IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A PROSPECTIVE OBSERVATIONAL STUDY ON PRESCRIBING PATTERN AND QUALITY OF LIFE IN PATIENT WITH PERIPHERAL NEUROPATHIC PAIN - A PILOT STUDY

ADHITHYA A[1], ADITHYA SATHEESH KUMAR[1], SREE LAKSHMI D R[1], VARSHA VINCENT[1], Mrs SOUMYA R V[2], Dr MALINI GOPINATH[3], Ms ANJANA U J[4], Dr PRASOBH GR[5], Dr NITHIN MANOHAR R[6]

1 Fifth year Pharm D students, Sree Krishna College Of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India

2. Associate Professor, Dept. of Pharmacy practice Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India

3.MD (Medicine), DM (Neurology) Senior Consultant, Department of Neurology, Cosmopolitan Hospital Post Graduate Institute of Health Science & Research, Trivandrum.

4. Assistant Professor, Dept. of Pharmacy practice Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

5.Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

6.HOD&Proffessor Dept. of Pharmacy practice Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

ABSTRACT

Peripheral neuropathic pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The most commonly prescribed drugs for neuropathic pain include Pregabalin,Gabapentin and Methylcobalamine along with other drugs for co-morbid conditions.Neuro-Qol scale is used to assess the health-related quality of life of patients with neurological conditions.

METHODS:

The study was carried out in 10 patients with neuropathic pain.The study was conducted only after getting informed consent from the patient.The prescribing pattern of the patient was analysed from the prescription and proper counselling was provided.The health -related quality of life was assessed by using NEURO-QOL scale.

RESULT

The most commonly prescribed drugs for neuropathic pain were found to be Pregabalin,Gabapentin,Lacosamide and Methylcobalamine. A significant increase in quality of life was found in patients after treatment and patient counselling.

CONCLUSION

It was concluded that anti -convulsant like Pregabalin,Gabapentin,lacosamide along with Methylcobalamine and other drugs for co-morbid conditions.There is significant improvement in the QOL scoring in patients after treatment and proper counselling.

KEYWORDS:

Neuropathic pain,Neuro Qol,Diabetics,Pregabalin,Gabapentin,

NEUROPATHIC PAIN

Pain is a distressing sensory and emotional experience connected to real or potential tissue damage, or one that is portrayed as such damage, according to International Association for the Study of Pain (IASP)[1]. There are many pathophysiologic processes and interpretation of pain, which can vary greatly in severity, quality and duration. Injury to neural tissue in Central Nervous System (CNS) or Peripheral Nervous System (PNS) initiates or causes neuropathic pain. Neuropathy is a disturbance of function or a change in one or several nerves.[2] Patients with neuropathic pain frequently express discomfort from stimuli that are not typically harmful, such as a breeze or light touch, in addition to spontaneous pain. Peripheral neuropathy is a commonly encountered disorder presenting to primary care physicians and neurologist in the community[3]. Peripheral neuropathy can be subdivided into 3 types, mononeuropathy, mononeuropathy

multiplex and polyneuropathy, based on the involvement of single nerve, multiple single nerves, or many nerves respectively, in a symmetric length-dependent fashion[4].

Types of Neuropathic Pain[5]

Types of Neuronal Pain	**Causes**
Trigeminal Pain	Compression of trigeminal or its branches
Post herpetic Pain	Shingles
Complex regional pain syndrome	Trauma
Diabetic neuropathy	Persistent Hyperglycemia
Central Pain	Trauma to spinal cord
Phantom Pain	Amputation

ETIOLOGY

Possible etiologies of peripheral neuropathies[6]

Endocrine disease

- Hypothyroidism
- Diabetes Mellitus
- Nutritional Diseases

Connective tissue diseases

- Rheumatoid arthritis
- Systemic Lupus erythematous

Infectious diseases

- AIDS
- Lyme disease

- Hereditary diseases

Neuropathies caused by drugs[7]

1. Antineoplastic Agents

- Cisplatin
- Taxanes
- Vincristine

2. Antimicrobial Agents

- Chloroquine
- Dapsone
- Isoniazid

CLINICAL PRESENTATION

- Gradual beginning of tingling, prickling, or numbness in your hands or feet that may go up into your legs or arms.
- Pain that is throbbing, searing, jabbing, or sharp[8].
- A high threshold for touch
- Pain that occurs during actions that shouldn't cause it, such foot pain when placing weight on it or when it's covered by a blanket.
- Falling and poor coordination[9]

DIAGNOSIS

- **TAKING A THROUGH MEDICAL HISTORY:** The doctor will take complete medical history of the patient, including symptoms, lifestyle, toxin exposure, Habits and any family histories of neurological problems[10].
- **NEUROLOGICAL EXAM:** Examination of body posture and coordination in addition to tendon reflexes, muscle strength, and muscle tone[11].
- **BLOOD TEST:** These tests are used to diagnose vitamin deficiencies, diabetes, immunological diseases, paraneoplastic causes and others[12].
- **IMAGING EXAMS:** CT or MRI scans to rule out tumors, herniated discs, pinched (compressed) nerves, blood vessels abnormalities, and other condition affecting the bones and blood vessels[13].

MANAGEMENT

PHARMACOLOGOCAL TREATMENT

Therapeutic agents with greater efficacy and safety are necessary because traditional analgesics like non-steroidal anti-inflammatory medication (NSAIDs) and opioid agonists (e.g.; morphine) are ineffective in some pain disorders and have side effects[14]

- **TRYCYCLIC ANTIDEPRESENT**

Such as amitriptyline and imipramine are useful for treating neuropathic pain because they prevent serotonin and noradrenaline from entering the ascending analgesic pathways[15].

- **ANTI-CONVULSANT**

Such as pregabalin and gabapentin are recommended as the first-line treatment for neuropathic pain. It has been discovered that anti-convulsant including carbamazepine, sodium valproate, lacosamide, oxcarbazepine, topiramate, vigabatrin, and levetiracetam have analgesic effects because they increase GABA activity, reduce glutamate release, block NMDA receptors, and block Ca and Na channels on neuronal membranes[16]. glutamate release at presynaptic and post synaptic locations, both peripherally and centrally.

- **OPIOIDS AND GABAPENTIN**

These drugs together have been shown to have synergistic effects in reducing neuropathic pain. There has long modulatory mechanism for pain alleviation. It is hypothesized that this mechanism contributes to the analgesic effect of Some of the more popular analgesics, such as paracetamol[17].

NONPHARMACOLOGICAL TREATMENT

Although many patients with neuropathic pain pursue complementary and alternative treatment, rigorous evidence supporting the efficacy of non-drug therapy is limited. Some reports suggest benefits of conservative interventions such as Transcutaneous Electrical Nerve Stimulation, Percutaneous Electrical Nerve Stimulation, acupuncture and others.

ACUPUNCTURE

Inserting tiny needles into various body sites may lessen the symptoms of peripheral neuropathy. It can take several sessions before you start to see progress. When carried out by a licensed professional using sterile needles, acupuncture is typically regarded as safe[18].

