ORIGINAL ARTICLE

Memory Retraining for Post-Chemotherapy Breast Cancer Survivors

Guru Prasanna Lakshmi

Clinical Psychologist, Cognizance Institute of Mental Health and Neuro Sciences, Nizampet, Hyderabad, India

ABSTRACT

Background: Breast cancer is the most common in the cities of India and the second most common in the rural areas. Due to the advancement in treatment, survival rate is increasing, but information related to cognitive retraining to focus on impaired neuropsychological functioning is limited in disease-free breast cancer survivors. **Methods:** Five breast cancer survivors, who had undergone adjuvant chemotherapy visiting for follow-ups took consent for neuropsychological assessment (pre- and post-intervention) to understand the functional impairment and to evaluate the effectiveness of intervention. **Results:** The pre-assessment results were indicated significant problems in visuospatial memory, verbal memory, and sustained attention with subtle difficulties in working memory. Patients treated with cognitive retraining showed apparent differences in post-assessment. Results were statistically analyzed through paired sample *t*-test, there is no significant difference in simple tasks, but the difficulty was observed as the complexity of the task increased. Sustained and focused attention (from 23.1 to 53.1 $P = 0.01$), working memory (verbal - from 31 to 54.5 $P = 0.05$ and visual - from 22 to 56.5 $P = 0.01$), auditory verbal learning (immediate recall [IR] - from 15.5 to 43 $P = 0.05$ and delayed recall [DR] - from 7 to 42.5 $P = 0.05$). Visual memory (IR - from 62.5 to 80 P = 0.01) (DR - from 58.5 to 79.5 P = 0.01), which is showing significant improvement statistically between the two assessments. **Conclusion:** Cognitive Retraining is an evidence based intervention to improve the level of cognitive areas functioning not only in neurological conditions but even in other chronic illness like Cancer. This result will be showing the implementation of neuropsychological techniques will improve the level of functioning in patients with post-chemotherapy.

Key words: Breast cancer survivors, chemotherapy, cognitive impairment, memory retraining

INTRODUCTION

Breast cancer is most common non-skin cancer in urban Indian females and the second most common in the rural Indian women.[1] In India, the health-care facility pattern is heterogeneous, with numerous regions where the benefits of the awareness, early diagnosis, and multidisciplinary treatment programs have not reached.[2] Breast cancer awareness programs are more concentrated in the cities and have not reached the remote and rural parts of the country.[3,4] Women often do not present for medical care early enough due to various reasons such as illiteracy, lack of awareness, and financial constraints. It is hardly surprising that the majority of breast cancer patients in India are still treated at locally advanced and metastatic stages.[3,5] Lack of an organized breast cancer screening program, paucity of diagnostic aids, and general indifference toward the health of females in the predominantly patriarchal Indian society do not help early diagnosis of breast cancer.[7] A multidisciplinary approach to breast cancer treatment, that is, so vital is available only at a few select regional centers.[2] Cancer often affects the nervous system and may result in significant neurologic morbidity and mortality. These effects may be direct - with direct cancer involvement of the brain, spine, or peripheral nervous system - or indirect as in paraneoplastic neurologic syndromes. Treatment of cancer can also damage the nervous system.[6]

Address for correspondence:
Guru Prasanna Lakshmi, Clinical Psychologist, Cognizance Institute of Mental Health and Neuro Sciences, Nizampet – 500 085, Hyderabad, India. Phone: +91-9515690010. E-mail: cognizance.guru@gmail.com

Anticancer treatment and cognition Minisini *et al*. evaluated eight studies of effective anticancer treatment on cognitive function. Their findings indicated that patient experienced cognitive changes due to treatment.[8] Jansen *et al*. evaluated 16 studies and found significant chemotherapy-induced impairment in visual memories. When the samples were compared with normative subjects found to have negative effects in 4 domains of cognitive function, executive function, information processing speed, verbal memory, and visual memory. These findings provide evidence that due to anticancer treatment, cancer survivors suffer cognitive deficits that may interfere with their daily living.[9] 10–40% of cancer survivors associated with memory problems were labeled as "Chemo Brain," "Not as sharp," and "Wooly Headedness."[11]

The memory loss and concentration difficulty experienced in cancer patients and cancer survivors have often been attributed to anxiety, depression, and/or physical fatigue resulting from anticancer treatment in early studies that did not evaluate cognitive function.[10]

