Original Article DOI: 10.22114/ajem.v0i0.129

Comparison of Analgesic Effects of Nebulized Morphine with Fentanyl Transdermal Patch and Oral Methadone for Cancer Patients in Terminal Stages; a Double-blind Randomized Controlled Study

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Published online: 2019-04-30

Abstract

Introduction: Recent years have witnessed widespread reports on the effectiveness of nebulized morphine for dyspnea, yet there is no evidence for its effectiveness in analgesic therapy.

Objective: This study aims to compare effectiveness and side effects of inhalation morphine with oral methadone and transdermal fentanyl in sequential days in end stage cancer patients.

Method: This double-blind, randomized controlled study conducted between April and September 2017. Ninety eligible cancer patients presenting to Sayed al-Shohada Hospital were selected non-randomly according to inclusion criteria and then divided to 3 groups in random order. Pain severity was scored by Visual Analog Scale (VAS). Patients were followed up for 3 days and then data were analyzed by SPSS. The benchmark of success was set as marking 4 or below on VAS and a reduction ratio of 50 percent.

Results: Pain severity was equal for 3 groups before the first administration ($p>0.05$), but it decreased significantly from 8.45 (range 6-10) at baseline to 2.46 (range 1-4) at the end of the 3rd day in the nebulized group. The decrease ratio was equal to 70.8% after three days ($p<0.05$). Pain severity reduced from 8.45 (range 7-10) to 1.8 (range 1-3) ($p<0.05$) in the methadone group, and reduced from 8.5 (range 6-10) to 2.13 (range 1-3) in the fentanyl group.

Conclusion: Our study showed that nebulized morphine, just like oral methadone and transdermal fentanyl, is effective, safe, and well-tolerated for pain management in patients with cancer.

Key words: Cancer Pain; Fentanyl; Methadone; Morphine; Nebulizers and Vaporizers; Pain Management; Transdermal Patch

Cite this article as: Majidinejad S, Ebrahimi M, Heydari F, Ahmadpour M, Esmailian M. Comparison of Analgesic Effects of Nebulized Morphine with Fentanyl Transdermal Patch and Oral Methadone for Cancer Patients in Terminal Stages; a Double-blind Randomized Controlled Study. Adv J Emerg Med. 2019;3(3):e23.

INTRODUCTION

Although cancer elicits an array of physical and emotional symptoms, pain is often identified as one of the most distressing (1). So, pain management is often a critical yet problematic part of the treatment plan of such patients (2). Pharmacologic therapy is the mainstay of cancer pain relief, and satisfactory pain control can be achieved for 90% of the patients with minimal adverse side effects. Despite of patient's urgent need for analgesic medication, a prospective study found that 670 patients (34%) of the more than 2,000 of cancer patients with pain were not getting adequate pain medication. Twenty-three percent of the patients with severe pain and 27 percent of those with moderate pain were getting no analgesic at all, and only 40 percent of the patients with severe pain and 27 percent of the patients with moderate pain were treated with a strong opioid (3).

Opioids are the most usual medicines for analgesic therapy, and morphine, methadone and fentanyl are three extensively used opioids in this regard (4, 5). Fentanyl patches are a good choice for patients with swallowing difficulties, adherence problems, consciousness changes, and those needing opioid rotation due to side effects. They are reported to cause less constipation compared with other opioids. Plasma fentanyl concentrations are barely detectable for about 2 hours after patch placement. Eight to twelve hours after patch placement, concentrations approximate those achieved with equivalent intravenous doses of fentanyl (6).

Methadone is often used as a second-line agent in difficult pain, instead of, or in conjunction with, other opioids. This opioid is difficult to use because of significant inter-patient variation in efficacy and unpredictable adverse effects. Dose titration is complex due to the highly variable pharmacokinetic profile of the drug. Patients must

be closely monitored because of the possibility of drug accumulation and unintended overdose. Methadone is frequently used in the scenario of opioid rotation or switching (7).

