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Research Article

Effectiveness of subcutaneous morphine in the treatment of pain crises in cancer patients

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Abstract

Objective: The purpose of this study was to evaluate the efficacy of subcutaneous morphine for managing pain crises resulting from various causes in cancer patients attended by the Pain Clinic in the immediate care area of the National Cancer Institute in Mexico City.

Materials and Methods: This study was analytical, observational, retrospective, and descriptive. The oncology patients treated in the immediate care area for pain crises between August 1, 2020, and July 1, 2023, made up our study population. We documented the management of pain crises for patients who needed subcutaneous morphine treatment.

Results: Considering a reduction in Numeric Rating Scale (NRS) score >30% as effective and a reduction <30% as ineffective, 566 patients didn't require an additional dose of subcutaneous morphine to control the pain crisis; 11 patients reported a decrease of <30%. A total of 24 patients needed a second rescue. Among this group, only 5 responded well to the second morphine rescue; in the remaining 19 patients, the rescue was deemed ineffective if the NRS decreased by at least 30%. Only 5 individuals experienced moderate pain, and only one patient reported severe pain. The variables were compared using the non-parametric Mann-Whitney U test with significance <0.05. Consequently, it may be said that there is a statistically significant difference between the first and subsequent NRS values obtained.

Conclusion: For oncology patients treated by the Pain Clinic in the immediate care section of the National Cancer Institute in Mexico City, subcutaneous morphine is beneficial in managing pain crises of different origins.

Keywords: Morphine, Subcutaneous Pain crises, Efficacy, Numeric rating scale

INTRODUCTION

In 2020, an estimated 19,292,789 patients worldwide were diagnosed with cancer. Pain is a serious and very common problem for many people. Pain is experienced by about 53% of cancer patients at some stage during their cancer treatment. The prevalence of discomfort in patients with metastatic illness varies from 59% to 64%. In addition, up to 59% of individuals may report pain during oncological treatment. According to recent research, up to 33% of cancer survivors may still experience discomfort [1, 2].

Hospitalized patients face a higher risk of experiencing this symptom. In the US, 114 oncology hospitalization units (n = 810 patients) were included in a study that reported on pain. The average pain intensity score was 5.9 on a scale of 0 to 10, where "0" means "no pain" and "10" means "the worst possible pain." Of these hospitalized patients, one-fourth reported experiencing either persistent pain or frequent, strong pain (>50% of the time) [3,4].

Pain is defined by the IASP (International Association for the Study of Pain) as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." The definition focuses on six etymologically significant points:

- Pain is always a subjective experience impacted by biological, psychological, and social variables in different proportions.
- Pain cannot be exclusively deduced from sensory neuron activity; pain and nociception are two different phenomena.
- People pick up on the idea of pain from their encounters in life.

- It is appropriate to accept someone's report that they experienced discomfort.
- Although pain frequently serves an adaptive purpose, it can also negatively impact psychological health, social well-being, and function.
- Verbal description is just one of several behaviors to express pain; the inability to communicate does not negate the possibility that a human or non-human animal experiences pain [5].

Cancer pain continues to be underestimated, poorly assessed, and undertreated, especially in patients experiencing severe pain. Following the World Health Organization's (WHO) three-step pain ladder helped reduce pain in 75% to 90% of patients, according to early research on cancer pain management techniques. European and local guidelines recommend the use of strong opioids for moderate to severe cancer pain, as they constitute the cornerstone in the management of oncological and end-of-life pain. Morphine, the primary alkaloid derived from immature opium poppy pods (Papaver somniferum), was first isolated in 1803 and serves as the prototype for opioid agonists [6, 7, 8].

The National Comprehensive Cancer Network (NCCN) offers an algorithm for the management of adult cancer-related pain that differentiates between three levels of pain intensity based on a numerical value from 0 to 10, obtained using a numeric or pictorial rating scale (where 0 indicates no pain and 10 represents the worst pain). Three categories of pain intensity are mentioned in the algorithm: mild pain (1-3), moderate pain (4–7), and severe pain (8–10) [9].

Patients experiencing severe pain requiring urgent relief should be treated with parenteral opioids, typically administered intravenously or subcutaneously. The corresponding dose is one-third of the oral amount when given intravenously. Patients who have never used opioids before (sometimes known as " naïve patients") should start with a dose of 2 to 5 mg of intravenous morphine sulfate or its equivalent. 10% to 20% of the total opioid dose from the previous 24 hours should be the rescue dosage for patients who take opioids chronically [10].

