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Original Article

Analysis of Morphine Sulphate and Methadone Hydrochloride in Pain Management of Advanced Cancer Patients

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ABSTRACT

Introduction: - Pain is one of the most prevalent cancer symptoms. There is individual variability in analgesia and adverse effects to different opioids. So, we did this study to provide the comparative information about Morphine and Methadone for intractable pain control and their potential for adverse effects in advanced cancer patients.
Aims and Objectives: - To evaluate analgesic effect and safety of Morphine and Methadone for management of chronic sever pain. To identify adverse effects of study drugs
Method: - Total 50 patients were enrolled randomly and divided randomly in Morphine group and Methadone group of 25 patients in each. Patients were selected according to inclusion and exclusion criteria. Group 1: - received oral Morphine. Group 2: - received oral Methadone. We assessed pain control by monitoring VAS and escalated dose of opioids as required for adequate pain control, observed side effects and treated, did ECG to see QTc changes on follow-up.
Result: - As for adequate pain relief, we increased dose in both group of patients according to patients' severity of pain. There was less average dose of methadone is required in terms of Morphine Milligram Equivalent (MME) than average dose of morphine. We find different side effects with different frequency and treated with rescue medication.
Conclusion: - Morphine and Methadone both are very effective in management of severe pain in advance cancer patients. We didn't observe any major side effect. So, one should not hesitate to start either of them in advance cancer patients to treat pain.

Key Words: *Morphine, Methadone, Pain management, Cancer pain*

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INTRODUCTION

Despite significant developments in cancer prevention, early detection and newer treatment techniques, cancer remains one of the most debilitating and lethal disease [1]. Cancer is the second biggest cause of death worldwide and accounting for an estimated 9.6 million deaths or one in six deaths, in 2018[1]. Cancer may be a terrifying experience for everyone who is diagnosed with it. Pain is arguably one of the most prevalent and terrifying cancer symptoms that cancer patients face [2]. About 52-77% patients suffer pain despite treatment by analgesics given according to step ladder guideline by World Health Organization (WHO). Out of total, one-third patients suffer moderate to severe pain [3].

Morphine is usually considered the preferred drug for the severe cancer pain because of its wide availability, varied formulations and well characterized pharmacologic properties. Morphine is metabolized in liver and its metabolite is excreted by kidney. Active metabolites of morphine can accumulate in body in patient with impaired renal function with long time treatment, dose escalation or dehydration [2]. Accumulation of active morphine metabolites causes major side effects like neurotoxicity during chronic use [2]. Strong opioids are included in stage 3 of analgesics ladder by the World Health Organization.

Methadone is a synthetic opioid and easily produced. Methadone has number of potential advantages compared with other opioids, including morphine. Methadone does not have any active metabolite which is excreted via faecal and renal route [4]. Thus, it can be a good choice of an opioid for cancer pain treatment [5].

Compared to other opioids methadone is potent antagonist of N-Methyl D-Aspartate (NMDA) receptor, which give advantage to methadone over other opioid for effectiveness in treatment of neuropathic pain [6]. NMDA is an excitatory amino acid found responsible in the development of neuropathic pain and opioid tolerance. Methadone has long and unpredictable half-life causing difficulties in dose titration, which is one disadvantage of methadone, but titration might be easier and safer in patients who are opioid naïve [7].

However, there are no opioid better or worse than others in development of adverse effects. There is individual variability in analgesia and adverse effects to different opioids [8], so we have to choose opioid with more favourable therapeutic window corresponds to the balance between analgesia and side effects.

So, present study is an attempt to provide the comparative information about Morphine and Methadone for intractable pain control and their potential for adverse effects in patient suffering from advanced cancer

AIMS AND OBJECTIVES

- To evaluate analgesic effect and safety of Morphine and Methadone for management of chronic sever pain in advanced cancer patients
- To identify adverse effects of study drugs

MATERIALS & METHODS

This Prospective analytic study was conducted at department of palliative medicine, tertiary cancer hospital during August 2019 to July 2021. Total 50 patients were enrolled randomly in this study. They were divided randomly in Morphine group and Methadone group of 25 patients in each. The study protocol was reviewed and approved by the Institutional Review Committee.

