographic features, baseline MMSE and pre-operative Beck's depression score [Table 1].

The comparison of individual pre-operative neuropsychological test scores showed no significant difference between the two groups. But a significant difference was observed when pre and post-operative test scores were compared in both group H and N separately. [Table 2] This shows worsening of neuropsychological performance in both the groups one week after the surgery. The comparison of post-operative neuropsychological test results between the two groups shows that the time taken to perform trail making test part B was significantly longer in group H (*P* = 0.033). This shows significant worsening of cognitive function in the hypertensive patients postoperatively. There was no significant difference in the other post-operative test results between the two groups [Table 2].

The Z scores for each test were calculated for each patient. The median Z score for each test and the combined Z score in each group were computed [Table 3]. All the individual Z scores and the combined Z score of each patient at one week were counted to identify those with scores less than - 2. This number estimated the occurrence of POCD in both groups. Six (20%) normo-hypertensive and seven hypertensive patients (23.3%) developed POCD, the difference between the groups was not statistically significant.

Hypertensive patients had a significantly higher value of mean minimal MAP (*P* = 0.001) and maximal MAP (*P* = 0.001) compared to normo-tensive patients. The duration of total anaesthesia time during which MAP was 20% below or above baseline was calculated as percentage. The hypertensive patients had a lower fractional minimal MAP compared to normotensive patients (*P* = 0.011). The vasopressor (mephentermine) boluses used to maintain blood pressure were larger and more frequent in hypertensive patients compared to normotensive patient groups (*P* = 0.041) [Table 4].

Table 1: Patient characteristics

	N=30		*P* value
	Group H	Group N	
Age (years)	49.68±5.4	48.71±5.55	0.9
Sex: Male/female (%)	60/40	43/57	0.3
Duration of Anaesthesia (minutes)	136±11.2	132±8.6	0.11
Years of education	12.23±1.7	12.3±1.7	1
Becks depression inventory score	8.3±2.3	8.4±1.9	0.15
Mini Mental State Examination score	28.36±0 0.99	28.3±1.2	0.15

Values are in mean±SD. Statistics: Chi square test-sex. Independent *t* test in other parameters

There was no association between postoperative combined Z score and fractional min MAP {R^2 = 0.03 (hypertensive); R^2 = 0.006 (normotensive)} or duration of low unstable MAP {(R^2 = 0.05 (hypertensive); R^2 = 0.0006 (normotensive)} among hypertensive patients and normotensive patients, respectively. The effect of fractional minimal MAP on the occurrence of POCD was explored in both the group using binary logistic regression. The odds ratio in hypertensive patients was 0.76 (95%, CI = 0.46-1.28, *P* = 0.31) and in normotensives was 0.93 (95%, CI = 0.70-1.23, *P* = 0.61).

DISCUSSION

The incidence of POCD in middle aged hypertensive and normotensive patients have been found to be 20-23%, which is comparable to earlier findings by ISPOCD 2[25] (19.2%) and Monk *et al.*[24] (30.4%) in the same age group in non-cardiac surgery. The incidence of early POCD in hypertensive patients (23.3%) was similar to that in non-hypertensive patients (20%). The magnitude of effective size that we found is clinically insignificant though the study design could have detected a 38% or more difference in the incidence of POCD between hypertensive and non-hypertensive patients. In the current study, patients in non-hypertensive group were ASA I whereas the hypertensive group included patients with hypertension as the only co-morbidity. Thus it eliminates the influence of multiple co-morbidities on POCD, unlike the previous studies [11,24,25] and assesses the effect of hypertension alone on occurrence of early POCD.

