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ASSESSMENT OF THE COGNITIVE FACULTIES IN BREAST CANCER PATIENTS UNDERGOING ADJUVANT CHEMOTHERAPY.

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ABSTRACT Post-chemotherapy cognitive impairment (PCCI) also called as chemo brain or chemo fog is a significant impairment of cognitive faculties among patients and survivors of various forms of malignancies after undergoing chemotherapy that sufficiently impairs their activities of daily living and overall quality of life (QOL). In our study we have assessed cognitive functions of breast cancer patients receiving chemotherapy over three time points i.e. prior to chemotherapy, immediately after chemotherapy and three months after chemotherapy. The Psychology Experiment Building Tool (PEBL) was used for the assessment of cognitive function. We have used the selective tests out of the given battery of tests of PEBL version 2 such as Berg's card sorting test, Corsi block tapping test, Digit span test, Simon's interference task those are targeting executive function, visuo-spatial memory, phonological memory and attention respectively. Out of 60 patients screened 39 satisfied the inclusion and exclusion criteria to be enrolled in the study. The second follow up recording was done for 30 patients. 23 subjects could complete the two follow up. All data was expressed in terms of mean ± standard deviation and repeated measures of ANOVA were used for analysis and $p<0.05$ was considered statistically significant. All the tests showed significant cognitive impairment immediately after chemotherapy and this cognitive deficit was shown improvement after three months of chemotherapy.

KEYWORDS :

INTRODUCTION:

Breast cancer is the most frequent cancer among women in the world with an estimated 1.67 million new cancer cases diagnosed every year which constituted about 25% of all cancers[1]. Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women[2]. Survivors of breast cancer treated with chemotherapy experience a definite challenge to get back to normal life as well as to resume the professional career due to PCCI which leading to deterioration in QOL and incurring catastrophic insults to psychological, economic, professional and emotional domains of life[3]. PCCI related to breast cancer remains the most common, because the combination of pharmacotherapy used in the treatment of breast cancer particularly incurs neurotoxic insult[4].

The chemotherapeutic regimen is administered as an adjuvant treatment following successful surgical intervention. Chemotherapy induced cognitive complains are especially severe during and immediately after chemotherapy and subsequently improves[5]. However, it continues to bother a subgroup of patients for several years deteriorating the QOL[6]. In our study we have recruited cohort of breast cancer patients scheduled for adjuvant chemotherapy after undergoing modified radical mastectomy (MRM) and evaluated prospectively for cognitive domains over three time points i.e. prior to chemotherapy, immediately after chemotherapy and three months after chemotherapy.

MATERIALS AND METHODS:

This study was conducted in the Department of Physiology, JIPMER in collaboration with the Department of Medical Oncology, JIPMER, Puducherry after the approval from JIPMER Post- Graduate Research Monitoring Committee and Institute Ethics Committee. We recruited breastcancer patients scheduled for adjuvant chemotherapy after undergoing MRM surgery from the December of 2018 to the March of 2020.

According to our institutional policy, all patients of breast cancer, without any other contraindications are administered three cycles of epirubicin, cyclophosphamide and 5-flourouracil over a period of 9 weeks followed by four cycles of docetaxel over a period of 3 weeks a total duration of 12 weeks of treatment with above mentioned chemotherapeutic agents. This study is a prospective cohort study and study participants are recruited after meeting the following inclusion and exclusion criteria.

Inclusion Criteria:

Already diagnosed stage 2 and stage 3 breast cancer patients belonging to the age group 30-60 years undergone MRM surgery and scheduled for adjuvant chemotherapy

Exclusion Criteria:

Patients with stage-four disease with metastasis elsewhere, those administered hormonal agents as chemotherapy**,** history of psychiatric disorders, substance abuse, peripheral neuropathy, previous chemotherapy**,** stroke, neurosurgery, dementia, head injury.

Administration of PEBL2 and evaluation of scores: PEBL2 is free, open source psychology software comprising of battery of cognitive tests. It is written in C++ programming language, licenced under GNU public license 2.0. This allows the researchers to comfortably design, run and share neuro-behavioural tests[7]. We have used the selective tests out of the given test battery, of PEBL version 2, targeting executive function, visuo-spatial memory, phonological memory and attention in our study population.

