ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 05 | May - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARISON OF POST OPERATIVE COGNITIVE DYSFUNCTION FOLLOWING INHALATIONAL ANAESTHESIA AND TOTAL INTRAVENOUS ANAESTHESIA IN ONCOSURGICAL PATIENTS– A PROSPECTIVE OBSERVATIONAL STUDY.

Anaesthesiology

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ABSTRACT

Background And Aims: POCD is a major complication which affects post operative quality of life. With advanced cancer treatment modalities, survival rates are increasing. The subtle changes affecting many domains like memory, executive function, attention, verbal fluency affects patients' health and functional recovery. This study aims to compare the incidence of POCD between inhalational anaesthesia and Total Intravenous Anaesthesia (TIVA) and other possible contributing factors causing it in oncosurgical patients, so as to address the issue in the perioperative period. **Methods:** A prospective observational study was conducted in 84 oncosurgical patients, undergoing elective laparotomies for gynecological or gastrointestinal tract malignancies under general anaesthesia (GA), who received either inhalational agents (Group 1) or TIVA (Group 2) as maintenance as per the consultant anaesthesiologists preference. Cognitive level was assessed by an anaesthesiologist on the preoperative day, postoperative day one and on the day of discharge using minicog scoring and trail making test. Incidence of POCD was then calculated and compared in the two groups using chi-square test. **Results:** Overall incidence of POCD was found to be as high as 55% in the postoperative day one (POD One) which declined to 27 % by the day of discharge (DOD) by mini cog scoring. There was no significant difference between two groups assessed by minicog scoring and trail making test (POD one p = 0.562 and DOD p= 0.429)). **Conclusion:** POCD emerged as a significant complication of concern in oncosurgical patients, however the choice of anaesthesia didn't have any effect. Advanced age, low educational status, history of hypertension, previous history of GA , were identified to be possible contributing factors.

KEYWORDS

Postoperative cognitive dysfunction, general anaesthesia, Inhalational anaesthesia , Total intravenous anaesthesia

INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a complication with significant perioperative morbidity. The main challenge involved in the study of POCD is the lack of uniform definitions, tools to assess POCD and time points for assessment. Broadly POCD can be defined as an objective measurable cognitive decline from day 1 to 7.5 years after surgery. [1]

Unfortunately, currently POCD mostly remains undetected. The aetiology of POCD remains unclear; a combination of surgery, anaesthesia, and patient-related factors are likely to have a role. [2] The risk is expected to be more pronounced in oncosurgical patients [3], probably due to advanced age, complex and lengthy surgeries, associated chemo and radiotherapy However existing literature is lacking in oncosurgical patients. Understanding and studying POCD is important in cancer patients so as to improve their post operative quality of life. Anaesthetists should be aware of the current evidence base, counsel patients and adopt techniques that minimise any further insults to high-risk patients. Previous studies are done to analyses POCD at a longer time interval, however it's important to assess the cognition earlier, as patient needs to comprehend the perioperative instructions. Our study aims to find the incidence of POCD on Post operative day one and on the day of discharge and compare its incidence following inhalational anaesthesia and total intravenous anaesthesia (TIVA) in oncosurgical patients, as well as to identify the possible factors contributing to it in the study population.

METHODS

After obtaining Institutional review board (11/2019/18) and Ethical committee clearance (HEC No 04/20), this single centre prospective observational study was conducted in a tertiary care oncocentre from January 2020 to December 2020.Written informed consent was obtained from all patients and the study was done in accordance with the guidelines of the Declaration of Helsinki.

All mentally competent patients above 18 years of age,of American society of Anaesthesiologists(ASA) Physical Status I to III scheduled to undergo elective laparotomy for gastrointestinal and gynaecological malignancies, under general anaesthesia (GA) were included in the study. Those patients needing postoperative ventilation, those patients unable to read or obey commands due to visual or auditory impairment, and illiterate patients were excluded.

