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Opioid use and Pain Intensity as Risk Factors of Cancer-Related Depression

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Abstract:- Background: Opioid has become one of main therapies in palliative care regarding to cancer pain. Management of chronic cancer pain by opioid may affect patient's quality of life. Nevertheless, oral opioid therapy has been reported correlated with increasing incidences of depression in chronic non-cancer pain. This study is the first study to analyze correlation of opioid with depression in chronic cancer pain. The aim of this study is to investigate the effect of oral opioid therapy, including its duration and dosage, with the degree of depression in chronic cancer pain.

Methods: This is a retrospective study including all patients who visited palliative outpatient clinic of Soetomo Hospital from April to June 2021. History of opioid therapy and depression scale collected from medical records. Depression assessed by trained physician using Hamilton Depression Rating Scale (HDRS). Data was analyzed using Chi Square and Spearman tests.
Results: This study included 87 patients, consisted of 59 males and 38 females. Fifty-three (60.9%) patients were found given oral opioid therapy. Significant association found between oral opioid prescription and incidence of depression (p = 0.003). Opioid dosage (MED) (p=0.0001) and using opioid ≥90 days (p=0.011) were also found associated with the severity of depression. Severity of pain was also analyzed and found to be associated with severity of depression (p<0.0001). Multivariate analysis of all factors was done and found that severe pain [OR 8.99 (CI 95%, 1.68-48.13)] have the highest risk of getting depression in chronic cancer pain although oral opioid therapy also increased the risk [OR 2.91 (CI 95%, 1.07-7.96)]. Duration and dosage of opioid use were not significantly associated with severity of depression.
Conclusion: Oral opioid therapy and severity of pain were associated with severity of depression in chronic cancer pain. Nevertheless, opioid prescription to achieve adequate pain management may still be beneficial in preventing depression in cancer patients.

Keywords:- *Opioid, Duration of Opioid, Opioid Dosage, Severity of Pain, Severity of Depression, Chronic Cancer Pain.*

I. INTRODUCTION

Cancer still becomes a burden around the world, with new cases reported more than 10 million in 2020[1]. Cancer is typically diagnosed at late stage and was accompanied by complications that made the management should be holistic. Nowadays, cancer patient's lifespan may be prolonged by recent advances in technologies while definitive therapy was still not ensuring. Quality of life must be taken care and managed carefully by the physician who treat cancer patient.

Cancer pain is a form of chronic pain which is experienced by cancer patient, typically in their late stages. It was found in 30-40% cancer patient, even up to 70-90% in advance stage[2]. Pain was defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[3]. In cancer pain, the mechanism was told to be complex and its management was expected to be related with many aspects.

Opioid has become one of the main therapies in cancer pain. Its use is beneficial in cancer patients due to its mechanism of action and included in WHO step-ladder pain management[4]. Despite of its benefits in managing pain, opioid has some complications to be considered. Side effects which were well-known including nausea and vomiting, constipation, cognitive dysfunction, pruritus, etc.

Depression and chronic pain were told to be closely related although their relationship cannot be explained in detail yet. Nowadays, depression has become important and common morbidities in many countries, so was pain. One study reported that 40-60% patients who have chronic pain were also have depression[5]. Opioid use was reported to be associate with depression. It was reported by some studies which were done in chronic non-cancer pain. It was believed that opioid and depression have two-way relationship and one presence could affect another. Chronic pain patients who were also have depression had an increased risk of using opioid for their pain. Higher doses of opioid were needed in chronic pain patient who were depressed, even opioid abuse may be a more difficult problem. Meanwhile, some evidence reported that incidence of depression may be a complication of opioid therapy in chronic pain[6,7]. Longer use of opioid also told to be risk factor of getting depression in chronic pain patients[7]. Those evidences were interesting because opioid therapy was broadly used in cancer pain but no studies in their relations have been taken yet. This study aims to investigate the association between oral opioid therapy and severity of depression in chronic non-cancer pain.