Then again, morphine is the preferred medication because of its availability, varied formulations, and well-characterized pharmacologic properties; and World Health Organization (WHO) still recommends morphine as the first-line analgesic therapy (4, 8). It is commonly administered via intravenous, rectal and oral routs (8). However, nebulized morphine is another administration route that there is not proper evidence for its effectiveness and complications yet (9-11). Therefore, this study aims to compare effectiveness and side effects of nebulized morphine with oral methadone and transdermal fentanyl patch in end stage cancer patients.

METHODS

Study design and setting

This prospective, double-blind, randomized controlled trial was conducted between April and September of 2017 in Sayed al-Shohada Teaching Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The study was approved by the research ethics committee of Isfahan University of Medical Sciences (Ir.mui.rec.1396.3.129). The study protocol was also registered at the Iranian Registry for Clinical Trials and the code of IRCT20171211037834N1 has been assigned for it. Patients were briefed on the process of treatment and probable side effects, signed informed consents, and were told they could quit the study any time.

Participants

End stage cancer patients older than 18 years with moderate or severe pain [Visual Analog Scale (VAS) ≥ 5] were eligible. Allergy to opioids, hypotension (systolic blood pressure lower than 110 mmHg), hypoxemia (Oxygen saturation lower than 90 percent in room air), rhinitis, liver and kidney disorders, hypothyroidism, Addison's disease and prostate hypertrophy were considered as exclusion criteria. Considering type 1 error (alpha) of 0.05 and study power of 84%, the sample size was calculated as at least 30 patients in each intervention group. All the patients were hospitalized, and the patients selected by hospital specialists non-randomly according to inclusion criteria and then divided to 3 groups in random order.

Intervention

Computer software was used for block randomization with a size of 6 blocks for 3 groups of nebulized morphine (group A), transdermal fentanyl (group B) and oral methadone (group C) by independent physician who was blinded to the study and no one except the in-charge physician was aware of this coding. Group A received 20 mg of nebulized morphine, repeated every 10 minutes with a maximum of 3 doses. Group B received 0.6 mg of transdermal fentanyl patch. The transdermal patch was changed every 72 hr. Group C received oral methadone (maximum dose of 45 mg/day) divided in three doses (4, 11, 12). It was supposed that if a patient did not response properly following administration of the maximum prescribed dose, the patient was excluded and treated with intravenous or subcutaneous morphine as rescue medicine.

Data gathering

A checklist was used for collecting required data including age, sex, cancer type, pain severity before and after drug administration, and probable side effects (apnea, nausea, vomiting, constipation, etc.). A trained medical student who was blinded to the study groups was responsible for data collection.

Outcome assessment

The primary outcome of this study was pain intensity, which was evaluated by VAS. VAS is a 10-cm horizontal or vertical non-graded line anchored at its ends by numbers or words describing the two extremes of a symptom. In the case of pain, for example, one end is labeled "0," or "no pain," and the other end "10," or "worst possible pain". Reduction of pain intensity by 1.5 times the initial pain, or 50% of the initial pain, or less than or equal to 4 out of 10 considered as successful pain management (11, 13, 14). The secondary outcome was side-effects including insomnia, nausea, vomiting and dizziness. The patients were followed up for three sequential days. Pain severity was measured at 8:00 AM on the first day before administering the first dose of the drugs and again at 8:00 PM on the first day and repeated for two more days at the same times.

Statistical analysis

First, we present data with frequency, mean and standard deviation. Second, we assessed VAS in independent study groups with one-way ANOVA and VAS in over the follow time with repeated measures of general linear model (GLM). We used Post-Hoc analysis based-on Bonferroni approach in repeated measures for assessed multiple comparisons of VAS in over the follow time in study groups. Data analysis was performed based on intention-to-treat approach. We used graphical approaches and D'Agostino-Pearson Test for

assessed normality assumption. Statistical tests were performed as two-tailed tests with a significance level of P-value<0.05. Data were analyzed with SPSS software (IBM Corporation, Armonk, USA).