Fasting guidelines and pre anaesthetic medication were followed as per ASA guidelines and institutional protocol. Pre operative baseline characteristics, presence of comorbidities like Diabetes, Hypertension, Dyslipidemia, Coronary artery Disease (CAD), Cerebrovascular accident (CVA), dementia, Psychiatric illness, Post Chemotherapy, Post Radiation Therapy, Hepatic / renal impairment, education level, h/o substance abuse, previous exposure to general anaesthesia and history of POCD in past were noted by an anaesthesiologist. Baseline Mini Cog score and trail making test score were calculated in all patients on preoperative day. Patients either receive Inhalational agents or TIVA as maintenance of anaesthesia depending on the consulting anaesthesiologists preference. Those received inhalational anaesthesia were categorised as Group 1. They were induced with intravenous propofol 2 mg/kg and anaesthesia maintained with sevoflurane. Group 2 were patients who received TIVA who were induced and maintained with intravenous propofol (2 mg/kg for induction and 100 to 125 µg/kg/minute for maintenance). All patients received fentanyl 2 µg/kg at induction. Adequate depth of anaesthesia was maintained by keeping Bispecteral index (BIS) value of around 50. Additional opioids or benzodiazepines if used, was documented.

Mini Cog score and trail making test score were then calculated on postoperative day one (within 24 postoperative hours) and on the day of discharge at the same time of the day by an anaesthesiologist.Mini Cog score is a three step test, which include three word registration, clock drawing test and three word recall. Maximum score is 5. A total score less than or equal to three was considered cognitive impairment. [4,5] Parallel versions of the test were used to minimise the practice effect. Trail making test was done by asking the patients to join the dots from 1 to 25 as fast as they can. Time taken to complete the task was noted. If taking more than 78 seconds, then the patient was considered to have a cognitive decline.[6]

Duration of anaesthesia, perioperative complications such as sepsis, respiratory and other infections, marked hemodynamic fluctuations, metabolic derangements like dysglycemia, benzodiazepine or opioids use perioperatively were also recorded. Sedation score based on Richmond Agitation Sedation Scale (RASS) and pain score based on Numerical Rating Scale (NRS) were noted simultaneously while administering the cognitive test.

The sample size was calculated using data reported in a similar study by Cai et al. [7] By comparing the incidence of decline in Mini Mental Scale examination score on POD 10, which had a mean difference of

1.2 and pooled standard deviation (SD) of 1.95, the estimated minimum sample required was 84 with 80% power and 5% level of significance.

Data was entered for statistical analysis in Microsoft Excel and Statistical Package for Social Sciences (SPSS). The categorical variables were presented using frequencies and percentages. Continuous variables are summarized using mean +/- standard deviation. The association between two categorical variables is assessed with Chi-square test/ Fisher's exact test. A p value of <0.05 was considered significant.

RESULTS

A total of 100 patients were evaluated for enrolling in to the study, eighty-four patients completed the study, 42 in each group. The flow of patients is shown in figure 1

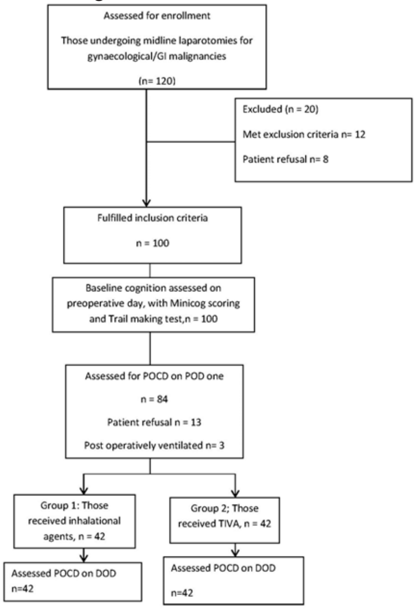

Figure 1: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram showing the flow of patients

The two groups were comparable in terms of age, weight, educational level, presence of comorbidities, duration of anaesthesia and incidence of post operative complications. Demographic features of the study population are given in the table 1.