II. METHODS

This study is a retrospective study included all chronic cancer pain adult patients who visited palliative clinic of Soetomo Hospital from April to June 2021. The patients were 18-65 years old. Diagnosis of cancer and chronic pain were based on the medical records. This study excluded patients with severe comorbidities (severe infection, heart failure, liver failure, and renal failure). The exclusion criteria included

patients who refused to be research subjects; patients who have severe infectious disorders, heart, liver, and renal failure; patients with hematology disorders, history of using steroid therapy, obesity (BMI >30), patients with a history of psychiatric disorders (schizophrenia, psychosis, etc.), and patients who have received interventional pain management.

A. History of opioid use

History of opioid use was obtained from medical records, classified as opioid users and non-opioid users. Oral opioid used in the palliative clinic of Soetomo hospital including codeine and morphine. Opioid dosage and duration of use was noted on the day of last visit during the data collection period. Dosage was converted into morphine equivalent dose (MED) in milligrams. Duration of opioid use was measured from the first time patient were prescribed from medical records and stated in days of opioid use. This study classified the duration in <90 days and ≥90 days.

B. Severity of pain

Pain intensity was obtained from the last visit during the data collection period in medical records. Pain intensity were measured by trained physician in the clinic using Wong Baker Faces Scale (WBFS), ranged from 0 (no pain) – 10 (most painful). This study classified severity of pain into three groups: mild, moderate, and severe pain.

C. Severity of depression

Depression was also obtained from the last visit during the data collection period in medical records. Severity of depression was measured using Hamilton Depression Rating Scale (HDRS), assessed by trained physician in our palliative clinic. For the analysis, severity of depression was classified into groups based on total scores obtained from questionnaire: no depression (score ≤7), mild depression (score 8-13), moderate depression (score 14-18), severe depression (score 19-22), and very severe depression (≥23).

D. Statistical analyses

Multivariate analysis was conducted to determine the relationship of more than one independent variable with one dependent variable. Multivariate analysis begins with bivariate analysis of each independent variable with the dependent variable. If the results of the bivariate analysis show a p value =0.25, the variables can be included in the multivariate analysis model. Bivariate analysis was conducted using chi-square test and Spearman correlation test. The logistic regression test which has a p value of <0.05 indicates a significant value. Data analysis was performed using SPSS ver.26.0 (SPSS, Chicago,IL).

III. RESULTS

This study included 87 patients based on the inclusion and exclusion criteria. Our demographic findings (Table 1) found the mean age of the subjects was 52.3±8.6 years old and mean BMI was 22.8±4.03 kg/m2. Cancer pain intensity was assessed using WBFS and classified into mild, moderate, and severe pain. This study recorded 35 subjects were in mild pain. 43 subjects were in moderate pain. and 9 subjects were in severe pain. Type of cancer diagnosed by our subjects were classified and most of them were pelvic organ cancer, lung cancer, and breast cancer with 31, 23, and 20 subjects respectively.

Variable	Mean±SD	N (%)
Age (years)	53.3±8.6	
Gender		
Male		59 (67.8)
Female		38 (32.2)
Body Mass Index (BMI) kg/m^2	22.8±4.03	
Duration of opioid use		
Non-opioid users		34 (39.1)
≤90 days		23 (26.4)
>90 days		30 (34.5)
Pain intensity		
Mild		35 (40.2)
Moderate		43 (49.4)
Severe		9 (10.3)
Severity of depression		
No depression		48 (55.2)
Mild		22 (25.2)
Moderate		16 (18.4)
Severe		1 (1.2)

Table 1. Demographics characteristics

Severity of depression were measured HDRS and classified as no depression, mild depression, moderate, severe depression, and very severe depression. From 87 subjects with or without opioid therapy, our findings found 48 patients (55.2%) were without depression. 22 patients (25.3%) were in mild depression. 16 patients (18.3%) were in moderate depression and 1 patient was in severe depression.