The berg's "Wisconsin" card sorting test (BCST) measures executive function particularly the "shift of set" phenomenon[7]. Set shifting is a cognitive ability to unconsciously shift attention between one task and another. It is a computerized version of Wisconsin card sorting testdeveloped at the university of Wisconsin in order to evaluate the frontal lobe dysfunction[8]. The subject was displayed with a cue card which she had to match with either one of the four other displayed cards based on a fixed set of rules, which changes after every tenth card. A total of 64 cards were displayed during the trial for matching. The cards had to be matched either according to colour or shape or number of the marks on the card. During the initial round the cards had to be matched based on the same colour of the marks on the cue card and the card to be matched (e.g. green star mark with green plus mark), the second round had to be matched on the basis of same number marked on the cards (e.g. 4 triangles with 4 stars) and finally alike shape had to be matched (e.g. green triangles with red triangles). The rounds demanded cards to be matched on the basis of colour, shape and number respectively. In our study we have measured the total correct score (TS) - total number of correct responses out of 64 total cards matched and the net reaction time (RT) - total time taken for the entire task.

The corsi block tapping test is an objective test assessing visuospatial short term and working memory[7]. A set of nine blue rectangular blocks were presented to the subject on the computer screen. During the first trial, two among the nine blocks lit up in a sequence one after the other. The subject was instructed to tap those two blocks in the same sequence as displayed. During the next round, more than two blocks lit up in a random sequence and the subjects had to tap them in the displayed sequence. Each round consisted of two chances to correctly tap sequentially. If the subject had given the correct response one out of the two times, then he qualified for the next round with higher number of blocks. However, each try, if correct, awarded a score of 0.5. The minimum score is 1 and for each correct response, a score of 0.5 was awarded. The net cumulative score in the end of the trial is referred to as block span (BS).The digit span test is a behavioural test of phonological/verbal working memory. During the digit span task, the subject was asked to view the display screen and to listen to the simultaneous audio carefully. During the first round of the trial three different numbers were displayed on the screen sequentially one at a time, with simultaneous voice reading the number aloud. In the end of the list, the subject was asked to enter the numbers in the same sequence through the keyboard input. The first round was of 3 numbers and each subsequent round added one number extra. Each round consisted of 2 trials with same number of digits. Getting one trial, out of two, correct lead to the second round with one extra number. The trial is deemed incorrect if one of the digits is missing or entered in the wrong sequence. The test ended if the subject had been incorrect for 2 trials of a single round involving a fixed number of digits. The score was generated at the end of the test as digit span (DS) – the maximum number of digits of a single trial entered correctly. The digit span score remained the same whether the subject had been correct for a single or both the trials of a single round.

The Simon's interference task is based on the principle of Simon effect. The Simon effect is a part of broader phenomenon called the stimulus response compatibility. The subjects were asked to focus on the central cross shaped cue mark, that appears before each trial and to press left shift bottom, if red circle appeared and to press right shift bottom, if the blue coloured circle appeared. The red and blue circles appeared randomly on either side as well as in the middle. It is easy to perform accurately with less reaction time when the colour stimulus appears on the same side of the response. E.g., the response was faster and more accurate when the red coloured circle had appeared on the left side of the screen than the right. The opposite is true for the blue colour response. There were 70 trials in a single round out of which the first 20 trials were used for thetraining and the last 50 were used for the evaluation. The scores generated were total correct response and the average response time.

RESULTS

All data was expressed in terms of mean ± standard deviation and repeated measures of ANOVA were used for analysis. IBM SPSS version 20 was used for statistical analysis. The level of significance was assumed at 5 percent and $p<0.05$ was considered statistically significant.

Table 1. Scores of cognitive tests at three time points.

Cognitive Test	Pre chemotherapy (PC) (n=39)	Post chemotherapy (PoC) (n=30)	3months after chemotherapy (3PoC) (n=23)
BCST-TS	59.87±2.80	53.65±2.64	55.46±2.36
BCST-RT (ms)	2590.93±19.71	3660.29±18.33	2982.16±14.19
CBTT-BS	4.54±0.78	4.00±1.11	4.57±0.84
DST-DS	6.74±0.32	4.16±0.52	5.85±0.83
SIT-TS	50.70±1.80	48.65±7.31	49.91±3.42
SIMON-RT (ms)	842.81±206.75	1214.17±747.13	916.87±284.05

TS-Total Score, RT-Reaction Time, PC-Pre chemotherapy, PoC- Post chemotherapy, 3 PoC-3 months after chemotherapy (3PoC), BCST-Berg's card sorting test, CBTT- Corsi block tapping test, DST-Digit span test and SIT-Simon's interference task.