Variable	Group 1	Group 2	P
Age (in years) Mean +/- SD	57.81 ± 9.759	53.31± 11.983	0.063
Weight (in Kg) Mean +/- SD	62.31 ±13.197	57.05 ±9.808	0.048
Education level(Frequency)			0.049
Below High school level	10	19	
High school level	18	17	
Above High school level	14	6	
Presence of comorbidities(Frequency)			
DM DLP HTN CAD CVA Dementia Hepatic or Renal impairment Previous surgery under GA	12 6 23 5 1 1 2 9	17 3 19 4 1 0 2 7	
Chronic alcohol abuse (Frequency)	4	7	
Duration of anaesthesia in minutes (Mean +/- SD)	238.57 ±40.278	243.57 ±38.497	0.562
Pain score (Average)	3	3	
Perioperative period complications (Sepsis, POPC, SSI, etc) (Frequency)	6	5	

Table 1 Demographic details of the study population* DM- Diabetes Mellitus, DLP - Dyslipidemia, HTN- Hypertension, CAD - Coronary artery Disease, CVA- Cerebrovascular accident, POPC - Postoperative pulmonary Complications, SSI- Surgical Site Infection

There were no statistically significant variations in POCD incidence between inhalational agent and TIVA at any time point. However, the overall incidence of POCD was found high in oncosurgical patients Fifty-five % patients developed POCD on POD one and 19 % remained to have it even on the day of discharge (Mean postoperative day 5) as assessed by Mini Cog score. Whereas by TMT scoring the results were 19 % on POD one and 7% by DOD

Incidence of POCD on POD one and DOD using minicog score and TMT given in Figure 2 and Figure 3

Figure 2: Incidence of POCD using Mini Cog Score on POD 1 and DOD (expressed in percentage) (*POCD: Post operative cognitive dysfunction, *POD :Post operative day, *DOD: Day of discharge)

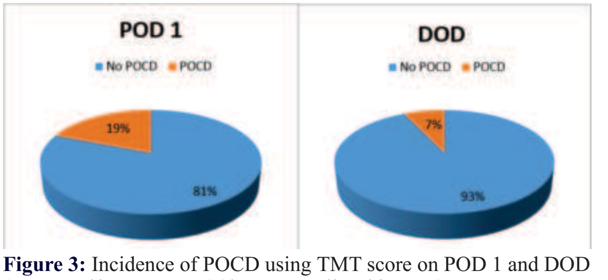

Figure 3: Incidence of POCD using TMT score on POD 1 and DOD (expressed in percentage)(* TMT : Trail making test)

While comparing the incidence of POCD in the two groups viz inhalational and TIVA, there was no significant difference (p = 0.562 in POD one and 0.429 on the day of discharge.) (Figure 4 and 5)

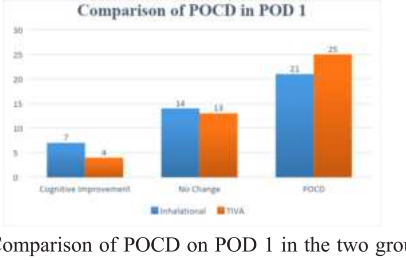

Figure 4: Comparison of POCD on POD 1 in the two groups using mini cog scoring (p= 0.562) (expressed in number of patients)

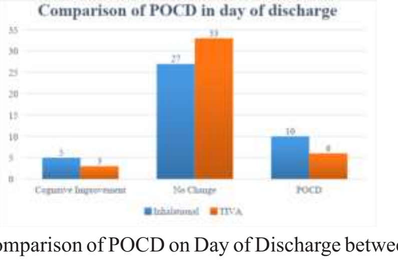

Figure 5: Comparison of POCD on Day of Discharge between the two groups (p = 0.429) (Expressed in number of patients)

Using Trail making test also, there was no significant difference between the two groups. (p=0 .578 on POD 1 and 1.000 on DOD)

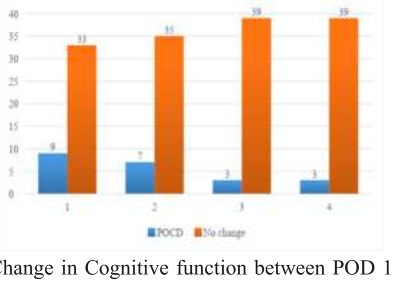

Figure 6: Change in Cognitive function between POD 1 and DOD

using TMT (expressed in number of patients) #1 and 2 POD one; #3 and 4 DOD

Though there was significant incidence of POCD in the POD 1, the cognition improved by the DOD in both the groups. This is statistically significant in both the groups with a p value of .001.