Among our subjects. 53 patients (60.9 %) were opioid users; 32 of them (61.4%) were male and 21 of them (39.6%) were female. Duration of opioid use was obtained and our study found that 23 subjects have used oral opioid for <90 days and 30 patients have used opioid for ≥90 days. Lastly. oral opioid dosage was also noted and converted to MED (mg) as seen in Table 2. Mean of opioid dosage given in our study was 10.29 mg.

A. Opioid Use and Depression

Fifty three of 87 subjects were noted as opioid users for their cancer pain. Severity of depression obtained from their medical records found that 29 of 53 patients (54.7%) had depression; 12 of them (41.4%) had mild depression, 16 of them had moderate depression (55.2%), and one of them (0.03%) had severe depression. In other hand, among 34 non-opioid users, we found 24 of them (70.6%) had no depression and the rest (29.4%) had mild depression. Bivariate analysis of opioid use and severity of depression (Table 3) found significant correlation (p = 0.003) with coefficient contingency (c) = 0.369.

Morphine Equivalent Dose (MED)	Frequency in mg (%)
0	34 (39,1)
3	2 (2.3)
6	9 (10.3)
9	9 (10.3)
12	1 (1.1)
18	14 (16.1)
20	8 (9.2)
30	11 (12.6)

Table 2. Opioid dosage frequency

Opioid dosage (in MED) use found in our study was ranged from 3-30 mg (seen in Table 4); codeine and morphine were the choice of opioid. Most of the opioid users in our study received 18 mg (n=14; 26.4%) followed by 30 mg (n=11;20.8%), 6 mg and 9 mg (each n=9;16.9%). Moderate depression was found mostly in subjects who received 18 mg, 20 mg, and 30 mg (5, 3, 6 subjects respectively), while mild depression was found mostly in subjects who received 3 mg, 6 mg, and 9 mg (1, 2, 5 subject(s) respectively). Bivariate analysis of opioid dosage and severity of depression also found a significant correlation (p=0.0001) with coefficient contingency (c) = 0.391.

In the opioid users, this study found 23 of 53 subjects (43.4%) were having opioid for <90 days and the 30 of 53 subjects were having opioid for ≥90 days. Severe depression was found only in one subject with opioid use for ≥90 days. Seven (7) subjects (<90 days) vs nine (9) subjects (≥90 days) were found having moderate depression, while nine (9) subjects (<90 days) vs 15 subject (≥90 days) were found having no depression (Table 5). Significant correlation was found between duration of opioid use and severity of depression (p=0,011) with contingency coefficient (c) = 0.272.

B. Severity Pain and Multivariate Analysis

Pain intensity was measured in this study and divided into 3 levels: mild, moderate, and severe. Among 87 subjects, 35 of them (40.2%) had mild pain in their last visit with 28 subjects had no depression and 7 subjects had mild depression. Forty-three (43) subjects (49.4%) had moderate pain in their last visit with 17 of them had no depression, 12 of them had mild depression, and 14 of them had moderate depression. The rest of the subjects (10.3%) had severe pain as their complaints in their last visit with 3 of them had no depression, 3 of them had mild depression, 2 of them had moderate depression, and one of them had severe depression (Table 6). Significant correlation was found between pain intensity and severity of depression (p<0.0001) with coefficient contingency (c) = 0.442.

Logistic regression analysis was conducted in all of previously significant variables in order to find out which variables affects severity of depression the most. Our analysis found that severe pain had the highest risk affecting severity of depression with OR 8.99 (95% CI, 1.68-48.13), while opioid use had the lowest risk with OR 2.91 (95%CI, 1.07-7.96) as seen in Table 7.

IV. DISCUSSION

Depression and cancer were known to be closely related and both of them together affected morbidities and social and economic burden around the world[8]. They were also told to be hard to manage if present together. Prevalence of cancer itself, which is reported to be 14.1 million in 2012, represented how this disease was still a burden for humankind[9].

