RESEARCH

Comparison of Fluoxetine (20 Mg) and Amitriptyline (12.5 Mg) As Adjuvants for The Combination of Paracetamol and Morphine in Cancer Patients' Pain Relief

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ABSTRACT

Background: Pain is one of the most common symptoms in cancer which affects 30–50% of patients on average and rises to 70–90% in cases of advanced disease. As cancer advances, so does the frequency of discomfort associated with the illness. When cancer is detected in its terminal stage, 30–40% of patients report experiencing moderate pain, and 60–100% report experiencing severe pain. Tricyclic antidepressants (TCAs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) are the four families of antidepressant medications that have been investigated for use in the treatment of neuropathic pain.

Objective: This research was conducted at the pain clinic of Adam Malik Hospital, this study intends to compare the effectiveness of fluoxetine with amitriptyline as an adjuvant to the combination of paracetamol and morphine in reducing pain symptoms in cancer patients.

Methods: This study was designed as a randomized, double-blind clinical experiment. The study was carried out in 2023 between July and September. Two groups of forty research participants receiving outpatient care at the pain clinic were formed. Fluoxetine, morphine, and paracetamol were administered to group A (n = 20), whereas amitriptyline, morphine, and paracetamol were administered to group B (n = 20). PainDETECT was used to measure the subjects' pain scores. Both univariate and bivariate data analysis was done. The Chi-Square test, Independent T-test, Paired T-test, and Mann-Whitney were used to examine the bivariate data.

Result: The delivery of amitriptyline and fluoxetine resulted in a substantial reduction in PainDETECT scores, with a p-value of less than 0.05.

Conclusion: This study show that PainDETECT score was statistically reduced in both the fluoxetine and amitriptyline groups but the reduction was not clinically meaningful because the target score drop was less than 4 on a scale of 0–10, or a 50% reduction in pain.

Keywords: amitriptyline; fluoxetine; neurophatic pain; NRS; PainDETECT

INTRODUCTION

Cancer is becoming more commonplace worldwide, particularly in developing country. Nearly 85% of the world's population lives in low- to middle-income nations, which greatly increases the cancer burden worldwide. 50% of cancer patients worldwide are found in Asia, Africa, and Latin America combined, and over half of cancer-related fatalities worldwide occur in Asia alone. The majority of the time, physical pain, psychological, social, spiritual, and emotional problems are the symptoms associated with cancer.[1] Pain is the primary symptom that prompts people to seek medical attention for a variety of conditions, including cancer, degenerative changes, myocardial ischemia, acute and chronic traumas, and more.[2] As the disease advances, so does the frequency of cancer-related discomfort. The World Health Organization (WHO) reports that between 30% and 40% of cancer patients report having moderate to severe pain at the time of diagnosis, and that number rises to between 60% and 100% in the late and final stages. Pain from cancer is a major global health issue. Actually, the majority of cancer patients report experiencing pain during their illness, and cancer is a prevalent disease. More than half of oncology patients experience pain due to their disease, according to a meta-analysis of over fifty US research; comparable figures are also available from Europe and East Asia.[3] As the illness worsens, the pain may lead to psychological issues and a decline in the patients' quality of life. Cancer pain has a complicated etiology, making it possible for the patient to experience nearly every kind of pain.[4]

Cancer patients are prone to having neuropathic pain due to a variety of factors, including tumor infiltration, tumor metastasis, adverse reactions to diagnostic or therapeutic interventions, infection reactivation, and paraneoplastic syndromes. Neuropathic pain was reported to be experienced by 31.2% of cancer patients in a 2016 survival research.[5] Sadly, despite the fact that opioids the primary medication for cancer pain do not successfully treat neuropathic cancer pain, this pain is not specifically investigated.[6] Additional co-analgesics, such as antidepressants and anticonvulsants, are needed to treat cancer pain. Given that neuropathic cancer pain typically lasts longer and is more intense than other types of pain, waiting to diagnose the condition and start treating the patient can lower their quality of life.[7]

Tricyclic antidepressants (TCAs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) are the four families of antidepressant medications that have been investigated for use in the treatment of neuropathic pain.[8] Antidepressants are sometimes administered to patients with moderate to severe pain in combination with other analgesics, such as opioids, even though they can be used alone. By lowering the necessary dosage and lessening side effects, they can function as adjuvant medicines and raise the therapeutic value of opiates.[9]