Patients were selected according to inclusion and exclusion criteria, who were suffered from severe pain due to advance cancer and visited palliative medicine department.

Inclusion Criteria are as follow:

1. Advanced cancer patient (locally advance, recurrence or metastatic disease)
2. Pain score VAS >7.
3. Requirement of strong opioid for severe pain in patient who was already on other analgesics.
4. Patient is able to take medicine orally or via naso-gastric feeding tube.
5. Patient has normal mental state to recognize his/her pain score
6. Patient has normal kidney and liver function.
7. Willing to participate in study
8. Patient's age between 18 years and 75years.
9. Patient is able to give follow-up

Exclusion Criteria:

1. Patient has already received strong opioid for cancer pain.
2. Patient is receiving other therapy for pain control such as radiotherapy, neurolytic blocks. 3. Patient is taking drugs that effects on methadone metabolism like delavirdine, fluconazole, fluvoxamine, efavirenz, lopinavir, nelfinavir, nevirapine, carbamazepine, phenytoin, rifampicin, grapefruit etc.
3. Cardiovascular dysfunction like severe hypotension, prolonged QTc
4. Respiratory conditions like acute or severe asthma, severe respiratory depression
5. Patients having paralytic ileus, gastrointestinal obstruction
6. Patient has no known allergy to this both study drugs.

Data collection: A pre-designed, pre-tested, semi-structured questionnaire was used that elicited information on demographic profile of individuals in addition to information related to the objectives. The informed consent was taken from each participant before the interview started.

Group 1: - 25 patients were enrolled in this group who were given oral Morphine for pain relief. Starting dose was 5 mg 4 hourly

Group 2: - 25 patients were enrolled in this group who were given oral Methadone for their pain relief. Starting dose was 2.5 mg (0.5 ml oral Syrup) 12 hourly.

All patients were prescribed Tablet Paracetamol 500mg 8 hourly for synergistic analgesic effect. All patients were given Tablet Bisacodyl 10mg HS to prevent constipation (well- known side effect of Opioids).

All patients were followed up after 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks. In follow up, we assessed pain control by monitoring VAS and escalated dose of opioids as required for adequate pain control (to keep VAS <2), observed side effects and treated or alleviated those. ECG was done on 2nd week, 4th week, 8th week and 12th week.

Complete blood count, Serum electrolytes, renal function tests and liver function tests were done on 4th week, 8th week and 12th week as routine protocol.

Data Analysis: - After collecting data from patients; record was compiled in WPS software and analysis of different variable associated with study like socio-demographic factors, doses of drugs, side effects etc. was done using SPSS software. For analysis of data we use statistical formula like mean, standard deviation(SD), percentage according to qualitative or quantitative data. For comparison of dose of drug required for adequate pain relief, we calculate Morphine Milligram Equivalent (MME) [9].

RESULTS

This prospective analytic study conducted in palliative medicine department among 50 advanced cancer patients show following results.

Out of total 50 patients, there were 35(70%) male and 15(30%) female patients. Mean age was 49 years in methadone group and 51 years in Morphine group.

Data regarding primary disease of patients and ECOG score are shown in table 1.

Table 1: Primary cancer and ECOG score

Characteristics	Methadone Group (n = 25)		Morphine Group (n = 25)	
	No. of Patients	%	No. of Patients	%
Primary cancer				
Gastrointestinal	2	8%	4	16%
Breast	5	20%	5	20%
Gynaecological or Genitourinary	4	16%	3	12%
Lung	5	20%	7	28%
Other	9	36%	6	24%
ECOG score				
ECOG (0,1)	8	32%	15	60%
ECOG (2)	11	44%	9	36%
ECOG (3)	6	24%	1	4%

Table 2 shows mean VAS score of both group of patients on every follow up. As for adequate pain relief (keep VAS below 2), we increased dose in both group of patients according to patients' severity of pain. Average dose of medication required in both group during follow-up are shown in table 3. During 8^{th} and 12^{th} week follow-up we find, there were less average dose of methadone is required in terms of Morphine Milligram Equivalent (MME) than average dose of morphine for adequate pain relief.