Another advantage of the current study was that the outcomes were assessed by a single investigator thus eliminating inter-observer variability as compared to other studies which could not do so.[8,11,25,26] Though previous studies have used a variety of neuropsychological tests,[1,10,26,27] we used a test battery similar to the one used

Table 2: Neuropsychological tests

	Group H			Group N			*P* value (Gp H vs N Postop)
	Pre-op	Post-op	*P* value	Pre-op	Post-op	*P* value	
Verbal learning test Cumulative (number of words)	24.3±3.2	22.83±3.22	0.001*	23.73±3.56	22.9±3.79	0.006*	0.07
Delayed verbal recall (number of words)#	10 (9,11)	10 (9,11)	0.15	11 (10,11)	10 (9,11)	0.001*	0.72
Stroops test part 3 (time in seconds)	80.6±12.25	85.76±13.37	0.001*	81.1±12.6	84.20±15.38	0.01*	0.45
Stroop test part 3 (number of errors)#	1 (1,2)	1.5 (1,3)	0.09	1 (0,2)	1 (1,2)	1.00	0.13
Trail making test part b (time in seconds)	91.63±6.3	95.36±9.54	0.001*	92.00±7.25	92.66±13.75	0.63	0.03*
Trail making test part b (number of errors)#	1 (1,2)	1 (1,2)	0.062	1 (1,2)	2 (0.75,2)	0.29	0.91
Symbol digit modality test (number of correct answers)	7.6±2.15	7.33±2.38	0.163	10.1±2.68	9.86±2.47	0.40	0.90

Values are mean±SD. Statistics: Independent *T* test. * Indicate $P<0.05$. #indicate values in median (interquartile range). Statistics: Mann-Whitney U test/ Wilcoxon test

Table 3: Individual Z scores of the two groups

Z	Group H (*n*=30)	Group N (*n*=30)
Z_1 (Verbal learning test cumulative (number of correct answers))	0.09 (−0.78, 0.95)	−0.18 (−0.96, 1.38)
Z_2 (Delayed verbal recall (number of words))	−0.02 (−0.6, 0.7)	−0.47 (−1.1, 0.76)
Z_3 (Stroops test part 3(time in seconds))	0.20 (−0.77, 0.56)	0.38 (−0.97, 0.71)
Z_4 (Stroop test part 3(number of errors))	−0.34 (−0.53, 0.63)	−0.26 (−1.05, 0.52)
Z_5 (Trail making test part B (time in seconds))	0.15 (−0.72, 0.82)	−0.012 (−0.59, 0.57)
Z_6 (Trail making test part B (number of errors))	0.19 (−0.44, 0.34)	0.06 (−0.40, 0.52)
Z_7 (Symbol digit modality test (number of correct answers))	−0.51 (−0.51,1.10)	−0.17 (−1.16, 0.81)
Z_C (Combined Z score)	0.58 (−1.69, 2.38)	0.02 (−1.62, 1.99)

Values -in Median with Inter-Quartile range

Table 4: Comparison of Fractional minimal MAP, Fractional maximal MAP, and duration of unstable MAP

	Group H	Group N	*P* value
Baseline MAP (mm Hg)#	100.33±7.94	93.86±7.32	0.32
Min MAP (mm Hg)#	74.1±6.30	68.6±5.13	0.001*
Max MAP (mm Hg)#	108.16±7.21	101.86±7.88	0.001*
Fractional minimal MAP (%)	1.69±2.58	3.59±3.15	0.01*
Fractional maximal MAP (%)	0.042±0.23	0.34±0.95	0.14
Duration of unstable MAP (low)(%)	8.3±11.5	15.31±15	0.08
Duration of unstable MAP (high)(%)	0.36±1.7	2.3±6.3	0.33
Vasopressor-mephentermine (mg)	96	51	0.04*

Values are mean±SD Statistics: Mann-Whitney U test. #indicates statistics: Independent *t* test. * Indicates $P<0.05$

by ISPOCD-2[25] and Monk *et al.*[24] to enable interpretation and comparison of the findings easier.