RESULTS

Baseline characteristics of the patients

Totally 90 patients divided in 3 groups were participated. CONSORT flowchart of the study is shown in figure 1. Descriptive variables are shown in table 1, including male/female ratio, mean age, diagnostic groups, and vital signs. Eight patients (9.3%) suffered from side effects and most of them (5 patients) had constipation and all belonged to methadone group. However, the number of patients with side-effects was not enough to be analyzed.

Response to treatment

First of all, pain severity was compared among the groups before the administration of the first dose. Mean pain severity was not significantly different in three groups (P=0.821).

Frequency of pain severity at each follow up time are shown in figure 2, and marginal means of VAS in the follow time by the three study groups are shown in figure 3. Overall, pain intensity for study groups, were not significant in the beginning and at the end of the 1st day, but in other intervals, VAS was significantly lower in Fentanyl group than two other groups (Table 2). Results of repeated measure showed VAS in each three-group decreased significantly during study period (P<0.001). Multiple comparisons based-on Post-Hoc tests showed decrease of the VAS over the follow time for Fentanyl group was significantly higher than nebulized morphine group [Mean difference= -1.17 (95%CI: -1.6, -0.73), P<0.001] and methadone [Mean difference= -0.81 (95%CI: -1.3, -0.36), P<0.001]. Mean difference of VAS over the follow time in nebulized morphine group and oral methadone group was not statistically significant (P=0.173) (Figure 3).

Nebulized morphine

According to the results, nebulized morphine could reduce the severity of pain at the end of the day (8:00 PM) compared with the beginning of each day (8:00 AM). Furthermore, this reduction increased on the second and third days (p<0.05). However analgesic therapy was not completely successful at the end of the first day. In fact, 13 patients had pain with the severity of 5, but treatment was completely successful on the second and third days (Figure 2). Our goal was achieved as seen in the reduction ratios in Table 3. After 3 days, pain severity was reduced about 70 percent, which is a success. Average number of appointments in this group was equal to 2.1 a day.