Because of their excellent side effect profiles, the selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and paroxetine) have become the most widely used antidepressants. Since they don't have strong analgesic effects when taken alone, SSRIs are second-line treatments for chronic pain.[8] A significant decrease in pain levels was

observed in studies comparing fluoxetine 20 mg with placebo and amitriptyline 25 mg in people with fibromyalgia. within the group taking fluoxetine.[10] In a different trial, patients with advanced cancer who received fluoxetine vs a placebo showed improvements in quality of life, good fluoxetine tolerance, a decrease in pain scores, and a decrease in depressive symptoms.[11]

In a different trial, 10 mg of fluoxetine was used to treat patients with chronic pelvic pain syndrome and chronic prostatitis. The patients' quality of life was improved by the study's reduced levels of depression and pain symptoms.[12] The analgesic effect of fluoxetine was also demonstrated by another investigation that yielded the same results. The ensuing analgesic effect may be connected to fluoxetine's depressive impact, even though it is thought to be a safe medication that works better than a placebo in treating persistent somatoform pain syndromes.[13]

The purpose of this study was to compare pain scores between the fluoxetine 20 mg, paracetamol 1000 mg, and morphine 10 mg group and the amitriptyline 12.5 mg, paracetamol 1000 mg, and morphine 10 mg group using the PainDETECT questionnaire.

METHOD

This study was designed as a randomized, double-blind clinical experiment. From July to September of 2023, this study was conducted at the pain clinic of the Adam Malik Hospital, Medan. All outpatient cancer patients who met the inclusion and exclusion criteria for research subjects were part of the research population, which was located in the pain clinic at the Adam Malik Hospital, Medan. The following are the inclusion criteria: individuals with cancer who are treated at pain clinics, between the ages of 18 and 65, whereas the following are the exclusion criteria: Individuals who are pregnant, have a history of uncontrolled hypertension, liver disease (Class-Pugh b or c), kidney disease (AKI or CKD), vascular disease, heart attack history, or use monoamine oxidase inhibitors (selegiline, isocarboxzaid, phenelzine, and tranylcypromine) are among the patients who should not be given fluoxetine. Patients with pain not related to cancer, patients who refuse to take fluoxetine, and triptan medications (sumatriptan, rizatriptan, almotriptan, naratriptan, zolmitriptan, and frovatriptan) as well as SNRIs (venlafaxine, desvenlafaxine, duloxetine, and reboxetine). If the patient discontinues taking the drug, cannot be reached, or experiences an allergic response after taking the drug under study, the test will be terminated.

The collerative analytical procedure for unpaired categories was used to calculate the sample size. There were 40 samples in total for this investigation, split into two groups. 20 mg of fluoxetine, 1000 mg of paracetamol, and 10 mg of morphine were given to group A (n = 20), while 12.5 mg of amitriptyline, 1000 mg of paracetamol, and 10 mg of morphine were given to group B (n=20).

Non-probability sampling with successive sampling was the method of sampling that was employed. wherein the study included every participant who fulfilled the inclusion and exclusion criteria. Using a computer and the randomizer.org website, the sample was randomized. The health research ethics commission of the Faculty of Medicine at Universitas Sumatera Utara has granted authorization for this study with