Table 2: Frequency of VAS Score in Methadone group and Morphine group

(Methadone group) (No. of patients)						
VAS Score	Baseline/ Day 0	1^{st} Week	2^{nd} Week	4^{th} Week	8^{th} Week	12^{th} Week
Mean	9.04	3.88	3.68	3.00	2.32	1.94
±SD	0.79	1.17	1.38	1.38	1.31	0.94

(Morphine group) (No. of patients)						
Mean	7.72	3.28	3.56	3.32	3.84	2.60
±SD	0.74	0.94	1.16	1.22	2.23	1.00

Table 3: During follow up Week Wise Average dose of medicine required by patients for adequate pain relief

Dose (mg/day)		Day 0	1st Week	2nd Week	4th Week	8th Week	12th Week
Methadone	Mean	5	7	10	11	12	11
	±SD	3.95	5.83	6.88	6.92	6.57	4.69
Morphine	Mean	30	36	46	50	60	62
	±SD	0.74	0.94	1.16	1.22	2.23	1.00

There was no significant difference found between mean baseline QTc and at 1st, 4th, 8th, 12th, week mean QTc in both Methadone and Morphine Group of patients as shown in table 4.

Table 4: Average QTc of patients in study group as per follow up

QTc (mSec.)		Day 0	1st Week	4th Week	8th Week	12th Week
Methadone	Mean	0.358	0.359	0.357	0.363	0.352
	±SD	0.04	0.04	0.03	0.03	0.03
Morphine	Mean	0.338	0.364	0.353	0.355	0.352
	±SD	0.05	0.05	0.06	0.05	0.05

In Methadone group, we have observed side effects like dry mouth (36%), sedation (72%), constipation (76%), weakness (92%), mucositis (12%), nausea/vomiting (84%), itching (8%), insomnia (20%), edema (44%) and confusion (44%) with different frequency in each week, shown in table 5.

Table 5: - Frequency of different side effects in Methadone and Morphine group

Side effects	Methadone group N (%)	Morphine group N (%)
Dry mouth	9(36%)	19(76%)
Sedation	19(76%)	11(44%)
Constipation	20(80%)	22(88%)
Weakness	23(92%)	23(92%)
Mucositis	2(8%)	0(0%)
Nausea/Vomiting	21(84%)	23(92%)
Itching	1(4%)	0(0%)
Insomnia	5(20%)	0(4%)
Edema	11(44%)	0(0%)
Confusion	11(44%)	11(44%)
Breathlessness	0(0%)	1(4%)
Sweating	0(0%)	11(44%)

In Morphine group, we have observed side effects like dry mouth (80%), sedation (44%), constipation (88%), weakness (92%), breathlessness (4%), nausea/vomiting (88%), itching (4%), sweating (44%), drowsiness (8%) and confusion (44%) with different frequency in each week as shown in table 5. These side effects were treated with rescue medication.

We did not find any abnormality in laboratory parameters in any patient.

DISCUSSION

Pain is a major symptom in cancer patients and interferes with patient's quality of life and general functioning as well as numerous psycho-social responses [10].

The WHO analgesic ladder was a strategy proposed by the World Health Organization (WHO) in 1986 to provide adequate pain relief for cancer patients. According to that, step 3 analgesics like Morphine, Methadone, Fentanyl, Oxycodone, Buprenorphine, Hydromorphone, Oxymorphone with or without non-steroidal anti-inflammatory drugs (NSAIDs), with or without Adjuvants can be used for relieving moderate to severe pain [11].

This study was conducted by Palliative Medicine department to see efficacy and safety of Methadone and Morphine for sever chronic pain in advanced cancer patients.