Chemotherapy-Induced Cognitive Impairment

A total of 32 women with a mean age of 54 (standard deviation [SD] = 14) who underwent surgery for localized (Stage I or II) breast cancer showed deficits in attention within 3 days following mastectomy (Cimprich, 1992). Their attentional fatigue increased as the number of postsurgery days increased. In another study, recall of information related to treatments and associated risks was poor among 71 women diagnosed with breast cancer (mean age was 48.71 [SD = 11.02]).[12]

Matsuda *et al*. reviewed 10 studies of mild cognitive impairment in breast cancer patients who had completed adjuvant chemotherapy. The cognitive symptoms identified included memory loss, lack of attention, and concentration difficulties.[13]

Anderson-Hanley *et al*. included patients (n = 838) who were on average 49 years of age and 86 weeks (SD = 124.1) from either a diagnosis or treatment. Sex of the sample was not provided, although only 28% of the sample was breast cancer patients. Negative effects were most pronounced in the three cognitive domains of executive function, verbal memory, and motor function.[14]

Jansen *et al*. reviewed 16 studies that included eight cognitive domains. The review included 996 patients who averaged 48 years of age (SD = 7.54). Most (84%) of the patients were female and 56% of the sample were in breast cancer studies. Even though all significant effect sizes were in the negative direction, visual memory was the sole cognitive domain that showed significant chemotherapy-induced impairment in all comparisons.[9]

Falleti *et al*. reviewed six studies that included six cognitive domains. They concluded that cognitive impairment occurred in women who had undergone adjuvant chemotherapy for breast cancer, but the magnitude of this impairment found depended on the study design.[15] Jim *et al*. reviewed 17 studies of 807 patients previously treated with standard-dose chemotherapy for breast cancer. The individuals treated with chemotherapy performed worse than comparison subjects did in verbal and visuospatial ability.[16]

Breast cancer patients with Stages 1–3, average age of 55 years, were tested prior and after adjuvant treatment. Patient's score on reaction time was significantly lower than healthy controls. The patients were significantly more likely to have lower than expected overall cognitive performance.[17]

Role of Menopausal status in resulting cognitive difficulties - post-chemotherapy

Most evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy. The transition from pre- to post-menopausal status is associated with alterations in cytokines such as interleukin-6[18] and cognitive difficulties in learning and memory.[19] Case studies in cancer reveal that cognitive difficulties can vary among patients who received the same course of chemotherapy; this could be related to menopausal status.[20]

METHODS

Participant's information

Case group consists of five breast cancer survivors (Stage-2), who had undergone adjuvant chemotherapy in either of two specialized cancer clinics in Hyderabad. The female patients with breast cancer who had taken a six cycles of CMF chemotherapy as adjuvant treatment and been survivors, that is, three of them for 1 year and two of them for 8 months.

Inclusion criteria

Participants who were 30–60 years old, female breast cancer survivors, literates, Stages 1 and 2 breast cancer who underwent only chemotherapy cycles as a part of treatment, and only those women who never had a relapse, secondary primary tumor, or distant metastasis were selected.

Exclusion criteria

Exclusion criteria were ever used of adjuvant endocrine therapy.

Table 1 shows the sociodemographic details of the patients.

Measures

Participants underwent neuropsychological examination using five selected tests from NIMHANS neuropsychological battery.

Table 1: Sociodemographic details

Sample size	Age	Education	Socioeconomic strata	Domicile
05, female breast cancer survivors with mild cognitive impairment post-chemotherapy	30–40 years-3 patients	School-1 patient	*LSES-1 patient	Suburban- 3 patients
	41–45 years-2 patients	College-4 patients	*MSES-4 patients	Urban-2 patients

*LSES: Low socioeconomic strata, *MSES: Middle socioeconomic strata

These tests yielded 10 outcomes in the following cognitive domains: Sustained and focused attention, working memory (visual and verbal), visual memory, auditory memory, visuospatial memory, and other elements of executive functions such as verbal learning, recognition, visuoperceptual skills.

NIMHANS Neuropsychological battery: Selected tests

Digit Vigilance

It consists of numbers 1–9 randomly ordered and placed in rows on a page (Lezak, 1995). There are 30 digits per row and 50 rows on the sheet. The digits are closely packed on the sheet. The same level of mental effort or attention deployment is required over a period of time. The subject has to focus on the target digits, that is, 6 and 9 among other distracter digits. Inability to sustain and focus attention leads to both increased time to complete the test as well as errors. Score was observed by the time taken to complete the task and error score, that is, omissions and commissions.

Verbal - N-Back test

The 1 back and 2 back versions of the N-back test were used to assess the verbal working memory (Smith and Jonides, 1999). The 1 back version requires verbal storage and rehearsal, while the 2 back version requires, in addition to the above, manipulation of information. Therefore, the 1 back version would involve the articulatory loop in the verbal modality and the visuospatial sketchpad in the visual modality. The 2 back version would involve the central executive in both modalities. Score would be assessed by observing the number of hits and errors. This test takes approximately 12 min.