HERBS

Some plants, such evening primrose oil, may assisst diabetics with neuropathy experience less pain[19]

AMINO ACID

Individual with diabetes and those who have had chemotherapy may benefit from amino acids like acetyl-L-carnitine. Chemotherapy can cause nausea and vomiting in patients[20]. Amino acids like acetyl-L-carnitine can help in reducing this nausea and vomiting in patients.

MATERIALS AND METHODS:

Data source: All the relevant information regarding the study was collected from case Records and direct interview with patients and care givers. Data from case records and care Givers was collected by using suitably designed proforma. The study was approved by Research and Ethical Committee of Cosmopolitan hospital, Thiruvananthapuram.

Study population: Patients were taken from Neurologyy department of Cosmopolitan Hospital. Informed consent was obtained. The study was conducted for the period of 2 Months.

Assessment of quality of life: Details were collected from case records of Neuropathic patients and direct Interview with the patients and caregivers which is been recorded in Neuro-QOL questionnaire.

Statistical Analysis: Comparison of QOL of first and second follow up was analysed by paired t test according to the nature of the data.

OBSERVATION AND RESULTS:

The proposed study entitled "**A PROSPECTIVE OBSERVATIONAL STUDY ON PRESCRIBING PATTERN AND QUALITY OF LIFE IN PATIENT WITH PERIPHERAL NEUROPATHIC PAIN"** was carried out in a multispecialty tertiary care hospital. In this study, the data was collected from 10 patients diagnosed with neuropathic pain and prescription was analysed. Most commonly prescribed drugs were anti -convulsants like

Pregabalin,Gabapentin,lacosamide along with Methylcobalamine.This study also aims to improve the QOL of patients.

DEMOGRAPHIC DETAILS OF THE PATIENTS:

The data related to demographic details of patients were collected and recorded.

Table 1: Age Distribution in Study Population

AGE WISE DISTRIBUTION	NUMBER OF PATIENTS (N=10)	PERCENTAGE (%)
50-60	3	30%
61-70	4	40%
71-80	3	30%
81-90	0	0

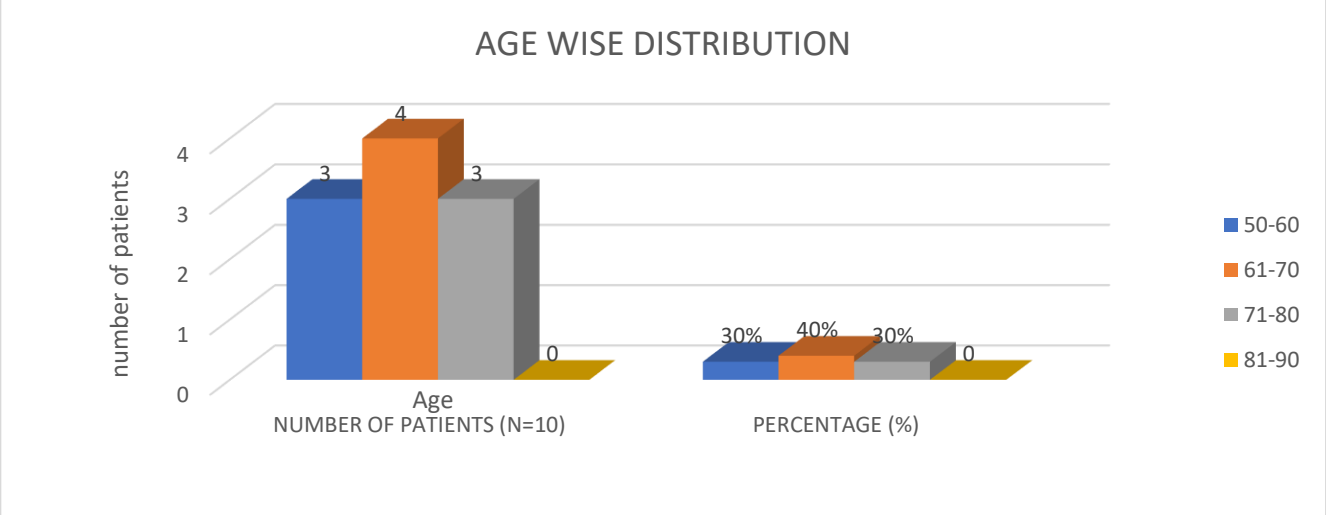

Figure 1: diagrammatic representation of age wise distribution of study population

In this study, patients of age above 18 were included.it was observed that majority of the patient presenting with neuropathic pain were from the age group 61 -70

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON GENDER:

The percentage distribution of patients based on gender is shown in the following table

Table 2: Percentage Distribution of Patients Based on Gender.

GENDER	NUMBER OF PATIENTS (n=10)	PERCENTAGE (%)
FEMALE	4	40%
MALE	6	60%

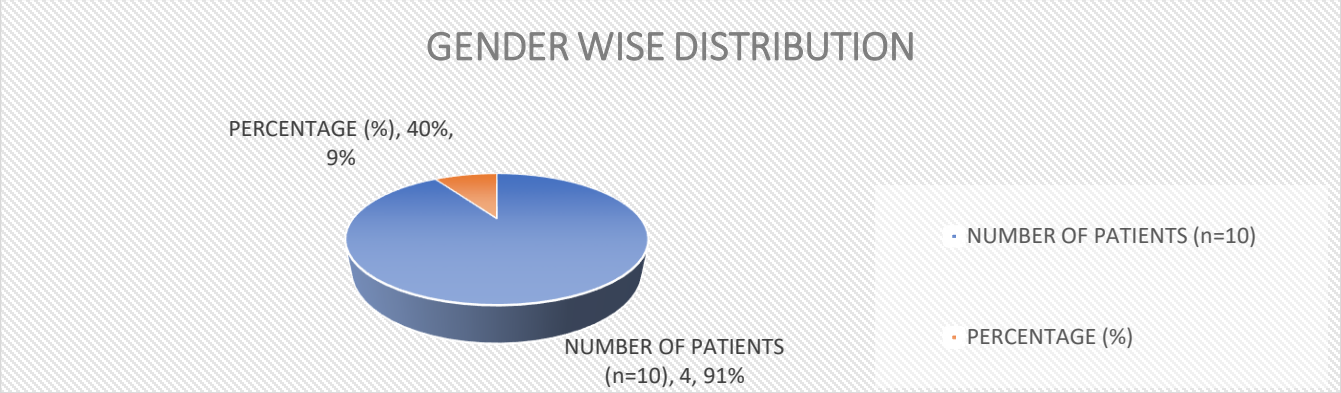

Figure2: diagrammatic representation of patients based on gender

Amongst a total of 10 patients included in this study, a preponderance of male patients was observed. In this study 4 patients were female (40%) while 6 patients were male (60%).