The objectives of pain management aim to optimize anti-algic treatment outcomes across five dimensions, often referred to as the "5 As" (the original "4 As" proposed by Passik and Weinreb, later modified to include "Affect"):

Analgesia: Optimize analgesia (pain relief).

Activities: Optimize daily life activities, including psychological functioning.

Adverse effects: Minimize adverse events.

Aberrant drug use: Avoid aberrant drug use (outcomes related to addiction).

Affect: Recognize how pain and mood are related [10].

Parenteral opioids, which are usually given subcutaneously (SC) or intravenously (IV), should be used to treat and titrate patients who are experiencing severe pain and need immediate relief, according to the World Health Organization [(11)]. Because cancer has a multifaceted etiology and might be connected to comorbidities, cancer therapies, or psychological aspects that frequently accompany chronic or terminal illnesses, cancer-associated pain continues to present a challenge for doctors providing care for these patients. 33% of patients after curative treatment, 64% of patients with severe disease, and 59% of patients undergoing treatment have reported having it. Stress and pain are intrinsically linked due to the overlapping interactions between neurochemical mechanisms regulating stress and pain. Maladaptive alterations brought on by prolonged stress both cause and worsen pain. The use of subcutaneous morphine can provide a method for relieving this symptom in oncology patients [11, 12, 13].

MATERIALS AND METHODS

A descriptive, retrospective, observational, and analytical study was carried out at the National Cancer Institute in Mexico City. Patients with cancer receiving immediate care owing to pain crises between August 1, 2020, and July 1, 2023, made up the working population for this study. A register of pain crisis management was created based on notes made in that area, with an emphasis on patients who needed subcutaneous morphine injection. The Numeric Rating Scale (NRS) score after subcutaneous morphine administration, the dosage in milligrams, and the number of doses given were all included in this registry.

Inclusion Criteria:

1. Active clinical records.
2. Records of patients who experienced pain crises between August 1, 2020, and July 1, 2023, and were treated in the immediate care area by the pain clinic service.
3. Records showing subcutaneous morphine was used to address the patient's pain crisis.
4. Individuals with a score of >5 or =5 on the Numeric Rating Scale (NRS).
5. Records containing the reported score on the visual analog scale following the administration of morphine.

Exclusion Criteria:

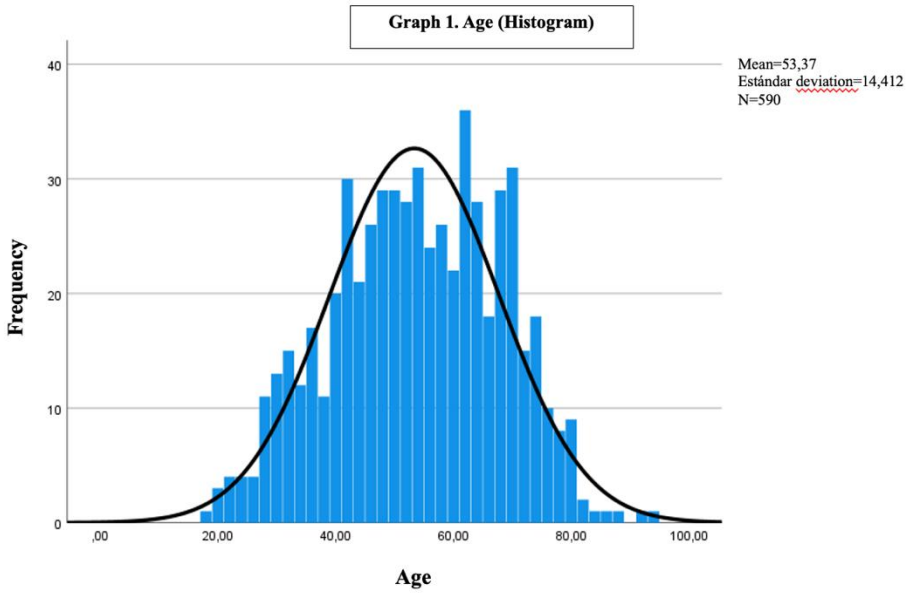
1. Incomplete or inactive clinical records.
2. Records indicating that the patient was admitted to the hospital.
3. Records where the Numeric Rating Scale (NRS) recorded score is less than five.
4. Records stating that morphine was not the only medication used to address the pain crisis, or that another medication was given in addition to morphine.
5. Records reporting that the patient did not experience a pain crisis.