Corsi block-tapping test

This test assesses the visuospatial short-term working memory. It involves mimicking a clinician as he/she tap a sequence of up to nine identical spatially separated blocks. The sequence starts out simple usually using two blocks but becomes more complex, that is, increases in length up to nine blocks, until the subject performance suffers. fMRI studies revealed that the ventrolateral prefrontal cortex is highly involved in performing the task. The format of the forward and backward Corsi block test is analogs to digit span test, but this measures the visuospatial memory span.

Rey's Auditory Verbal Learning Test (AVLT)

The AVLT (Schmidt, 1996) adapted for different cultures by the WHO (Maj *et al*., 1994) was adopted to suit conditions in India. Rey was originally developed the test in 1964. It consists of words designating familiar objects such as vehicles, tools, animals, and body parts. There are two lists A and B, with 15 different words, in each list. Words in List A are presented at the rate of one word per second during five successive trials. The words are presented in the same order in every trial. In each trial after presenting all the 15 words asking the subject to recall the words irrespective of the sequence with no cues. After completion of List A, words in List B are presented once and an immediate recall (IR) is taken for the same. The presentation of List B serves as an interference and prevents the subject from recalling the words from List A subsequently from immediate memory. This is followed by the IR of words from List A. After a delay of 20 min, words from List A are again recalled to form the delayed recall (DR) score. Following DR, recognition of the words in List A is tested. The words in List A are randomly mixed with 15 new words, which were phonemically or semantically similar to words in List A. The words are called out one at a time and the subject indicates whether each word belonged to List A or not. Hits and errors are recorded. Score can be analyzed by the number of words correctly recalled in each of the five trials of List A as well as the total number of words recalled over all the five trials forms the learning score. The number of words recalled correctly in the IR trial, DR trial, and the recognition trial forms the memory score. In recognition trial, the hits are scored separately. Test takes about 30 min.

Tests of Visual Learning and Memory: Complex Figure Test

The visuoconstructive ability was tested using the Rey's complex figure test (Meyers and Meyers, 1995). Rey developed the test in 1941. The test consists of a complex design which is abstract in nature which has an overall structure and multiple subcomponents. The subject is asked to recall the figure twice: The 1st time is an IR 3 min after the copying is completed, and the 2nd time is a DR 30 min later. The complex figure is exposed to the subject only during the initial copying. It is not exposed before IR or DR.

Design

Pre- and post-design, data were analyzed using paired sample *t*-test within the same sample at pre- and post-intervention levels.

Procedure

Patients who visited for the follow-ups were stated the difficulty in daily living activities due to forgetting issues. Main concern was to resolve the memory problems which were hampering their daily living. Patients completed an interview, considering clinical history and mental status examination, neuropsychological testing's was administered as pre-assessment, before the intervention to understand the baseline level at functioning and the areas of difficulty with their intensity. After the results, process of intervention, that is, memory retraining along with attention enhancement techniques was planned for 12–16 weeks, twice a week lasts for 1–1½ h per session. Post-assessment was done to understand the efficacy of the intervention quantitatively by statistical analysis using paired sample *t*-test and qualitatively by subjective report.

RESULTS

The post assessments results were showing significant difference of improvement levels. Results were statistically analyzed through paired sample *t*-test, there is no significant difference in simple tasks, but the difficulty was observed as the complexity of the task increased. Sustained and focused attention (from 23.1 to 53.1 $P = 0.01$), working memory (verbal - from 31 to 54.5 $P = 0.05$ and visual - from 22 to 56.5 $P = 0.01$), auditory verbal learning (IR - from 15.5 to 43 $P = 0.05$) and DR - from 7 to 42.5 $P = 0.05$). Visual memory (IR - from 62.5 to 80 P = 0.01) (DR - from 58.5 to 79.5 $P = 0.01$), which is showing significant improvement statistically between the two assessments [Table 2].

Memory Retraining with attention enhancement techniques

Therapeutic techniques: Intervention sessions were planned for each client individually

Psychoeducation

Patients were discussed about neuropsychological assessment results, distress was addressed. Family members of each patient were also psychoeducated by providing factual information about the symptoms and also the condition in which the patient is undergoing. Acknowledged their emotional aspects, understanding their perspective, appreciated for being supportive and empathetic. The levels of distress were targeted by changing their maladaptive coping style in to positive approach to instill hope for their well being.