Prevalence of depression in chronic pain patients were reported by many studies. A study in chronic pain patients had

Opioid use	Severity of depression				N (%)	P value
	No	Mild	Moderate	Severe		
Yes	24	12	16	1	53 (60.9)	0,003
No	24	10	0	0	34 (39.1)	
Total	48	22	16	1	87 (100)	

Table 3. Correlation of opioid use with severity of depression

Opioid dosage (MED)	Severity of depression				N (%)	P value
	No	Mild	Moderate	Severe		
3	1	1	0	0	2 (5.7)	0.0001
6	5	2	2	0	9 (16.9)	
9	4	5	0	0	9 (16.9)	
12	1	0	0	1	1 (1.9)	
18	7	1	5	0	14 (26.4)	
20	1	4	3	0	8 (15.1)	
30	5	0	6	0	11 (20.8)	
Total	24	12	16	1	53 (100)	

Table 4. Correlation of opioid dosage with severity of depression

Duration of opioid use	Severity of depression				N (%)	P value
	No	Mild	Moderate	Severe		
Non-opioid users	24	10	0	0	34 (39.1)	0.011
≤ 90 days	9	7	7	0	23 (26.4)	
> 90 days	15	5	9	1	30 (34.5)	
Total	48	22	16	1	87 (100)	

Table 5. Correlation of duration of opioid use with severity of depression

Severity of pain	Severity of depression				N (%)	P value
	No	Mild	Moderate	Severe		
Mild	28	7	0	0	35 (40.2)	<0.0001
Moderate	17	12	14	0	43 (39.4)	
Severe	3	3	2	1	9 (10.3)	
Total	48	22	16	1	87 (100)	

Table 6. Correlation of severity of pain with severity of depression

Variable	P values	OR (CI 95%)
Opioid use	0.037	2.91 (1.07-7.96)
Moderate pain	0.001	6.90 (2.05-16.95)
Severe pain	0.010	8.99 (1.68-48.13)
Opioid dosage	0.460	1.026 (0.69-1.09)
Duration of opioid use	0.678	0.772 (0.23-2.62)

Table 7. Multivariate analysis of risk factors causing depression in chronic cancer pain patients

reported 57.1% patients with opioid therapy solely had depression and 51.4% patients with opioid therapy and medical marijuana had depression[10]. Similar number was also found in our study. Age is one of important demographic factor which is concerned. This study found median age of the subjects was 59 (21- 63) years old, which was considered quite old. That was similar to other study done by Iqbal et al which 275 cancer patients had median age of 59 (25-74) years old[11]. Another study in Dr. Kariadi hospital in Semarang, Indonesia also reported their cervix cancer patients had ages ranged from 45 to 55 years old[12]. Among our subjects who had depression, which was 32 subjects, 27 of them (69.2 %) were male and those findings similar to a study conducted by Iqbal et al which found depression suffered by male (57%) more than female[11].

Opioid had become treatment of choice according WHO pain ladder which was often prescribed for cancer pain. Its use sometimes combined with other drugs such as antidepressants, anticonvulsants, non-opioid analgesics, or anti-spasticity agents[2]. It inhibits pain transmission by activating opioid receptors which is often found in medulla spinalis[13].

Depression was told closely related to chronic pain, typically severe, multifocal, persistent pain, and accompanied by disability. In other hand, pain is often complained by depressed patient so many believed than pain and depression had bidirectional relationship. Each presence can worsen another in one patient. Many studies had reported about those relationship, such a study reported a lesser reduction of pain in chronic low back pain patients who were also had depression, even had managed by opioid compared to patients who were not depressed[14]. Those relationship were so close that they were considered having similar biological mechanism, risk factors, and depend to each other. Few literatures had shared their inter-mechanism, between chronic pain and mental disorders[6,15].