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON SYMPTOMS

The percentage distribution of study population in the basis of symptom is shown in the following table

Table 3: Percentage Distribution of Patients Based on Symptoms

Symptoms*	Number	Percentage
WEAKNESS	6	60
TINGLING SENSATION	6	60
NOCTURNAL AGGRAVATION	3	30
NUMBNESS	8	80
PARASTHESIA	10	100

*Multiple Symptoms exist

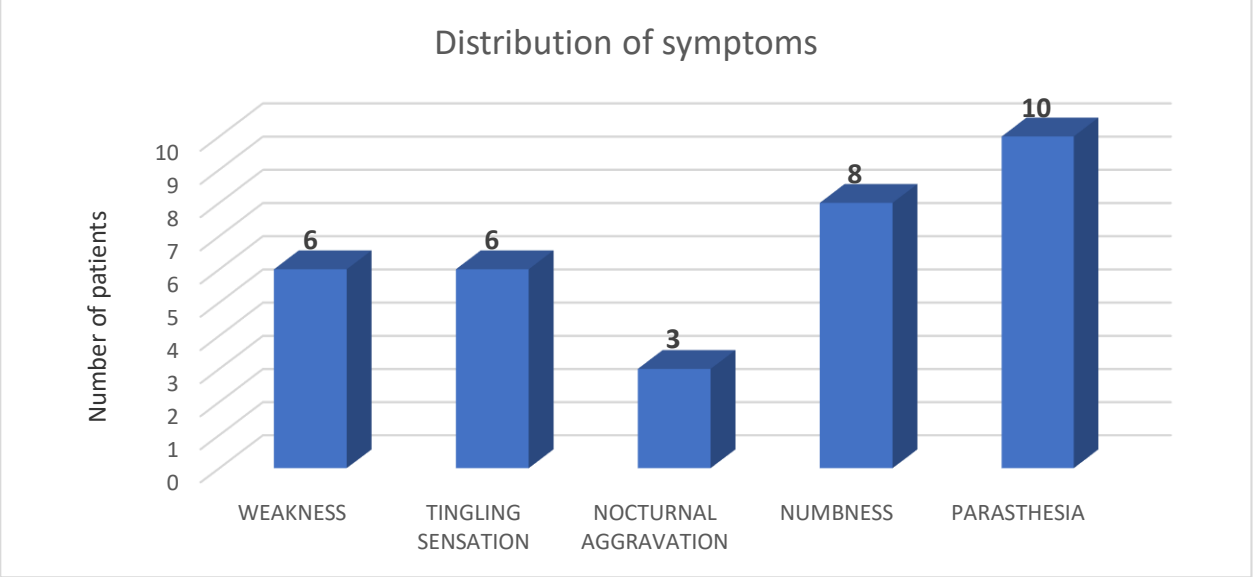

Figure 3 : diagrammatic representation of percentage distribution based on symptoms

PERCENTAGE DISTRIBUTION OF PATIENTS BASED ON CO-MORBIDITIES

The percentage distribution of patients based on co-morbidities are shown in the following table

Table 4: Percentage Distribution of Patients Based on Co-Morbidities

Distribution of co-morbidities*

Co-morbidities*	Number	Percentage
HYPERTENSION	6	60
DIABETES	10	100
HEART DISEASE	4	40
THYROID DISEASE	4	40
KIDNEY DISEASE	7	70

*Multiple co-morbidities exit

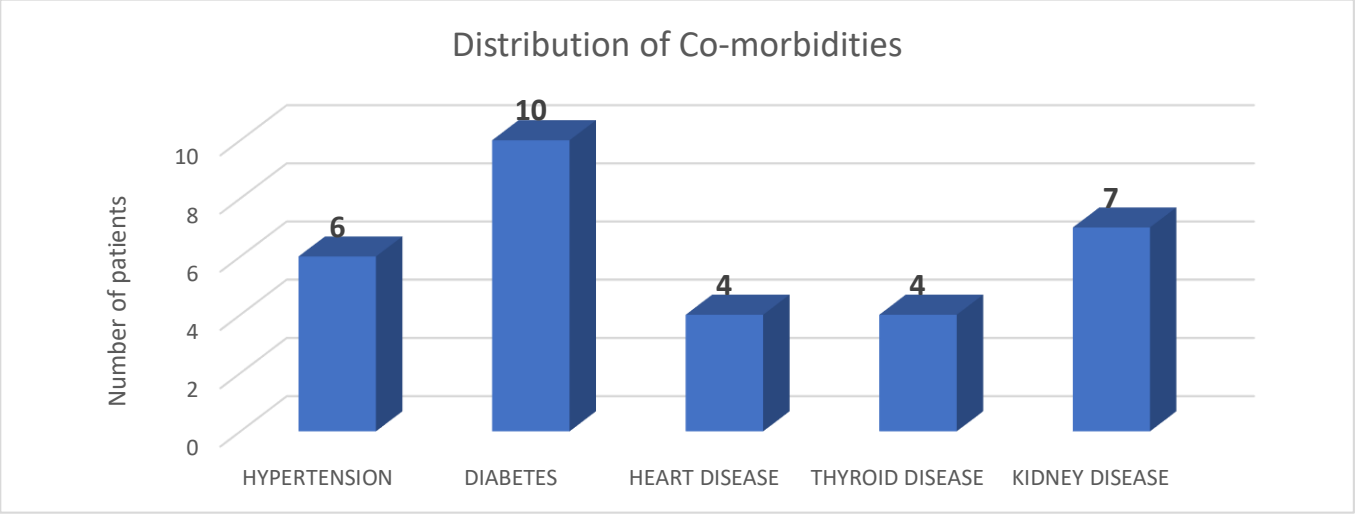

Figure 4 : diagrammatic representation of percentage distribution based on co-morbidities

PERCENTAGE DISTRIBUTION OF DRUG PRESCRIBED

The percentage distribution of drugs based on prescribing pattern is shown in the following table

TABLE 5:Distribution of drug prescribed*

Drug Prescribed*	Number	Percentage
PREGABALIN	4	40
GABAPENTIN	6	60
METHYLCOBALAMIN	8	80
TRAMADOL	2	20
LACOSAMIDE	2	20
Total	10	100