On comparing the post-operative neuropsychological tests individually against their baseline, significant difference was found in early verbal memory and executive functions as measured by verbal memory tests[17] and time taken for Stroop's Color Word Test[18,19] indicating loss of early cognitive functions in normotensive and hypertensive patients. This is comparable to the findings of Hudetz *et al.*,[26] who demonstrated dysfunction of recent verbal and executive functions. On comparing the two groups, hypertensive patients had overall low mean post-operative neuropsychological test scores, with statistical significance only in trail making test part B (P = 0.033). This could be due to the small sample size being a pilot trial. The trail making test measures visual or non-verbal intelligence, attention and information processing.

In our study, the fall in MAP in the hypertensive patients was not significant. The hypertensive patients had a higher minimal MAP (P = 0.001) and a lower fractional minimal MAP values (P = 0.01) reflecting lesser fluctuations in intra-operative MAP, which may probably be due to higher doses of vasopressor therapy (P = 0.04). The relation between the occurrence of POCD and intra-operative hypotension in elderly patients undergoing non-cardiac surgery has been studied earlier.[8,11] ISPOCD-1 defined hypotension binomially as presence of at least one period of mean blood pressure below 60% of baseline and postoperative cognitive dysfunction was also taken as a categorical variable, based on comparison to nonsurgical controls. Unlike ISPOCD1,[8] Yocum *et al*.[11] considered 'hypotension' and 'POCD' as predefined discontinuous variables. We have also considered fractional minimal MAP and combined Z scores as continuous variables without accounting for Z score cut-off to define POCD. Despite these differences in defining the outcome measures, our findings are similar to Yocum *et al*. and ISPOCD 1.

Yocum *et al*.[11] in a post-hoc analysis, studied the fractional minimal MAP and its association with Z scores for neurocognitive tests in a univariate and multivariate models in the elderly patients. They found that in hypertensive patients, there was a significant linear relationship between fractional minimum intra-operative MAP and 1-day composite Z scores (P = 0.003), and lower minimum MAP was associated with lower Z scores. This association in elderly hypertensive patients had persisted even after one month. However, in our study we did not find any correlation between Z scores at one week and fractional minimal MAP (r = 0.13). Cerebral ischemia is believed to result from decreased cerebral perfusion over a period of time[28] and the minimum MAP measure used by Yocum *et al*.[11] does not incorporate a time component. We however, separately studied the effect of intra-operative MAP and the duration for which the intra-operative MAP was more than 20% below or above the baseline MAP. We could not demonstrate a significant association between the duration of hypotension and combined Z scores in the two groups.

There was no correlation between the fractional MAP values or the duration of low MAP and the combined Z scores. We can probably infer that if hypotension during general anaesthesia can be prevented in hypertensive patients, incidence of early POCD would not be more than that of age matched non-hypertensive patients. However, we cannot comment on the effect of hypotension on POCD, as our hypertensive patients did not show significant fall in MAP under general anaesthesia. ISPOCD 1 investigators attempted to study interactions of multiple co-morbidities with POCD, while we tried to find the relation of POCD with only hypertension as the single factor in middle aged patients. In the study by Yocum *et al*.[11] hypertensive elderly patients had multiple co-morbidities like diabetes mellitus, hypercholesterolemia and cerebrovascular disease, which may have confounded their observations.

One of the limitations of this study include lack of age-matched subjects as controls who did not have anaesthesia exposure, to account for the practice effect of the neuropsychological tests in our patient population. We also recognise that the sample size studied was small, and therefore the results are inadequately powered to calculate the exact incidence of POCD in middle aged hypertensive patients. We were unable to study POCD beyond one week after surgery and therefore, not able to comment about the recovery from POCD in our study population. This may be important as earlier investigators had found that cognitive dysfunction resolves in about 3 months in adult patients after major non-cardiac surgery.[25]

In conclusion, we found that the incidence of early POCD in middle aged hypertensive and non-hypertensive patients are similar after general anaesthesia. The minimal MAP was higher among hypertensive patients with a higher use of vasopressors intra-operatively in this group.

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