Our study shows that there is a positive association between advancing age and occurrence of POCD, especially in the immediate post operative period, (p value =0 .027 by minicog scoring and p= 0.002 by TMT). People above the age of 60 had increased risk of POCD with an odds ratio of 2.9.

Cognitive performance was less in people with below high school level educational status pre operatively, compared to people with educational status high school level or more (p = 0.001). Higher educational status showed a protective effect against POCD (Odds ratio = 0.038, when compared with ≤ Highschool level education on POD one. On POD one it was observed that there is a significant decline in cognitive level in lower educational groups (below high school level) (p = 0.001).By the DOD no patients above high school level education had cognitive decline

Among all the comorbidities, addiction and perioperative complications assessed, Hypertension had a positive association with POCD. On POD one 24 hypertensive patient developed POCD with a p value of 0.029 and 16 of them remained in the POCD group even on the day of discharge. (p=0.028). The risk of POCD in hypertensives were 2.66 times greater than non-hypertensives.

Another factor with a positive association with POCD was history of previous surgery under GA. This finding was significant while using TMT score, but Mini Cog scoring didn't show any significant positive correlation. Out of 16 patients who had previous history of surgery under anaesthesia, 6 patients already had a baseline cognitive decline. On postoperative day 1, the number of patients with POCD increased to 10, (p = 0.025) with an odds ratio of 3.485. By the day of discharge only 7 patients had residual POCD.

Logistic regression analysis of various contributing factors and the degree of association (R^2 given in table 2

Table 2: Binary Logistic Regression Analysis Of Various Associated Factors

POCD on Day 1 with Mini Cog scoring	R^2	P value	OR	95% Confidence interval	
				Upper	Lower
Age (≥60 vs <60)	0.078	0.027	2.914	1.129	7.525
Education level (High school vs Below HS)	0.357	<0.001	0.038	0.008	0.184
Education level (High School vs Below HS)		0.190	0.444	0.132	1.496
HTN (History vs No History)	0.075	0.030	2.667	1.099	6.468
POCD on DOD with Mini cog scoring					
Age (≥60 vs <60)	0.058	0.063	2.578	0.951	6.990
Education level (High School vs Below HS)	0.386	0.138	0.427	0.139	1.313
HTN (History vs No History)	0.083	0.031	3.077	1.106	8.558
POCD on POD one by TMT					
H/O previous surgery under GA (History vs No History)	0.076	0.031	3.485	1.123	10.815

DISCUSSION

We observed that there was significant incidence of POCD in oncosurgical patients, however it was comparable with the choice of anaesthesia technique used. Advanced age, low educational status, history of HTN, and previous history of GA emerged as possible contributing factors to cause POCD.

The ISPOCD -1 estimated the overall incidence of POCD to 25.8% at 1 week and 9.9% after 3 months in patients undergoing non cardiac surgeries. [8] Johnson et al found an incidence of 19.2% at 1 week after surgery in middle aged patients [9]. Rohan et al evaluated POCD following minor procedures under GA in elderly patients and found an incidence of 47% in the post operative day 1[10]. The higher incidence of POCD in post operative day 1 in our sample population is probably due to the use of highly sensitive mini cog scoring, which detects even mild cognitive decline. Our study population consisted of patients with malignancies, who are at increased risk of developing POCD, [11,12] probably due to the increased inflammatory mediators, malnourishment and associated essential nutrients deficiency, along with the psychological insult following the diagnosis of cancer.

All our patients underwent major surgeries with extensive dissection under combinedgeneral anaesthesia and epidural analgesia lasting for an average duration of 3 to 5 hours. Extensive surgeries are associated with marked neuroinflammation, implicated in the pathogenesis of POCD .[9] In our study incidence of POCD at the day of discharge was 19%. This result is in line with many studies evaluating POCD at 1 week after surgery. [13]. The drop in the incidence may be due to wearing off of the effects of anaesthetic drugs, decreased need for opioid analgesics. Also the patients are more motivated for cognitive assessment tests on the day of discharge when compared to the first 24 hours.It should be expected that, those who tend to remain in the POCD group at the time of discharge are more prone for persistent POCD in a long run . Also this cognitive impairment, may lead to inadequate comprehension of discharge advice which may lead to increased incidence of post operative complications, increased morbidity and significant reduction in the quality of life. Future studies are needed to establish the same.