Statistical Analysis

The SPSS 27 program was used to analyze the data. Measures of central tendency (means, standard deviations, medians, and ranges, respectively) were used to describe sociodemographic parameters. The effectiveness of subcutaneous morphine in managing pain crises was calculated, taking the initial Numeric Rating Scale (NRS) score as a parameter, and comparing it with the score reported after the administration of subcutaneous morphine. To improve the interpretation of the results, a normalcy test was performed with reference to the Numeric Rating Scale. Finally, the variables were compared using the non-parametric Mann-Whitney U test.

RESULTS:

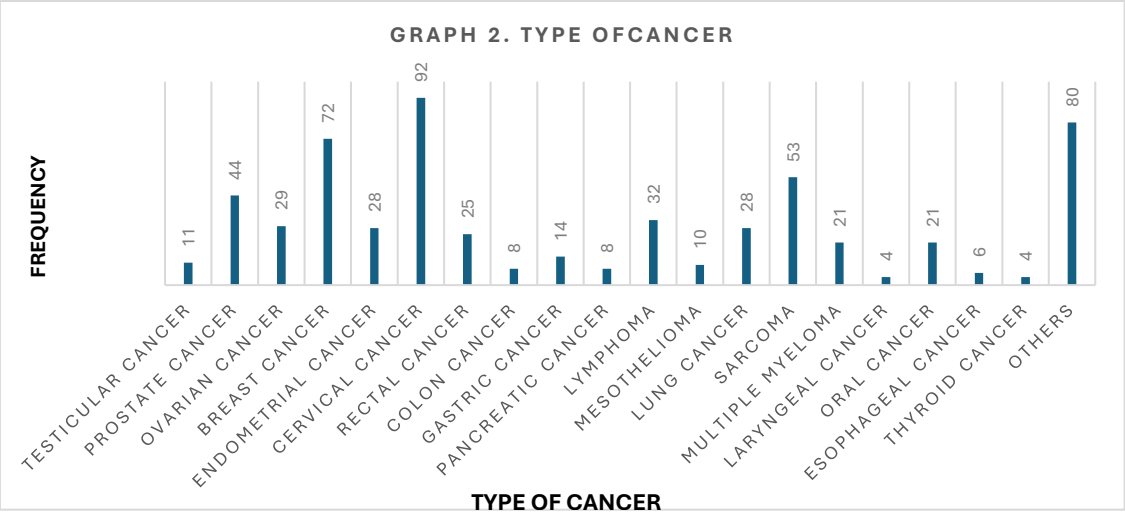
Following the review of clinical records, a total of 590 patients were obtained, with a mean age of 53.37 years. The maximum age was ninety-three, and the minimum was eighteen. (Graph 1).



The predominant gender was female, accounting for 67.5% (n=398).

Patients had a variety of comorbidities; the most common pathology was diabetes mellitus, which affected 18.4% of patients, and systemic arterial hypertension, which affected 15%. It is important to note that over half of the individuals had no comorbidities at all.

The following table describes the oncological diagnoses found in the population under study. With 92 cases, or 15.59% of all cases, cervical cancer was the most common. Breast cancer came in second with 12.2% of cases, while prostate cancer came in third with 7.46%. (Graph 2).



The algological diagnosis most frequently observed was visceral nociceptive syndrome, accounting for 29.49%, followed by somatic nociceptive syndrome, and nociceptive syndrome with a neuropathic component (pain of associated or mixed components). 1.8% (11 patients) presented neuropathy secondary to chemotherapy. (Table 1)

Table 1: Algological diagnosis.

PAIN SYNDROMES	FREQUENCY	PORCENTAGE
SOMATIC	131	22.20
VISCERAL	174	29.49
NEUROPATHIC	21	3.56
SOMATIC WITH NEUROPATHIC COMPONENT	111	18.81
VISCERAL WITH NEUROPATHIC COMPONENT	20	3.39
SOMATIC AND VISCERAL	10	1.69
HEADACHE	15	2.54
BONE PAIN	108	18.31
TOTAL	590	100.00
Source: Data obtained by the researcher.		

The mean pain intensity, as assessed by the NRS, was 7.87, indicating a severe level of pain, with a minimum NRS score of 5 and a maximum of 10. Upon meticulous case review, it was discerned that the daily equivalent dose of morphine amounted to 39.9mg, demonstrating a standard deviation of 50.44mg as part of the baseline treatment.