Demographic data like age, Gender, ECOG score, types of cancer were comparable, which is supported by double – blinded study done by Laur et al [12].

A randomized, double blind study done by Bruera et al [13], to compare Methadone and Morphine as a first line strong opioid for cancer pain on one hundred and three patients. They found at the end of 8 days, in both the groups, 75% of patients reported reduction of 20% or more pain intensity. At 4-week similar proportion of patients had found more than 20% of relief in pain intensity. Similarly, we also found significant reduction in VAS score in both treatment groups of patients after starting of study drug at 1st week and 12th week of follow-up. A study done by Gagnon et al [14] for role of methadone in neuropathic pain, found that the mean pre-treatment VAS ± SD around 7.7±1.5 cm and this dropped significantly to 1.4±1.7 cm on a stable dose of methadone with significant p value ($P<0.0001$). According to this study, Methadone might be useful in the treatment of neuropathic pain.

In our study initial average dose of was 5mg for Methadone and 30 mg for morphine. At the 12th week of follow up average dose was 11 mg for Methadone and 62.4 mg for Morphine. Ventafridda et al [15] did randomized study on oral administration of Methadone and Morphine for cancer pain to compare daily dose, analgesic effects, performance status and side effects of both drugs. They found similar analgesic efficacy & adverse effects for both drugs and methadone was effective in lower dose as compared to morphine. They found significant difference in initial average dose and finally escalated dose in Morphine group but not in Methadone group of patients. In our study also we find less dose of methadone in terms of MME/day.

A study done by Mercandante et al, [16] on morphine versus methadone for treatment of pain in advanced cancer patients found that patients treated with methadone required less dose escalation than morphine as reported by less values of opioid escalation index percentage in methadone group. In our study we found significant difference in number of patients required escalation in dose after one week between methadone and morphine group, as 72% in methadone and 20% in morphine group required increment in dose after one week. But there was no significant difference in dose escalation found at 12th week follow up. Our finding might be due to low starting dose of methadone. As patients get adequate pain relief further dose escalation might not require in methadone group as compared to morphine group in which 80% of patients required dose escalation at 12th week follow up. There might be other disease related factors which change the requirement of analgesics in patients.

Various studies done by Krantz et al [17] & Kornick et al [18] found that high doses of methadone were linked with a life-threatening prolongation of the QT interval resulting in a potentially fatal arrhythmia, called torsade de points. Various laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval. However, in our study we did not find any significant difference between baseline QT interval of patient and QT interval after 1st week and 12th week of follow up in ECG in either methadone or morphine treatment group. As maximum dose of Methadone received by patient in our study was 30mg/day, which might be one reason that we did not find QT interval prolongation in any patient.

WANG Li et al [19] did a retrospective study analysis of adverse effects of opioids in moderate to severe cancer pain in one hundred elderly patients. They found sixty-one percent incidences of adverse effects. Constipation (48%) was the most common clinical adverse effect, followed by nausea/vomiting (24%). Lethargy (12%), dizziness (5%), skin itching (5%), dysuria (4%), respiratory depression (2%) was rare adverse reaction found in his study. In our study we found various adverse effects like weakness, constipation, nausea/vomiting, dry mouth, insomnia, mucositis, itching, sedation, confusion and drowsiness with different frequency in follow up periods in both group of patients without any significant difference between two groups. Of these various side effects most common were constipation and nausea/vomiting, which is similar to the study done by WANG Li et al [19] as described above. Another study done by Phillip et al [20] to determine impact of opioid on patient consciousness, appetite and thirst when used to treat cancer pain found common side effects like constipation, nausea, dry mouth, vomiting and somnolence, which had similarity with our study findings.

STUDY LIMITATION

We did this as pilot study with small sample which is limitation of this study. This study was not blinded study. So large scale blinded study is needed for further better understandings.

CONCLUSION

From this study, we can say that morphine and methadone both are very effective in management of severe pain in advance cancer patients without any major side effects. So, one should not hesitate to start either of them in advance cancer patients to treat pain.

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