Fentanyl patch

Pain intensity was reduced in the fentanyl group at

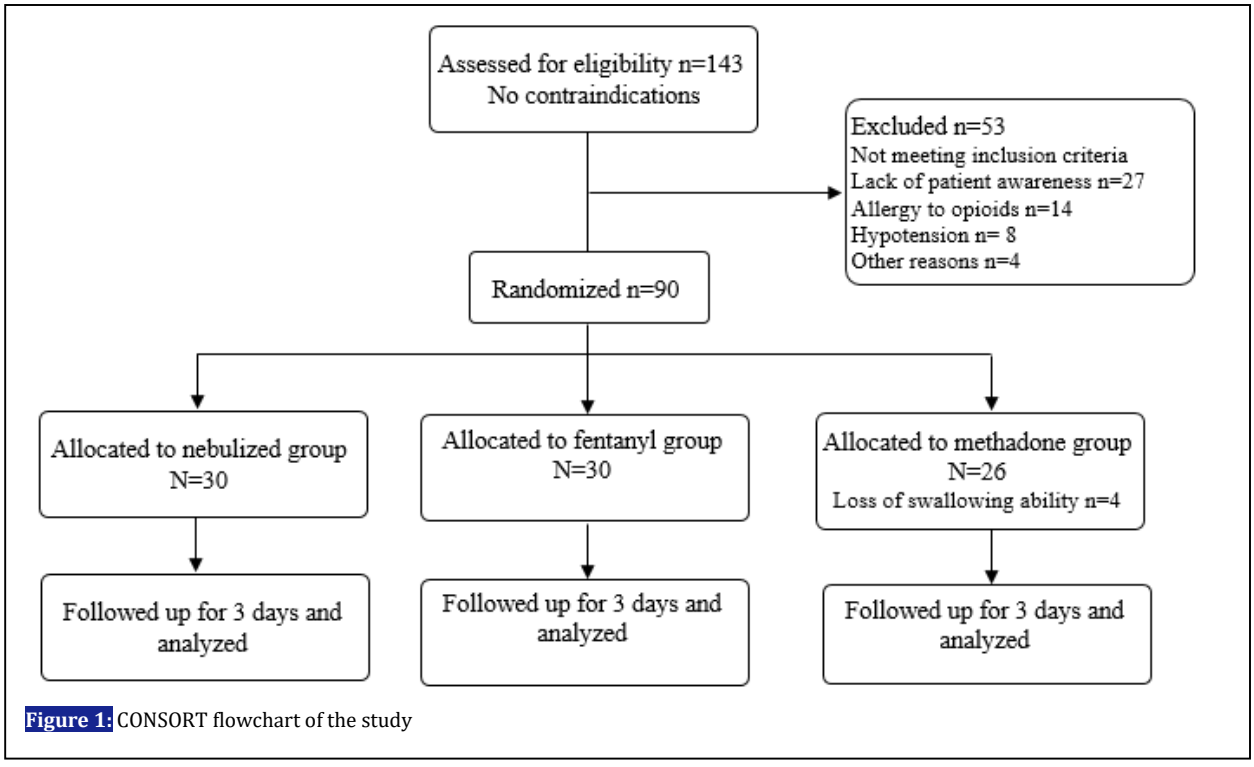

Figure 1: CONSORT flowchart of the study

Table 1: Descriptive statistics of studied patients

Variable	Group			Total (n=86)
	Nebulized morphine (n=30)	Oral methadone (n=26)	Fentanyl patch (n=30)	
Male/Female	13/17	15/11	12/18	40/46
Age [mean(range)]	65.03 (48-90)	63.46 (37-92)	63.2 (34-91)	63.9 (34-92)
Type of cancer				
Prostate	2	7	4	13
Breast	2	6	9	17
Liver	3	6	4	13
Colon	1	3	3	7
Stomach	6	2	2	10
Uterus	6	1	1	8
Bladder	-	1	3	4
Lung	10	-	2	12
Blood	-	-	2	2
Vital signs				
Blood pressure (mmHg)	136.3	134.03	134.3	134.9
Respiratory rate (/min)	16.2	16.38	15.9	16.15
Heart rate (/min)	80	81.27	80.2	80.45
Oxygen saturation (%)	92.7	92.5	92.8	92.7
Prescribed dose [mean (range) mg]	28.25 (20-45)	21 (10-45)	0.6 (fixed)	-
Mean number of drug administrations	2.1	2.5	Fixed	-
Side effect				
Dizziness	2	-	1	3
Nausea	-	-	1	1
Constipation	-	5	-	5

Table 2: Pain intensity based on visual analogue scale in studied groups in various intervals

Time	Group			P-value (between groups)
	Nebulized morphine	Oral methadone	Fentanyl patch	
1st day morning	8.47±1.28	8.42±1.36	8.27±1.23	0.821
1st day evening	4.33±0.84	3.88±0.95	4.03±0.81	0.145
2nd day morning	7.83±1.34	7.84±1.33	4.67±0.71	<0.001
2nd day evening	3.50±0.57	3.19±0.57	3.10±0.66	0.032
3rd day morning	6.80±1.13	6.50±1.21	4.17±0.59	<0.001
3rd day evening	2.47±0.68	1.88±0.59	2.17±0.65	0.005
P-value (internal group)	<0.001	<0.001	<0.001	

Table 3: Pain decrease ratio in studied groups in various intervals

Decrease ratio (%)	Group		
	Nebulized morphine	Oral methadone	Nebulized morphine
1st Day	48.75	54.08	51.76
2nd Day	55.2	62.05	33.47
3rd Day	63.8	72.3	48.04
3rd Day to 1st Day	70.8	78.7	74.94

the end of each day compared with the beginning of the same day (Table 2). This reduction was more significant on the first and second days than third day ($p<0.05$) (figure 2). Statistical analyses show that patients who received fentanyl transdermal patch suffered milder pain at the beginning of the second and third days than two other groups. Figure 2 shows that fluctuations of pain severity in fentanyl patch group was less than those in the two other groups ($p<0.05$).