In addressing pain crises, the mean dose of subcutaneous morphine administered was 2.34mg, exhibiting a standard deviation of 0.8mg. The ensuing intensity rating, as per the Numeric Rating Scale, averaged 2.43 post-application, signifying a state of mild pain. (Table 2.)

Table 2: Pain Intensity by NRS After Subcutaneous Morphine Administration

C		INITIAL NRS	DAILY EQUIVALENT DOSE OF MORPHINE	DOSE OF SUBCUTANEOUS MORPHINE	NRS AFTER SUBCUTANEOUS MORPHINE
N	Valid	590	590	590	590
	Lost	0	0	0	0
Mean		7.8780	39.9411	2.3449	2.4339
Median		8.0000	28.0000	2.0000	2.0000
Mode		10.00	0.00	2.00	2.00
Standard Deviation		1.66926	50.44050	0.80275	1.82834
Minimum		5.00	0.00	1.00	0.00
Maximum		10.00	490.00	5.00	10.00
Percentiles	100	10.0000	490.0000	5.0000	10.0000

Source: Data obtained by the researcher.

From the total patient cohort, 4% (n=24) necessitated a second dose of subcutaneous morphine for effective pain crisis management.

The mean dosage for the second application was 2mg, and the reported pain intensity, evaluated by the Numeric Rating Scale (NRS) post the second dose, registered at 2, with a minimum NRS of 1 and a maximum of 8.

Considering an NRS pain score reduction >30% as indicative of effectiveness and a reduction <30% as ineffective, 566 patients did not require an additional subcutaneous morphine dose for crisis pain control. Within this subgroup, 555 patients regarded subcutaneous morphine as effective, while 11 patients reported a decrease <30% by NRS. However, their pain intensity was classified as mild, obviating the need for a second subcutaneous morphine dose.

Among patients receiving an extra dose (n=24), effectiveness was observed in only 5 patients, while in 19 patients (considering a 30% reduction in NRS after the initial dose as effectiveness), the utilization of a second subcutaneous morphine dose was deemed ineffective. Nevertheless, only 5 patients reported moderate pain (NRS=4-6), and 1 reported severe pain (NRS=8-10), with the remaining describing mild or absent pain (n=13). (Table 3)

Table 3: Effectiveness in pain crisis control with the 2nd dose of subcutaneous morphine

Total number of patients	Efficacy		Number of patients who received a second dose of morphine	Efficacy	
	YES	NO		YES	NO
590	555	35	24	5	19

Source: Data obtained by the researcher.

**11 patients did not require a second dose as they had an NRS < /= 4*

A normality test was conducted regarding the Numeric Rating Scale (NRS), considering:

H0 = Acceptance that the variable has a normal distribution ($p>0.05$)

H1 = Acceptance that the variable has a non-normal distribution (non-parametric) ($p<0.05$)

An average initial NRS of 7.87 with a median of 8 was obtained, while for the subsequent NRS, the average was 2.43, with a median of 2. (Table 4).

Table 4: Assessment of Pain Intensity by NRS Pre and Post Subcutaneous Morphine

NRS				Statistic	Standard error
INITIAL	NRS Value	Mean		7,8780	,06872
		95% confidence interval for the mean	Lower limit	7,7430	
			Upper limit	8,0129	
		Trimmed mean at 5%		7,9200	
		Median		8,0000	
		Variance		2,786	
		Standard deviation		1,66926	
		Minimum		5,00	
		Maximum		10,00	
		Range		5,00	
		Interquartile range		3,00	
		Skewness		-,206	,101
		Kurtosis		-1,090	,201
POSTERIOR	NRS VALUE	Mean		2,4339	,07527
		95% confidence interval for the mean	Lower limit	2,2861	
			Upper limit	2,5817	
		Trimmed mean at 5%		2,3145	
		Median		2,0000	
		Variance		3,343	
		Standard deviation		1,82834	
		Minimum		,00	
		Maximum		10,00	
		Range		10,00	
		Interquartile range		3,00	
		Skewness		,907	,101
		Kurtosis		1,071	,201

The Kolmogorov-Smirnov test was employed, considering the number of patients (n=590), obtaining a p-value <0.05, concluding that the variables have a non-normal distribution. (Table 5).