Existing literature shows contradicting results in establishing a correlation with the choice of anaesthesia and POCD. In a metaanalysis of 28 Randomised Controlled trials (RCT), with 4507 patients, it was found with low certainty evidence that TIVA may reduce POCD. [13]Cai et al found that inhalational agents result in more cognitive decline when compared to TIVA, especially in the presence of apolipoprotein E4 allele in their gene. [7] Konishi et al found no significant relationship between the type of anaesthesia and incidence of POCD[15].Many studies have identified the role of propofol in reducing the inflammatory cascade[16,17], possibly resulting in the marginally reduced incidence of cognitive decline in many studies. A recent metaanalysis showed TIVA was associated with a lower incidence of POCD in the first 30 days postoperatively[18]. The comparable incidence of POCD in Inhalational and TIVA group in our study may be due to our routine practice of monitoring the depth of anaesthesia with the aid of BIS. Maintenance agents were titrated to maintain a BIS value between 40 and 60.

Advanced age is a well-established risk factor in developing POCD [13, 19]. ISPOCD study showed that the incidence of POCD at 3 months after surgery was 7% in those aged between 60–69 and 14% of those above 69 years old. [13].A recent metaanalysis also showed that patients above 65 years are more prone to develop POCD as well as they experience severe symptoms. [19]Another study with 1064 patients found POCD in 36% of young, 30% in middle aged and 41 % of elderly. This study also found increased risk of POCD in patients above the age of 60 years .This emphasize the need for more meticulous plan to prevent cognitive dysfunction for elderly people undergoing surgery. It isto be remembered that when it comes to the elderly people, the quality of life matters more than the survival benefit offered by the treatment of underlying disease.

In line with the results of many previous studies, level of education emerged as significant risk factor in our study also. The reason may be highly educated people tend to have more mental challenges, activating more and more neuronal connections, and will be having more cognitive reserve. As the level of education and socio economic status are positively related, they tend to have better access to health care facilities and less environmental insults to the brain.

Another contributing factor to POCD that came up in our study was the presence of hypertension (HTN).The incidence of POCD in hypertensives is slightly higher than those from the existing studies .[20] Another meta analysis with 24 studies didn't show any significant correlation[21], although 8 studies among the 24studies analysed showed a 27 % incidence of POCD in hypertensives-The reason for the increased incidence of POCD in the hypertensive patients may be due to the fact that they may be experiencing greater hemodynamic fluctuations during anaesthesia. Hypertensive patients tend to have a higher baseline blood pressure. The margin of safety for hypotension during anaesthesia is narrow for them. The duration of HTN, drugs taken, degree and duration of fall in blood pressure during surgery etc might be other influencing factors, which need to be evaluated in future studies.

History of previous GA exposure also contributed to the cognitive decline in our study, but this was evident only in the trail making test. This finding is in correlation with previous studies. [22]

Other associated comorbidities like DM, CAD, CVA, Dementia, post chemo, post radiation and psychiatric illness didn't show any significant association in our study. Perioperative period complications also had no significant correlation.

The major limitations of our study were small sample size, use of opioids and benzodiazepines were not restricted in the perioperative period, serial neurocognitive testing can cause practice effect in patients, i e change or increase in test performance due to the increased familiarity and exposure with test components. Since we did the tests thrice within a short span of 5 to 7 days this practice effect could influence our results. Mini Cog scoring is primarily a screening test and cannot be used for making a definitive diagnosis of POCD.

CONCLUSION

Post operative cognitive decline is emerged as an important complication in oncosurgical patients. Advanced age, low educational status, history of HTN and previous history of GA came out as possible risk factors in developing POCD. Unless specifically investigated for its occurrence, POCD usually remains undetected causing significant morbidity and increased dependency for daily activities. Preoperative evaluation and optimization of at risk individuals with careful intraoperative and postoperative monitoring, judicious use of drugs during anaesthesia, and early detection and cognitive training may help in reducing the incidence of POCD. Further studies are warranted to establish effective ways to reduce POCD .By better understanding the risk factors, mechanisms, and long-term impact of POCD, we can develop strategies to prevent, treat, and manage this condition.

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