Tasks	
Memory	Attention
Temporal encoding	Grain sorting
Spatial encoding	Finger dexterity
Frequency encoding	

Attention

Attention is the means by which we actively process a limited amount of information from the enormous amount of information available through our senses, our stored memories, and other cognitive processes (Dewerd, 2003a). Conscious attention serves three purposes in playing a causal role for cognition.

1. Helps in monitoring our interactions with the environment through such monitoring, we maintain our awareness of how well we are adapting to the situation in which we find ourselves.
2. It assists us in linking our past (memories) and our present (sensations) to give us a sense of continuity of experience. This is useful for personal identity.
3. Helps in controlling and planning for our future actions.

Clients were informed to complete the task within 2 minutes, by placing 50 pins using tweezers with both the hands. The complexity of the task increased with increased in number of time limit per session.

Four main functions of attention : a) Signal detection and Vigilance b) Search c) Selective attention d) Divided attention.

Finger dexterity board

This test is the coordination of small muscles, in movements - usually involving the synchronization of hands and fingers - with the eyes.

Attention may also influence perceptual operations. It is common knowledge among neurologists that sensory examinations are virtually impossible to perform on inattentive subjects.

Furthermore, alterations in critical sensory fusion thresholds can arise not only from disturbances along sensory pathways but also from variations in the level of vigilance.

In this task, the finger dexterity board was presented which was having 100 holes, 100 pins, and Tweezers. During the beginning session, clients were asked to place the pins in the holes in a vertical manner with no time limit, using the right and left hands separately, to check their baseline ability.From the 2nd session time limit was mentioned 6minutes started with 50 pins, slowly increasing the number of pins and decreasing the time limit.

Grain sorting

This task challenges the subject to pay attention which is focused and selective to identify, categorize, and segregate within a time limit. As the task starts with the convenient time limit to complete the task with minimum number of grains, clients would be motivated with the reward of praise and tried to continue and complete within a short period of time, even though task complexity increases.

Table 2: Paired samples t-test

Variables	Pre mean±SD	Post mean±SD	*t*-values
Digit vigilance	23.1±21.8	53.1±12.5	−6.41**
Verbal-N-Back 1	49.5±31.4	72.5±0.00	−1.63
Verbal-N-Back 2	31.0±17.9	54.5±4.47	−3.88*
Spatial span	22.0±13.9	56.5±24.8	−6.86**
AVLT-IR	15.5±4.80	43.0±12.2	−3.64*
AVLT-DR	7.00±1.11	42.5±25.9	−3.07*
AVLT-recognition	40.5±24.4	51.0±20.5	−1.29
Visual memory-copy	37.5±27.7	53.5±19.8	−1.97
Visual memory-IR	62.5±9.35	80.0±9.18	−8.36**
Visual memory-DR	58.5±10.8	79.5±9.25	−21.0**

*0.05 level, **0.01 level, AVLT: Auditory verbal learning test, IR: Immediate recall, DR: Delayed recall

During the beginning session, three different colors of 200 grains (70 + 70 + 60) were mixed with the similar size and were asked each client separately to segregate two different colored grains, that is, 50 + 50 within a 6 min of time. Task continued with increasing in complexity, that is, decreased in time limit with increased number of grains to segregate with different colors of grains as distracters.

Memory

Memory is not a unitary concept and it recruits several cortical and subcortical brain regions.

Encoding is the crucial first step to create a new memory. It allows the perceived item of interest to be converted into a construct that can be stored within the brain and then recalled later from short-term or long-term memory. Encoding is a biological event beginning with perception through the senses. The process of laying down a memory begins with attention (regulated by the thalamus and frontal lobe).

Temporal encoding

It is the processing and encoding of words through auditory input for storage and later retrieval. This is aided by the concept of the phonological loop, which allows input with our echoic memory to be subvocally rehearsed to facilitate remembering.

In this task, a list of words started with 6, 9, 12, and 15 ended with 20. Example - asked the clients to make meaningful sentences of the first two words, middle two words, last two words, etc.

Clients were able to recall first five words in the first session, but on rehearsal, the output was started increasing. The length of the list was also increased.

Spatial encoding

Spaced retrieval is also called "expanding rehearsal" and helps to aid increased retention of information. This strategy is beneficial for face-name associations, object naming, memory for object location, and prospective memory assignments (Clare, 2008).

In this task started with five objects, continued up to 15 objects, placed on a table to observe, and asked to name and position each object. The individual has to recall the name and position after a number of set intervals (e.g., 5 s, 10 s, 30 s, 1 min, 2 min, 5 min, and 10 min).