The study group consisted of aged between 30 to 60 years with a mean age of 45.87 ±10.06 years. Out of 60 patients screened 39 satisfied the inclusion and exclusion criteria to be enrolled in the study. The second follow up recording was done for 30 patients. 23 subjects could complete the two follow up.

Table 2. Analysis of cognitive scores between three time points

Cognitive Test	PC vs PoC vs 3PoC (p value)	PC vs PoC (p value)	PC vs 3PoC (p value)	PoC vs 3PoC (p value)
BCST-TS	0.029*	0.015*	0.045*	0.058
BCST-RT (ms)	0.000*	0.001*	0.002*	0.014*
CBTT-BS	0.009*	0.006*	0.021*	0.012*
DST-DS	0.002*	0.007*	0.09	0.072
SIMON-TS	0.092	0.085	0.312	0.241
SIMON-RT (ms)	0.012*	0.024*	0.018*	0.075

*$p<0.05$, PC-Pre chemotherapy, PoC- Post chemotherapy, 3 PoC-3 months after chemotherapy (3PoC), BCST-Berg's card sorting test, CBTT- Corsi block tapping test, DST-Digit span test and SIT-Simon's interference task.

DISCUSSION:

Cognition is a complex mental function, an ensemble of faculties like working memory, attention and executive functioning, information processing speed and language. Optimal functioning of cognitive faculties is important for effortlessly carrying out activities of daily living like recognizing daily objects or familiar faces, specking, remembering and thinking. Cognitive processes are an outcome of complex interaction and connectivity of various brain areas like primary sensory cortices, association cortices with that of executive areas like prefrontal cortex and its feedback and re-entrant connection with hippocampus[9]. Memory is a significant and perhaps the most important cognitive faculty among all and an especially deranged ability among PCCI patients. Working memory is a cognitive system which stores information temporarily which can be manipulated for the executive goal oriented behaviour[10]. It has three subcomponents i.e. the phonological loop, the visuospatial sketch pad, episodic buffer which integrates polymodal components of visual, verbal and spatial information in form of a singular episodic representation[11]. In our study we have tried to evaluate each of them by exclusively targeted cognitive tasks. Attention is a cognitive process by virtue of which concentration is paid to particular information while simultaneously disregarding other competing perceivable sensory information. Attention is a key factor responsible for encoding of memory information in hippocampus. Therefore, malfunctioning of the attentional network is leading to dramatic deterioration in the quality of life, not to mention the resumption of normal professional work quite challenging. Again the inability to devote attentional resources leads to improper registration and encoding of the memory causing forgetfulness, even though they show no deficit in retaining and retrieval of the already encoded information[12]. Executive function is the control and coordination of motor and cognitive behaviour to attain specific goals. Smooth execution ofexecutive behaviour relies deeply on the working memory, cognitive inhibition, set shifting and the fluency[13].

The cognitive impairment was documented after chemotherapy among the patients in objective cognitive tasks in all the domains of the cognition. The TS as well as RT of BCST was significantly affected revealing the deficit in the executive function. The TS was significantly lower immediately after chemotherapy as compared to that of pre chemotherapy ($p=0.015$) and slightly increased three months after. The RT was significantly higher immediately after chemotherapy ($p=0.000$) as well as three months later, compared to the baseline value. The perturbation in visuospatial working memory domain was documented by significantly reduced BS ($p=0.006$) of Corsi block tapping test immediately after chemotherapy. There was concurrent reduction of DS score of verbal working memory task, which was significant, immediately after the chemotherapy ($p=0.007$); but not three months later. We used Simon's interference task, as a measure of attention, in our study. The TS of the Simon's interference task wasn't significantly altered; however, the RT was significantly higher immediately after chemotherapy ($p=0.024$) which persisted until three months later ($p=0.018$), compared to the baseline RT.

CONCLUSION

In our study derangement in cognitive faculties after chemotherapy was documented in the domains of executive function, verbal and visuospatial working memory and attention. This derangement was shown improvement at the end of three months of chemotherapy.

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