*Multiple Drugs administered

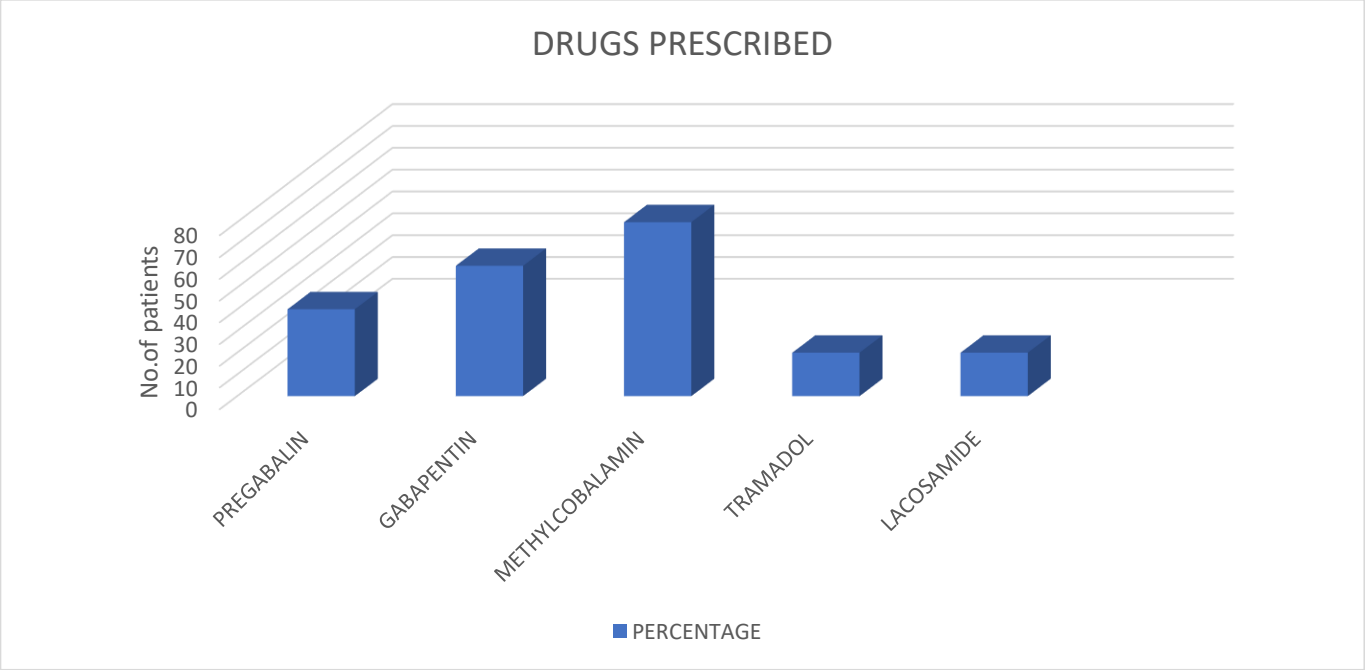

Figure 5 : diagrammatic representation of percentage distribution of prescribing pattern

COMPARISON OF COMMUNICATION

The comparison of communication before and after counselling and treatment are shown in the following table

Table 6: Comparison of communication before and after treatment and counselling respectively.

Communication	Before counselling and treatment	er counselling and treatment
Mean Score	19.20	10
SD	2.04	3
Significant value	.001* (p<0.05)	

Comparing before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

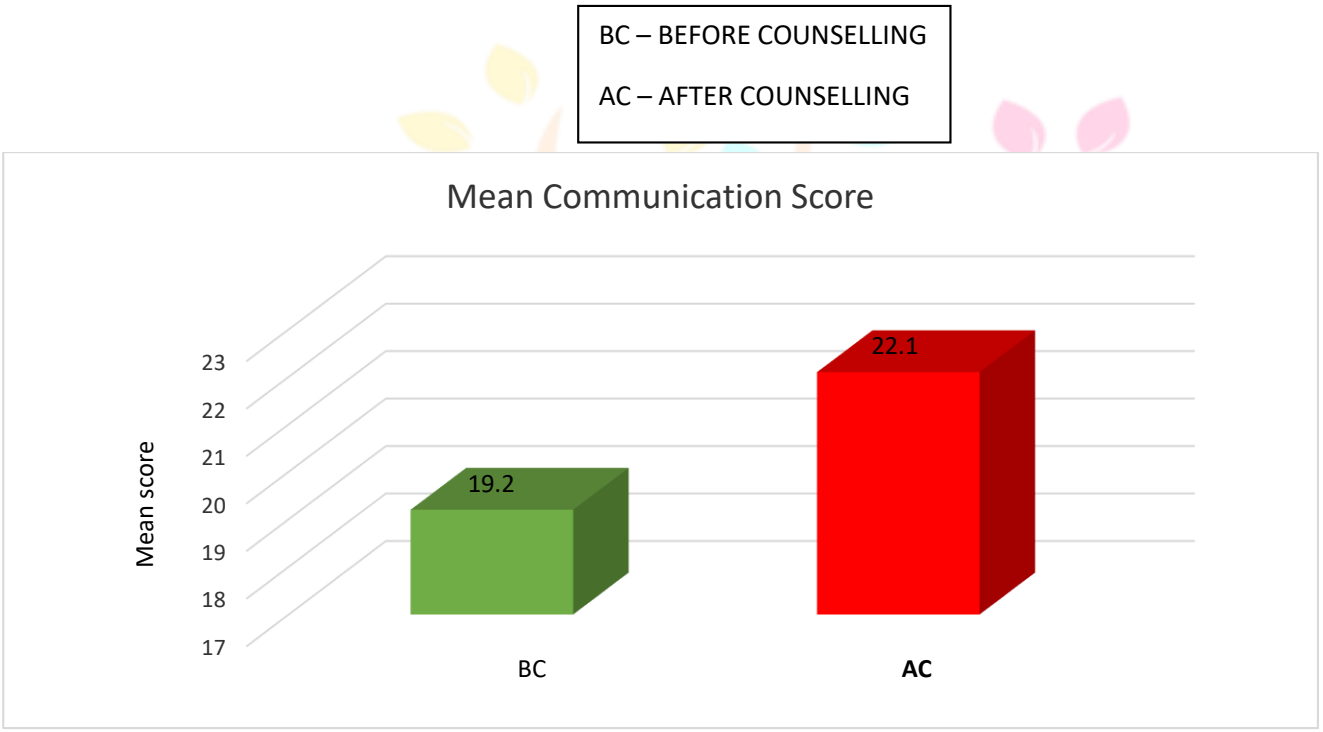

Figure 6: diagrammatic representation of communication before and after counselling and treatment

COMPARISON OF ABILITY TO PARTICIPATE IN SOCIAL ROLES

The comparison of ability to participate in social roles before and after counselling and treatment are shown in the following table

Table 7: Comparison of ability to participate in social roles between before counselling and after counselling

Social Roles	Before counselling and treatment	After counselling and treatment

Mean Score	34.40	39.00
SD	2.22	1.05
Significant value	.001* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

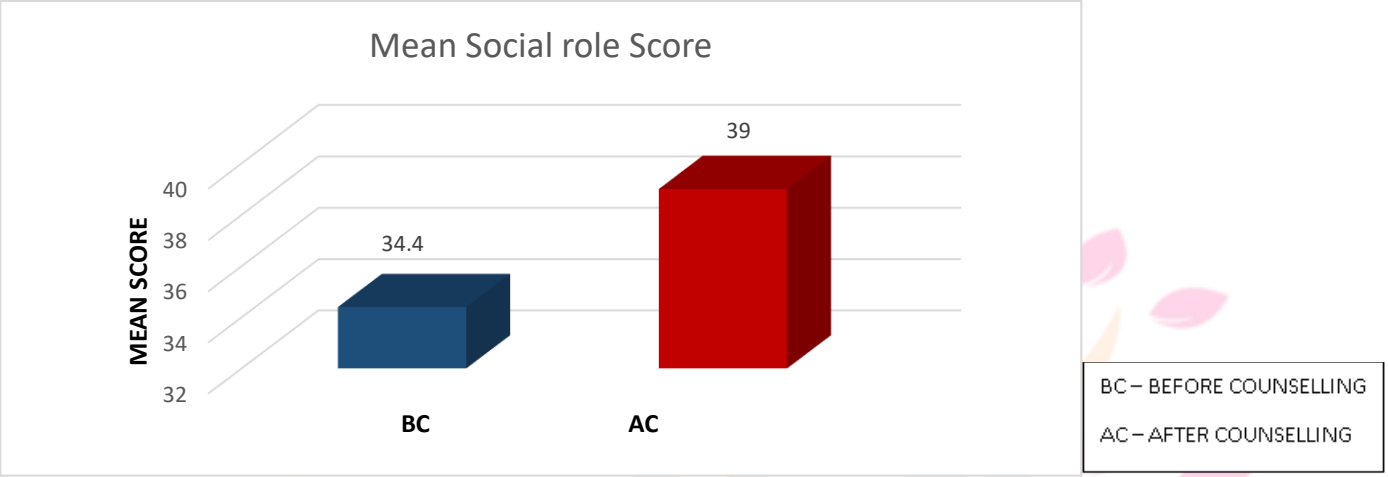

Figure 7: diagrammatic representation of ability to participate in social roles before and after counselling and treatment