Frequency encoding

Providing flash cards of four different list of words with a category frequency of animals, things, vegetables, and transport. Relevant cues were provided at recall can aid retrieval and can be useful (Clare - 2008). Two types of cueing techniques were used like - Vanishing cues (or cueing with decreasing assistance), Forward cues (or cueing with increasing assistance).

DISCUSSION

Analysis of our results indicated that a memory retraining program was effective and can feasibly implement in long-term survivors of breast cancer clients.

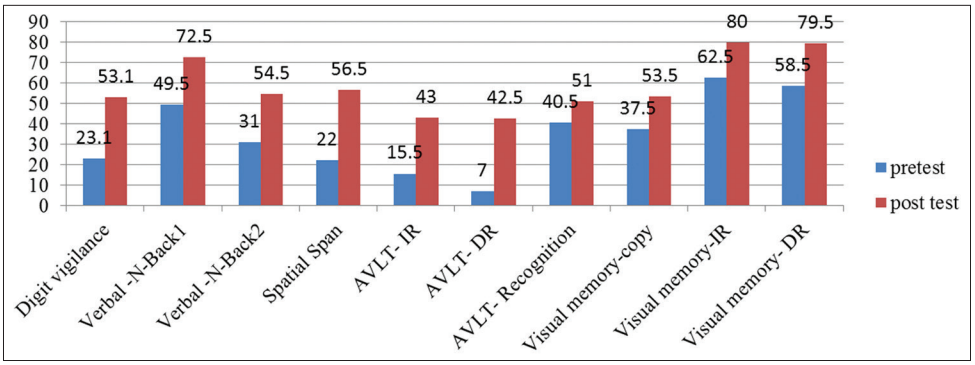
The memory retraining was positively associated with improvement in memory consecutively increased subjective satisfaction about their enhanced quality of life.

Limitations of the study

Small sample size, but as a pilot study, needs of more studies in this area.

Looking at the results in all the areas compare to pre and post, there is a significant difference showed in digit vigilance with *P* value statistically significant at 0.01 level. Improved focused and sustained attention played a prominent role in improving other areas of executive functioning. Whereas statistically no difference found in verbal - N-Back 1, but again verbal - N-Back 2 showed a statistically significant difference of *P* value at 0.05 level. This may be due to the level of complexity of the task. On spatial span again showed a statistical significance on *P* value at 0.01 level, which showed an increased visuospatial ability and also attention which helps in well-functioning of daily activities. Significance *P* value on AVLT (IR & DR) showed at 0.01 level and Visual memory (IR & DR) at 0.05 level. Which were significant in improved memory skills [Graph 1].

Evidence-based studies on cognitive retraining for breast cancer survivors Ferguson, Ahles, Saykin, McDonald, and Furstenberg *et al*. (2007) tested the effectiveness of a cognitive-behavioral intervention following chemotherapy for well-educated, middle-aged, women newly diagnosed with Stages I or II breast cancer. 29 women participated in



Graph 1: Significant change in Pre and Post Mean values

four in-office monthly visits (30–50 min each) with three contacts between visits, for seven contacts. The participants showed significant improvements over baseline in verbal and executive function, self-reported cognitive function, and quality of life, but there was no control group.

In a recent study, 82 breast cancer survivors completed a three-group randomized, controlled trial (Von Ah. Carpenter, Saykin, Monahan, Wu *et al*., 2012). Cognitive and affective outcomes included memory and speed of processing, perceived cognitive functioning, symptom distress (mood disturbance, anxiety, and fatigue), and quality of life. Data were collected at baseline, post-intervention, and 2-month follow-up; in particular, speed of processing improved at post-intervention and 2-month follow-up. The intervention was also associated with improvements in perceived cognitive functioning, symptom distress, and quality of life.

Ratings of satisfaction/acceptability were high.

Another cognitive-behavioral treatment (Ferguson *et al*., 2012) tested with 40 breast cancer survivors found improvements in verbal memory and spiritual well-being, but the subjective evaluation of cognitive complaints was unchanged. In summary, the treatment interventions to remediate memory impairment in breast cancer survivors or any cancer survivors are in the nascent stages of development.

CONCLUSION

Cognitive Retraining is an evidence based intervention to improve the level of cognitive areas functioning not only in neurological conditions but even in other chronic illness like Cancer. Without understanding the mechanism of recovery, there is no clear consensus as to how to rehabilitate cognitive sequelae of various conditions. This result will be showing the implementation of neuropsychological techniques will improve the level of functioning in patients with post-chemotherapy. However, there is a great need for more studies in implementing these techniques in the treatment process.

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