the following number: 604/KEPK/USU/2023. Prior to the procedure, patients are informed about the objectives, advantages, dangers, and other relevant information regarding the research. Next, individuals were required to complete an informed consent form indicating their willingness to participate in research. The medication class used in this study is one that is frequently prescribed to cancer patients who report pain. The patient gives the researcher a call if any drug adverse effects arise. Should the patient experience any emergency side effects, they should visit the emergency department right away. he subjects in this study are awakened and examined in accordance with standard operating procedures for pain clinics. Following this, they complete the PainDETECT questionnaire in the company of trained volunteers. Amitriptyline 12.5 mg per 24 hours, paracetamol 1000 mg per 8 hours, and MST 10 mg every 12 hours were administered to group B individuals, while fluoxetine 20 mg per 24 hours, paracetamol 1000 mg per 8 hours, and MST 10 mg per 12 hours were given to group A subjects. The medications amitriptyline and fluoxetine were previously concealed by breaking them up and putting them into opaque capsules. Participants were instructed to complete the PainDETECT questionnaire and be re-interviewed regarding any complaints they had about taking the prescribed medicine at the 4-week mark in order to be evaluated. Two assessments comprise the PainDETECT questionnaire: one measures the amount of pain as evaluated by NRS, while the other measures the quality of pain as measured by PainDETECT. The NRS score ranges from 0 to 10, with mild pain falling between 1-3, moderate pain falling between 4-6, and severe pain falling between 7–10. The PainDETECT score ranges from 0 to 38. A score of 0 indicates a low likelihood of neuropathic pain, a score of 13 to 18 indicates ambiguity regarding the presence of a neuropathic pain component, and a score of 19 to 38 indicates a high likelihood of neuropathic pain involvement. The higher the score, the better the high perceived neuropathic pain scale. Next, information was logged for every experimental group. SPSS software was used to test and analyze the data. Both univariate and bivariate analysis were used on the data. The Chi-Square test, Kolmogorov-Smirnov, Independent sample test, Mann-Whitney, paired sample test, and Wilcoxon were used to examine the bivariate data.

RESULTS

Regarding age, gender, length of pain, surgical history, kind of cancer, and stage of cancer, there were no statistically significant differences between the fluoxetine 20 mg and amitriptyline 12.5 mg groups ($P>0.05$; Table 1). Upon analyzing the features of the two treatment groups, it may be concluded that they are homogeneous. In this study, the NRS and PainDETECT scores showed a statistically significant decrease in pain before and after fluoxetine or amitriptyline administration ($p<0.05$; Table 2 and Table 3). After treatment, there was no significant difference in pain scores between the fluoxetine groups and the amitriptyline group ($p>0.05$; Table 2 and Table 3). The NRS score dropped from 6.1 to 5.8 in the fluoxetine group and from 6 to 5.6 in the amitriptyline group. PainDETECT score decreased from 18.7 to 18.1 in the fluoxetine group and from 18.2 to 17.2 in the amitriptyline group. n this study, the amitriptyline group had higher side effect reports than the fluoxetine group. A closer look revealed that there were more complaints of

headaches in the fluoxetine group and more complaints of nausea, vomiting, and constipation in the amitriptyline group, but there was no discernible difference in side effects between the two groups (p>0.05; Table 4). Group from 18.7 to 18.1, and from 18.2 to 17.2 in the amitriptyline group.

Table 1. Baseline characteristics of the study patient

Characteristics	Fluoxetine (n=20)	Amitriptyline (n=20)	P-value
Age (years), Mean (SD)	43.3 (9.3)	49.7 (11.8)	0.065[a]
Sex, n (%)			
Male	9 (45%)	11 (55%)	0.092[b]
Female	11 (55%)	9 (45%)	
Duration of pain felt, n (%)			
< 1 year	8 (40%)	4 (25%)	
1-2 years	6 (30%)	11 (55%)	1.000[c]
> 2 years	6 (30%)	4 (20%)	
History of previous surgery, n (%)			
Yes	9 (45%)	10 (50%)	1.000[b]
No	11 (55%)	10 (50%)	
Type of cancer, n (%)			
Adenocarsinoma (paru, rekti, bulli, mamae, serviks)	6 (30%)	15 (75%)	
Alveolar soft part sarcoma	1 (5%)	0 (0%)	
Carsinoma mamaliae recurrent	1 (5%)	0 (0%)	
Follicular neoplasma (mamae)	1 (5%)	0 (0%)	
High grade serous of ovary	1 (5%)	0 (0%)	
Hight grade infiltating urothelial Ca	1 (5%)	0 (0%)	
Invasive breast carcinoma	4 (20%)	0 (0%)	
Maligna Carsinoma	2 (10%)	0 (0%)	
Rhabdomyosarcma	1 (5%)	0 (0%)	
Squamous Cell Carcinoma	2 (10%)	1 (5%)	
Non Keratinizing Squamous Cell Ca	0 (0%)	4 (20%)	
Stage of cancer, n (%)			
Stage 1	3 (15%)	2 (10%)	
Stage 2	10 (50%)	8 (40%)	0.978[c]
Stage 3	2 (10%)	4 (20%)	
Stage 4	5 (25%)	6 (30%)	