COMPARISON OF ANXIETY

The comparison of anxiety before and after counselling and treatment are shown in the following table

Table 8: Comparison of anxiety between before counselling and after counselling

Anxiety	Before counselling and treatment	After counselling and treatment
Mean Score	36.00	38.40
SD	2.40	1.90
Significant value	.001* (p<0.05)	

Comparing before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

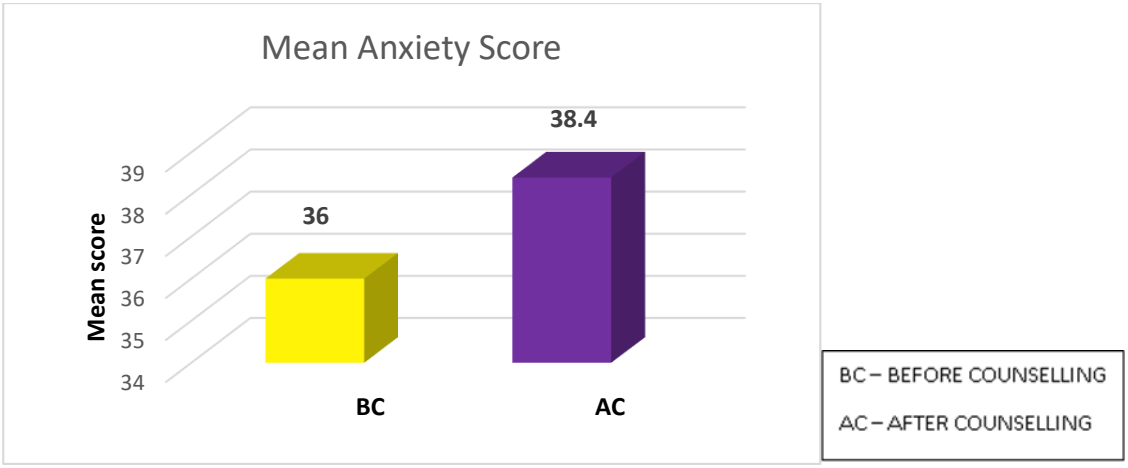

Figure 8: diagrammatic representation of anxiety before and after counselling and treatment

COMPARISON OF DEPRESSION

The comparison of depression before and after counselling and treatment are shown in the following table

Table 9: Comparison of depression between before counselling and after counselling

Depression	Before counselling and treatment	After counselling and treatment
Mean Score	35.60	38.80
SD	1.90	1.23
Significant value	.001* (p<0.05)	

Comparing the between before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

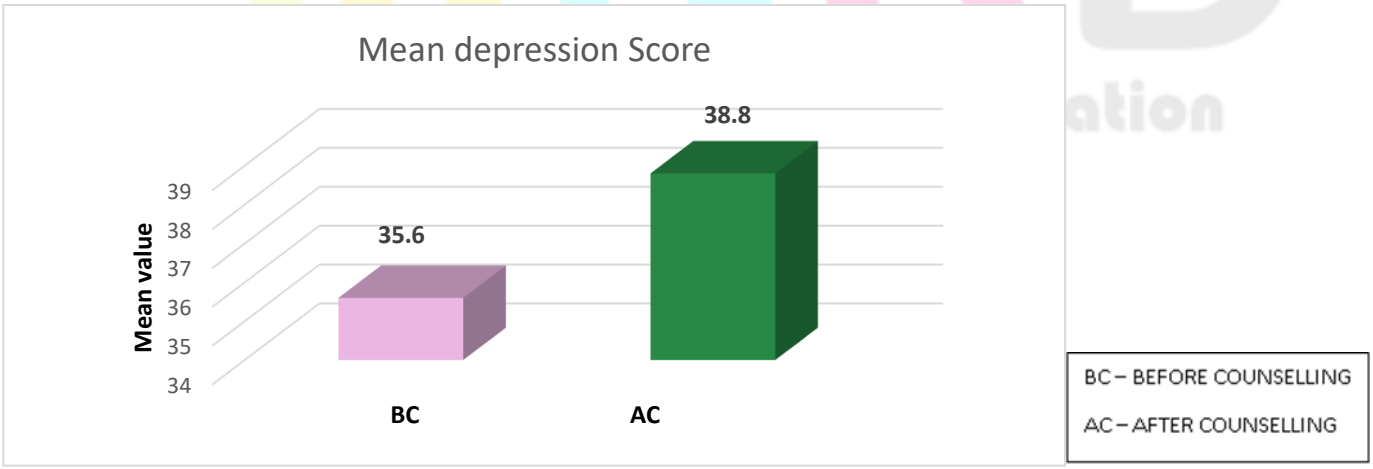

Figure 9: diagrammatic representation of comparison of depression before and after counselling and treatment

COMPARISON OF EMOTIONAL AND BEHAVIOURAL DYSFUNCTION

The comparison of emotional and behavioural dysfunction before and after counselling and treatment are shown in the following table

Table 10: Comparison of emotional and behavioural dysfunction between before counselling and after counselling

Emotional	Before counselling and treatment	After counselling and treatment
Mean Score	36.30	33.90
SD	1.95	2.03
Significant value	.005* (p<0.05)	

Comparing between the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that that the after counselling score is significantly different than the before counselling score.

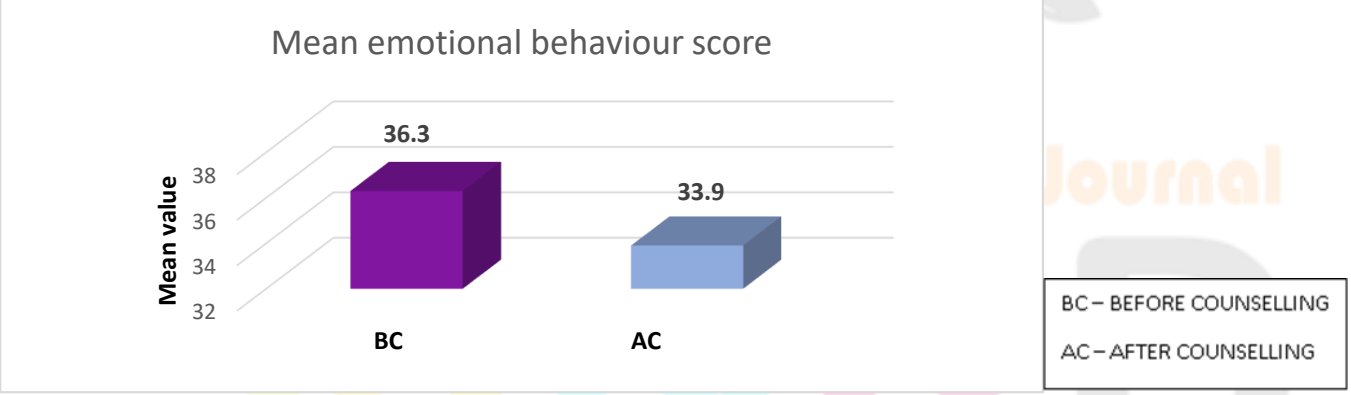

Figure 10: diagrammatic representation of comparison of emotional and behavioural dysfunction between before counselling and after counselling