Recent findings about chronic pain, opioid use, and depression have found another consideration. Salas et al reported in their retrospective study that there was increased risk of new onset depression in patients were given opioid for their chronic pain[16]. Our study found similar findings in the chronic cancer patients. Among 87 subjects, 53 was classified as opioid users and there was more severe depression assessed in that group compared to non-opioid users. Those findings may raise urgency in depression assessment and monitoring intensely in chronic cancer pain patients with opioid prescription. Novel studies in pain biomarker may be helpful in assessing pain accurately so pain may be treated properly and adjuvant therapies may be given early if comorbidities identified, especially in cancer pain.

Longer duration of opioid may end in drug accumulation inside the body and manifesting in side effects, including depression. Long term opioid use was reported to be either a risk factor or a consequence of depression. Depression and other mental disorders were also associated to increased need of high dose opioid. Depression was told to induce opioid use disorders (OUD). In other hand, long term opioid use was also increased the incidence and severity of depression, even caused treatment resistant depression[6]. Combination of those causal relationship may complicate treatment of pain and depression. A study conducted by Sullivan reported that duration of opioid use <90 days has less risk (OR = 3.0) in inducing depression and OUD compared to patients who use opioid ≥90 days (OR = 15.0), with range of dose in MED 1-36 mg[6]. Similar results were also reported by another study in US that duration of use ≥90 days increased the risk of getting depression (HR=1.25) and getting more increased if duration longer than 180 days (HR =1.51)[7]. Duration of opioid use was also told to increase risk of having recurrences of depression[7]. Despite all those findings were reported in chronic non-cancer patient, there was may be similar results in cancer pain patients. Our study in chronic cancer pain patients also found that duration of opioid use ≥90 days had more severe depression, although the OR was lower than the previous study. Based on those findings, it is clear that intense depression monitoring may be needed for long-term opioid use, especially if patients using opioid more than 90 days.

High dose of opioid was often necessary in managing cancer pain but that may be associated with drug accumulation in the body. Contradictive findings were reported by a retrospective study that duration of use, not the dosage, was associate with new-onset depression in chronic pain patients. Another cohort study was also concluded that there was not higher risk of depression in patients who used opioid regularly and higher doses compared to intermittent and shorter use, although those 2 groups had higher risk of depression compared to patients who use only minimal dose of opioi[6]. Range of dosage used in our study was found to be 1-30 mg after converted to MED and those numbers similar to a study by Sullivan[6]. In our study, higher dosage was correlated with severity of depression. While previous study reported that opioid dose (MED) <50 mg was associated with less risk of depression (HR=1.58), our study's dose still not lower than that study so it cannot be concluded yet how opioid dose correlated with depression precisely[6].

Depression was a multifactorial condition which were often complicated in cancer pain patients. Severity of pain may hold important roles in inducing depression. Thus, we analyze the correlation between severity of pain and depression. This study found depression suffered by patients who had moderate and severe pain, 44.8% and 43.6%, respectively. Most patients who had moderate or severe pain were given opioid so depression found may be caused by either factor. It will be a complex problem for physician to consider because chronic cancer pain may always be found. A study has reported that 56% adult cancer patient had moderate

to severe pain and opioid may always be given to such patients[17]. Cancer pain itself was well known as complex pain which has more than one pain pathway. Nociceptive and neuropathic may be present simultaneously in a patient[18]. Depression was considered to have similar anatomic structures and pathophysiology with chronic pain.

While depression was often correlated with chronic pain, there were just few studies that learned only about cancer pain. Some studies stated that up to 85% patients with depression suffered pain[19,20]. Our study also analyzed risk factors of severity of depression by logistic regression. Moderate and severe pain had the highest risk causing a depression with OR 6.90 (2.05-16.95) and OR 8.99 (2.05-16.95), respectively. Significant correlation was also found in opioid use, though it had a lower risk [OR 2.91 (1.07-7.96)], while duration and dosage of opioid given were not significant in regression analysis.

V. CONCLUSION

Depression can be prevented and managed by treating pain properly, and opioid use may be essential with proper prescription. Nevertheless, assessing and monitoring depression with validated tools still have to be done in cancer pain, especially ones who had opioid for their pain.

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