Methadone

On the first day, pain intensity was reduced to less than 4 in the patients who received oral methadone (Table 2). In fact, 20 patients had pain severity of 4 or below at the end of the first day. However, during the study, 4 patients left the study because of dysphagia. Also five patients were constipated and auxiliary medicine was prescribed for them. Although pain severity was lower in the oral methadone group than that in the two other groups on the first day, the difference was not statistically meaningful ($P=1.0$). Results of the second and third days show that pain severity was lower at the end of these two days in the methadone group than that in the fentanyl and nebulized groups ($p<0.05$), which was statistically meaningful.

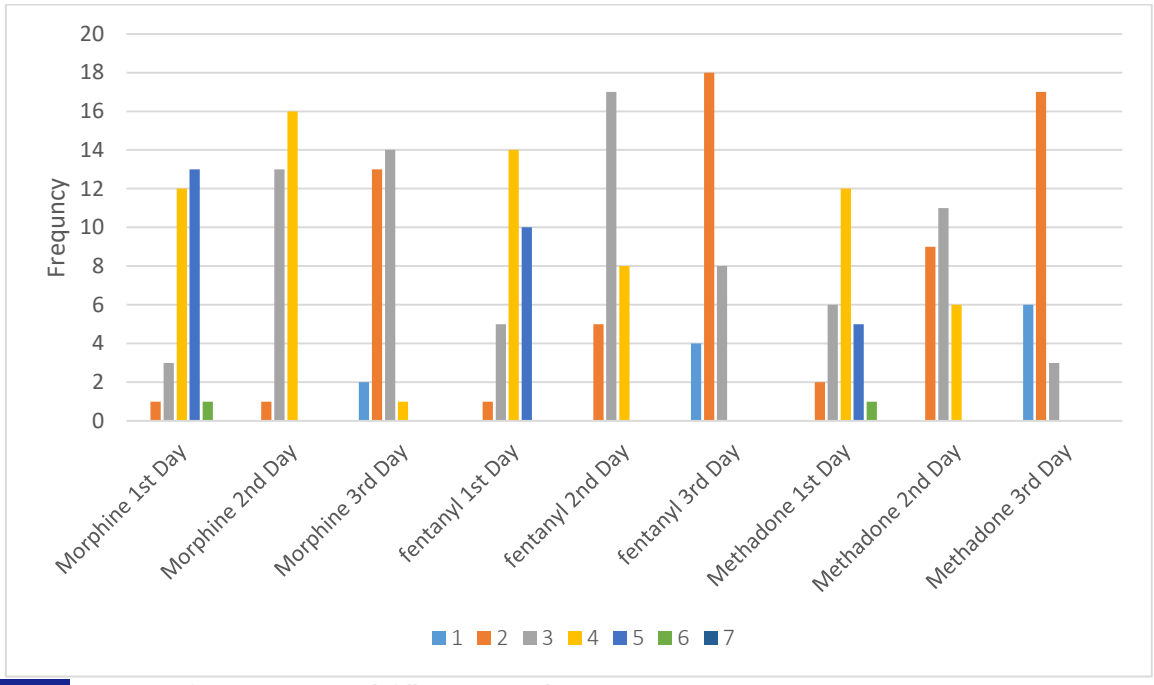

Figure 2: Frequency of pain severity at each follow up interval

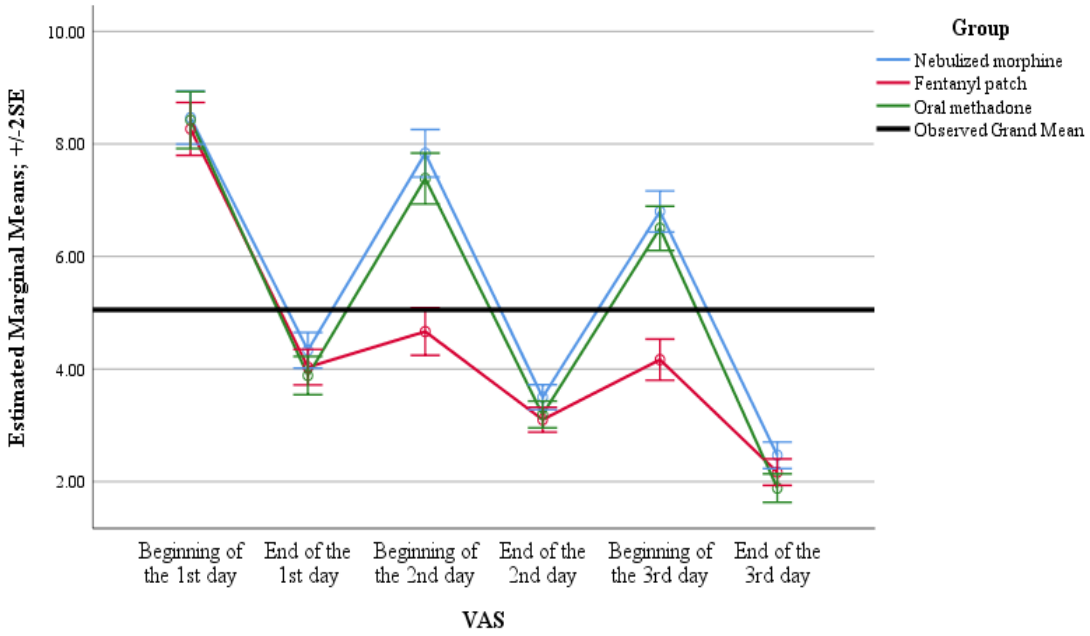

Figure 3: Marginal means (SE) of VAS in the follow time by the three study groups

Discussion

Our study results show that nebulized morphine, just like oral methadone and transdermal fentanyl, is effective for pain relief of patients with end stage cancer. Achieving a VAS score ≤4 was the study goal. Moreover, we considered pain decrease ≥50% as successful treatment. In all three groups, this goal was achieved. Pain decrease ratio was the highest in the methadone group, but it was acceptable in the two other groups. Because of gradual absorption of fentanyl and its 72-hour half-life, the fluctuation of pain severity in this group was less than that in other groups.

To the best of our knowledge, our study was the

first report on the effectiveness of nebulized morphine for chronic pain and cancer pain. Previous surveys just studied this method for acute pain and dyspnea. For example, Bruera et al. reported no significant difference in dyspnea intensity and dyspnea relief between nebulized and subcutaneous morphine at 60 minutes (14). Another study by Fulda et al. mentioned that nebulized morphine can be safely and effectively used to control post-traumatic thoracic pain while vital capacity, mean forced expiratory volume in