COMPARISON OF FATIGUE

The comparison of fatigue before and after counselling and treatment are shown in the following table

Table 11: Comparison of fatigue between before counselling and after counselling

Fatigue	Before counselling	After counselling

	and treatment	and treatment
Mean Score	33.40	29.60
SD	1.17	1.27
Significant value	.001* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

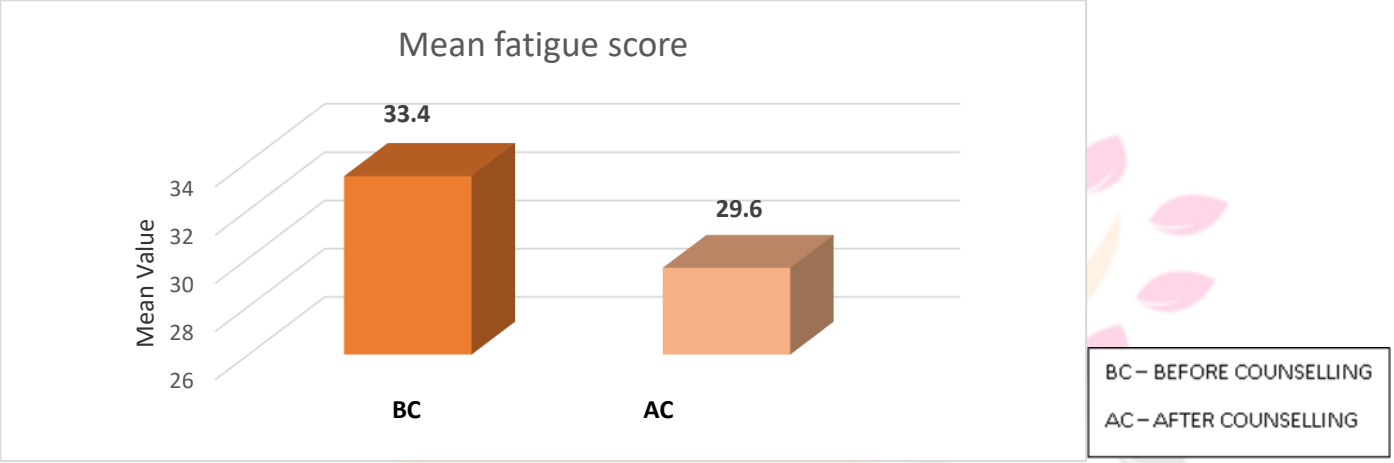

Figure 11: diagrammatic representation of comparison of fatigue between before counselling and after counselling

COMPARISON OF LOWER EXTREMITY FUNCTION

The comparison of lower extremity function before and after counselling and treatment are shown in the following table

Table 12: Comparison of lower extremity function between before counselling and after counselling

LE function	Before counselling and treatment	After counselling and treatment
Mean Score	24.80	28.90
SD	4.32	4.43
Significant value	.001* (p<0.05)	

Comparing between the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

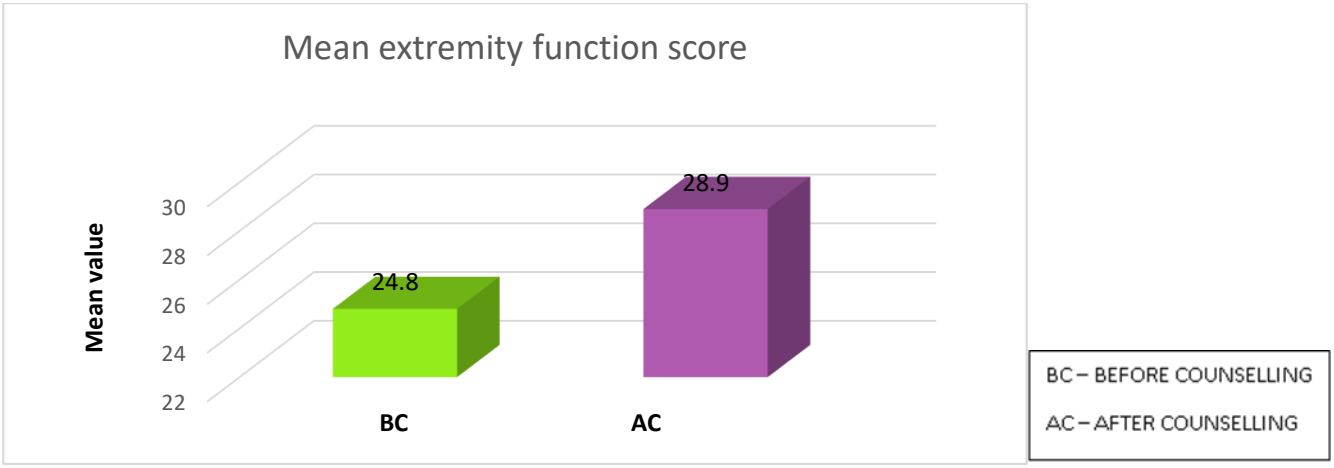

Figure 12: diagrammatic representation of comparison of lower extremity function between before counselling and after counselling

COMPARISON OF POSITIVE AFFECT AND WELL-BEING

The comparison of positive affect and well-being before and after counselling and treatment are shown in the following table

Table 13: Comparison of positive affect and well-being between before counselling and after counselling

Well-being	Before counselling and treatment	After counselling and treatment
Mean Score	30.20	33.60
SD	4.13	3.13
Significant value	.001* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

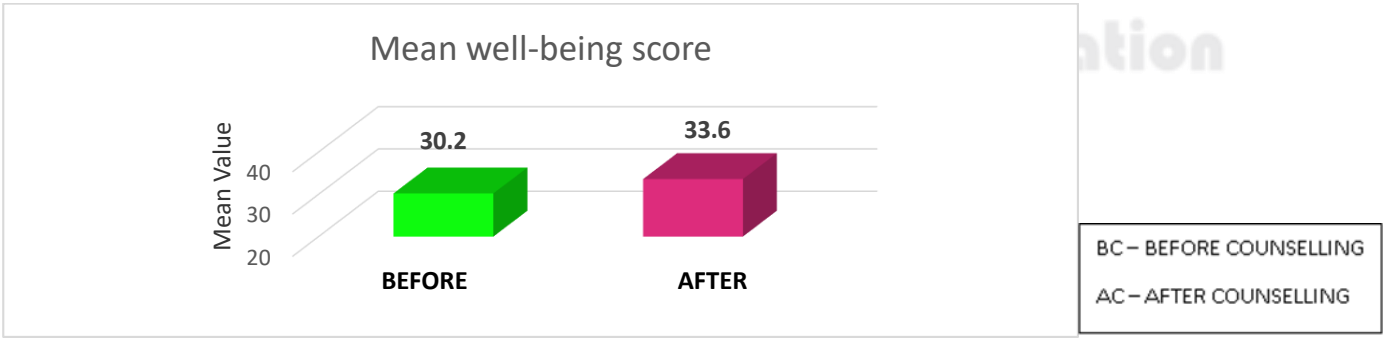

Figure 13: diagrammatic representation of comparison of positive affect and well-being between before counselling and after counselling