Table 2. Fluoxetine and amitriptyline in reducing NRS

NRS	Fluoxetine (n=20)	Amitriptyline (n=20)	P-value
NRS (T0), Mean (SD)	6.1 (1.4)	6 (1.1)	0.070[a]
NRS (T1), Mean (SD)	5.8 (1.2)	5.6 (1.2)	0.011[b]

a) Mann-Whitney, b) Independent Samples T-Tes

Table 3. Fluoxetine and amitriptyline in reducing PainDETECT

PainDETECT	Fluoxetine (n=20)	Amitriptyline (n=20)	P-value
PainDETECT (T0), Mean (SD)	18.7 (3.8)	18.2 (3.8)	0.679[a]
PainDETECT (T1) Mean (SD)	18.1 (3.2)	17.2 (3.2)	0.785[b]

a) Independent Samples T-Tes, b) Mann-Whitney

Table 4. Side effects of fluoexetine and amitriptyline

Side effects	Fluoxetine (n=20)	Amitriptyline (n=20)	P-value
Nausea and vomit	5 (25%)	8 (40%)	
Constipation	4 (20%)	7 (35%)	0.618
Nyeri kepala	4 (20%)	2 (10%)	

Chi-Square

DISCUSSION

The investigation found no statistically significant differences in the subject characteristics between the two groups (p>0.05). Therefore, it was determined that the two groups were similar and could be compared.

In this study, there was no significant difference in pain scores between the fluoxetine group and the amitriptyline group after treatment, but there was a statistically significant decrease in pain scores using the NRS and PainDETECT scores between before and after administration of fluoxetine and amitriptyline (p value <0.05). p value greater than 0.05. The mean NRS score decreased from 6.1 to 5.8 in the fluoxetine group and from 6 to 5.6 in the amitriptyline group. In the fluoxetine group, the PainDETECT score dropped from 18.7 to 18.1, whereas in the amitriptyline group, it dropped from 18.2 to 17.2. The average reduction in pain scores is still in the moderate pain category, which explains why the minimum reduction in pain scores using NRS and PainDETECT is not clinically meaningful. Studies show that if a patient experiences 50% less pain or a pain score of less than 4 (moderate discomfort) on a 0–10 scale, they would require less clinically appropriate analgesia. This is associated with higher patient satisfaction and a better quality of life.[15] Due to the use of fixed doses in this study—20 mg of fluoxetine and 12.5 mg of amitriptyline daily—neither medication had a clinical effect on pain. In contrast, other studies that used a larger dose range gave fluoxetine doses of 20–40 mg and amitriptyline doses of 12.5 mg–150 mg daily; however, using a larger dose results in more side effects.[14] Due to their favorable side effect profile, the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and paroxetine) have become the most widely used antidepressants; however, because they lack significant analgesic properties, they are better suited as second-line treatments for neuropathic pain. Antidepressant medications that block the re-uptake inhibitor of a single neurotransmitter, like SSRIs, are less effective in treating chronic pain; instead, medications that block the re-uptake inhibitor of multiple neurotransmitters, like dopamine-norepinephrine (DNRI) or serotonin-norepinephrine (SNRI), are required for greater efficacy. is the primary line of treatment in the therapy of persistent pain.[8]

The findings of this study are consistent with a study that examined the effects of fluoxetine, amitriptyline, and despipramine on individuals with diabetic neuropathy. That study discovered that fluoxetine was not any more successful than a placebo at relieving pain.[14] In other research, it was discovered that amitriptyline and fluoxetine worked better together to reduce fibromyalgia patients' pain levels.[10] Limitation of this study is the lack of direct monitoring to patient compliance in taking medication. The results of this study are recommended for additional cancer pain therapy in cancer patients in pain clinics.

CONCLUSION

There was no significant difference in pain scores between the fluoxetine and amitriptyline groups following therapy, while PainDETECT showed statistical significance before and after fluoxetine and amitriptyline delivery. NRS score decreased from 6.1 to 5.8 on fluoxetine and from 6 to 5.6 on amitriptyline. Reduced PainDETECT score from 18.7 to 18.1 when taking amitriptyline (18.2 to 17.2). Compared to fluoxetine, amitriptyline administration is associated with a higher frequency of complaints regarding side effects. Upon closer inspection, it was found that the amitriptyline group had more complaints of headaches, while the fluoxetine group had more symptoms of nausea, vomiting, and constipation.

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