one second, and spirometric parameters are maintained. Compared with Patient Controlled Analgesia (PCA) morphine, nebulized morphine provides equivalent pain relief with less sedative effects (10). Grissa et al. had the same results in their study about analgesic effects and side-effects of nebulized morphine compared with intravenous morphine for traumatic patients (11).

Limitation

Despite our positive results, they should be interpreted with caution because of some limitations. We could not blind the patients because of different routes of administration and lack of placebo drugs in this case. Because our study was conducted in a teaching hospital, it is necessary to repeat the study at home environment. A potential bias source for VAS score measurement is that patients may exaggerate their pain intensity to accelerate drug delivery. If we consider that all results are correct and all three methods are equally effective, there are more important criteria for choosing the administration route. One such important criterion is cost-effectiveness. Patient's conditions are important too, such as dysphagia, consciousness, and respiration. It appears that patient's preferences are also important. This study is the first clinical trial on the efficacy assessment of nebulized morphine in chronic cancer pain and more patients are needed for generalizability of our results.

Conclusions

Most cancer patients will experience pain during the terminal stages of the disease. Although the regular administration of oral opioids continues to be the hallmark of cancer pain therapy, many patients are unable to take oral medications. Nebulized morphine provides an alternative route of opioid administration to patients who are unable to use oral medications or those who prefer the convenience of an inhalation medication.

Acknowledgements

We would like to appreciate our patients and their families for their cooperation. We also would like to thank the staff of Sayed al-Shohada Hospital, Isfahan, Iran.

Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

Funding

None declared.

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