COMPARISON OF SLEEP DISTURBANCE

The comparison of sleep disturbance before and after counselling and treatment are shown in the following table

Table 14: Comparison of sleep disturbance between before counselling and after counselling

Sleep disturbance	Before counselling and treatment	After counselling and treatment
Mean Score	28.40	14.90
SD	10.60	1.52
Significant value	.003* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

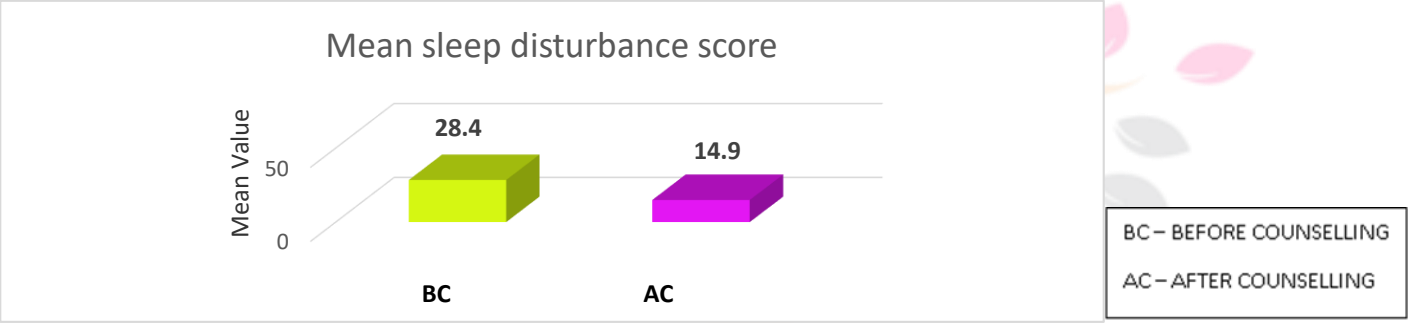

Figure 14: diagrammatic representation of comparison of sleep disturbance between before counselling and after counselling

COMPARISON OF UPPER EXTREMITY FUNCTION

The comparison of upper extremity function before and after counselling and treatment are shown in the following table

Table 15: Comparison upper extremity function between before counselling and after counselling

Upper extremity function	Before counselling and treatment	After counselling and treatment
Mean Score	31.30	36.50
SD	2.75	1.65
Significant value	.001* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

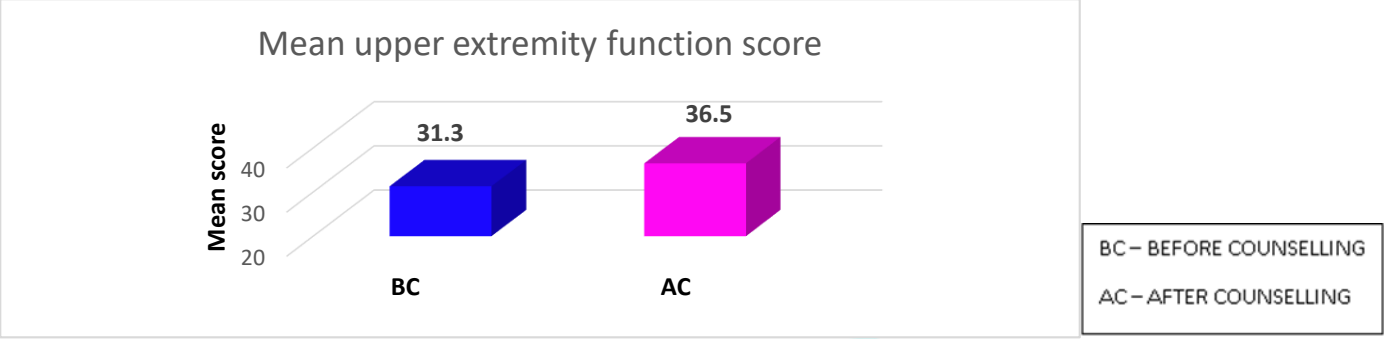

Figure 15: diagrammatic representation of comparison of upper extremity function between before counselling and after counselling

COMPARISON OF STIGMA

The comparison of stigma before and after counselling and treatment are shown in the following table

Table 16: Comparison of stigma between before counselling and after counselling

Stigma	Before counselling and treatment	After counselling and treatment
Mean Score	9.60	8.50
SD	1.43	0.53
Significant value	.007* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

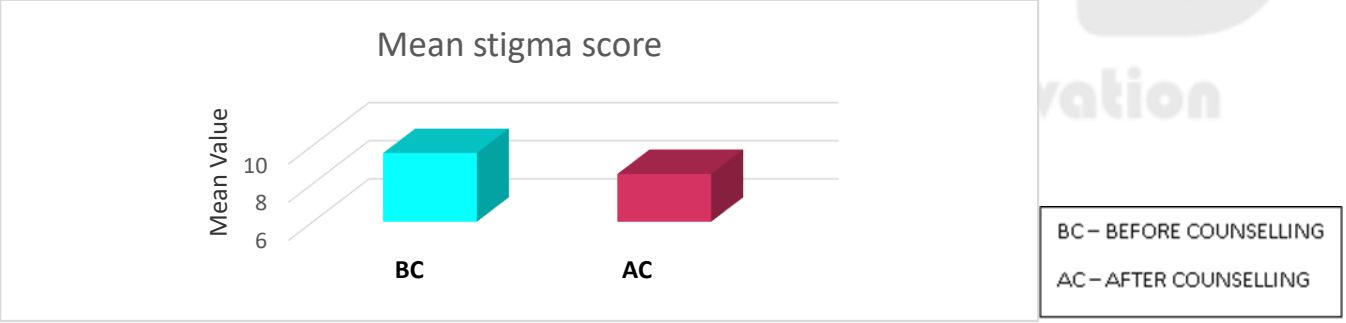

Figure 15: diagrammatic representation of comparison of stigma between before counselling and after counselling

COMPARISON OF COGNITION FUNCTION

The comparison of cognition function before and after counselling and treatment are shown in the following table

Table 17: Comparison of cognition function between before counselling and after counselling

Cognition function	Before counselling and treatment	After counselling and treatment
Mean Score	35.10	38.30
SD	0.74	0.48
Significant value	.001* (p<0.05)	

Comparing the before counselling and after counselling score a paired t-test is administered. The result is significant and we reject the null hypothesis that the scores are equal and conclude that the after counselling score is significantly different than the before counselling score.

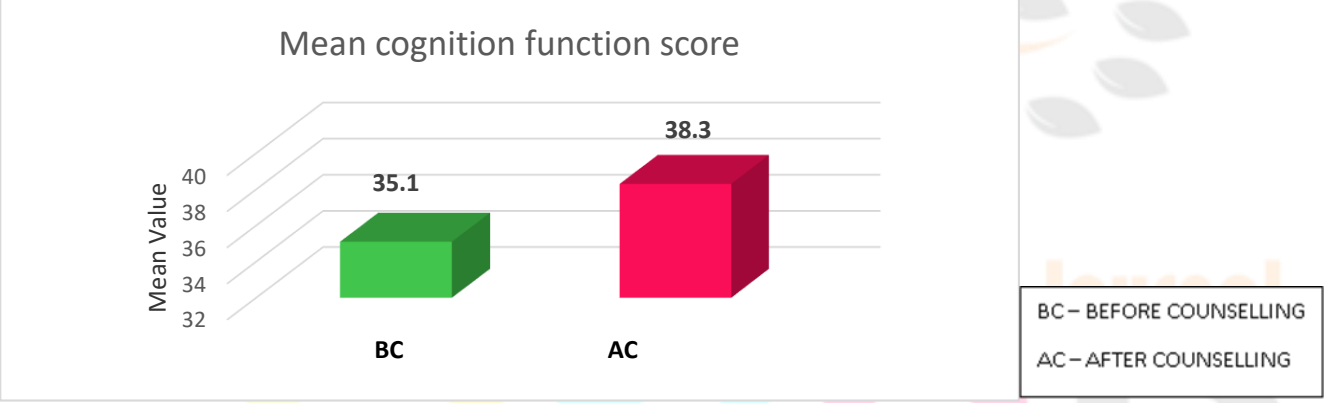

Figure 17: diagrammatic representation of comparison of cognition function between before counselling and after counselling

DISCUSSION

Peripheral neuropathic pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Patients may sometimes commit errors during drug consumption or follow an unhealthy diet, so proper counselling is provided to the patients using a patient information leaflet regarding food intake, diet as well as for diabetic foot care. The primary objective of the study was to determine the prescribing pattern of the drugs for peripheral neuropathic pain and to assess the quality of life of patients before and after counselling by using NEURO-QOL scale. In this study we considered a

total of 10 patients who satisfied the inclusion criteria. In our study, Pregabalin, Gabapentin, Methylcobalamine, Lacosamide were the mostly prescribed drugs.

The observations of our study is similar to that of the study conducted by **Parvan Banu et-al ;** in which it was found that Gabapentin, Pregabalin and Methylcobalamine were the mostly prescribed drugs. A study conducted **by Tanja Schlereth et-al** also shows that the first line treatment of the drugs were Pregabalin and Gabapentin .In a study conducted by **Allan J et-al** showed that quality of life in individual patients in neurological disorders is assessed by using neuro QOL scale.In our study also we use neuro QOL scale .In a study conducted by **Ian Gilron et-al** showed that Gabapentin and Pregabalin represents a novel class of drugs for the treatment of neuropathic pain.

The neuro-QOL questionnaire was used to assess the quality of life. The neuro-QOL questionnaire was performed to each patient before and after counselling. Neuro -QOL is assessed in the beginning of the study and followed up after one month when patients come for review. It consists of 12 domains. Proper diet plan and diabetic foot care were included in patient counselling.

CONCLUSION

Peripheral neuropathic pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. When compared to women, men are most commonly affected by neuropathic pain.

In this study, Pregabalin, Gabapentin and methylcobalamine were given to the respective group of patients, and improvement in quality of life was assessed using the neuro qol scale. It is concluded that a higher chance of occurrence of peripheral neuropathic pain was found to be between the age group of 61-70 years.

Pharmacists are in an ideal position to provide patient education and optimize patient care. Understanding the aspects of peripheral neuropathic pain, the effect of Gabapentin, Pregabalin and Methylcobalamine on health related quality of life and the efficacy of the drug yields better therapeutic outcomes. Hence the well-being of the patient is ensured. In the future, this study could help to ensure the most effective treatment for peripheral neuropathic pain.

REFERENCE

1.Donofrio PD, editor. Textbook of peripheral neuropathy. Demos Medical Publishing; 2012 Apr 17.

2.Cole M. Brain and Bannister's Clinical Neurology. Neurology. 1993 Jan;43(1_part_1):241-.

3.Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran pathologic basis of disease, professional edition e-book. Elsevier health sciences; 2014 Aug 27.

4.Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC. Neurology in clinical practice. Elsevier Health Sciences; 2012 Mar 29.

5. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, LeBel AA, Levy RM, Mackey SC. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. InMayo Clinic Proceedings 2010 Mar 1 (Vol. 85, No. 3, pp. S3-S14).

6. Banu P, Mondal S, Biswas A, Naser SM, Niyogi M. Prescribing trends in diabetic neuropathy at a tertiary care hospital. Asian Journal of Medical Sciences. 2018 Aug 31;9(5):8-11.

7. Sloan G, Selvarajah D, Tesfaye S. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. Nature Reviews Endocrinology. 2021 Jul;17(7):400-20.

8. 4. Perez-Matos MC, Morales-Alvarez MC, Mendivil CO. Lipids: a suitable therapeutic target in diabetic neuropathy? Journal of diabetes research. 2017;2017

9. Greig M, Tesfaye S, Selvarajah D, Wilkinson ID. Insights into the pathogenesis and treatment of painful diabetic neuropathy. Handbook of Clinical Neurology. 2014 Jan 1; 126:559-78.

10. Peltier A, Goutman SA, Callaghan BC. Painful diabetic neuropathy. Bmj. 2014 May 6;34

11. Dyck PJ, Giannini C. Pathologic alterations in the diabetic neuropathies of humans: a review.

12. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006;29(6):1294–9.

13. Arimura A, Deguchi T, Sugimoto K, Uto T, Nakamura T, Arimura Y, et al. Intraepidermal nerve fiber density and nerve conduction study parameters correlate with clinical staging of diabetic polyneuropathy. Diabetes Res Clin Pract. 2013;99(1):24–9.

14. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, Fadavi H, Asghar O, Alam U, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. Diabetes. 2013;62(1):254–60. doi:10.2337/db12-0574.

15. Low PA, Lagerlund TD, McManis PG. Nerve blood flow and oxygen delivery in normal, diabetic,and ischemic neuropathy. Int Rev Neurobiol. 1989;31:355–438.

16. Alleman CJ, Westerhout KY, Hensen M, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. Diabetes Res Clin Pract. 2015;109(2):215–225.doi:10.1016/j.diabres.2015.04.031

17. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med.2004;21(9):976–982. doi:10.1111/j.1464-5491.2004.01271.x

18. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022;28(10):923–1049. Doi:10.1016/j.eprac.2022.08.002.

19. 14. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes.Diabetes Care. 2006;29 (4):883–887. Doi:10.2337/diacare.29.04.06.dc05-2180.

20. Price R, Smith D, Franklin G, et al. Oral andtopical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. Neurology 2022;98:31–43