Table 5: Normality Tests

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
NRS		Statistic	gl	Sig.	Statistic	gl	Sig.
INITIAL	NRS VALUE	,161	590	,000	,896	590	,000
POSTERIOR	NRS VALUE	,192	590	,000	,917	590	,000

a. Correction of Lilliefors Significance

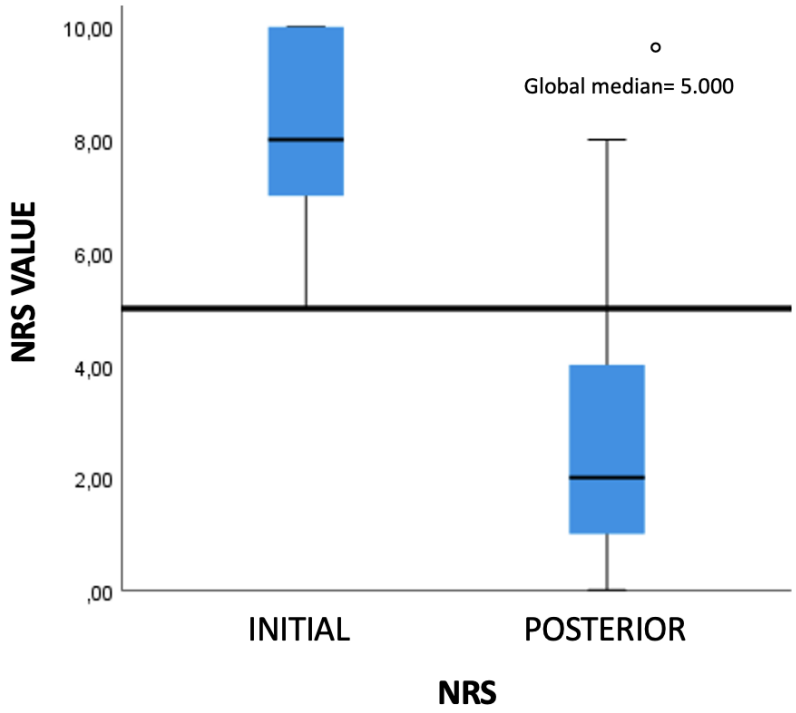
The non-parametric Mann-Whitney U test was employed to compare the variables, yielding the following results: The Mann-Whitney U value was 7734, considering the total ENA values (1180), with a significance level below 0.05. (Table 6.)

Tabla 6: Summary of Mann-Whitney U Test for Independent Samples

Total N	1180
Mann-Whitney U	7734,000
Wilcoxon W	182079,000
Test Statistic	7734,000
Standard Error	5820,855
Standardized Test Statistic	-28,572
Asymptotic Significance (Bilateral)	,000

According to these results, it is concluded that the values recorded in initial NRS and subsequent NRS are different and statistically significant. (Graph 3).

Graph 3. Comparison between initial NRS and posterior NRS



Less than 1% of the patients experienced adverse effects; nausea was the most prevalently identified, affecting 5 patients in the total sample.

DISCUSSION:

Pain is always a personal experience influenced by biological, psychological, and social factors. In this study, 590 patients were enrolled based on inclusion and exclusion criteria. The most prevalent algological diagnosis requiring pain crisis management was visceral nociceptive syndrome, at 29.49%. The reported pain intensity, assessed using the Numeric Rating Scale (NRS), had an average of 7.87, interpreted as severe according to the National Comprehensive Cancer Network (NCCN), which classifies pain into three levels: mild (1-3), moderate pain (4-7), and severe pain (8-10). [10] Patients experiencing severe pain requiring urgent relief should be treated with parenteral opioids, usually administered intravenously or subcutaneously. In our study, the minimum NRS value for inclusion was 5 (moderate), and the maximum value was 10 (intense).

On average, patients were being treated with a daily equivalent dose of morphine of 39.94 mg with a standard deviation of 50.44. The average subcutaneous morphine dose used for pain crisis management was 2.34 mg, with a standard deviation of 0.8 mg, in line with international recommendations suggesting an initial subcutaneous morphine dose of 2 to 5 mg. The NRS reported after the administration of subcutaneous morphine was 2.43 (mild pain), indicating effective pain crisis management.

Only 4% of the total patients required a second dose of subcutaneous morphine to control the pain crisis. The average dose administered was 2 mg, and the pain reported by NRS after this second dose was 2, with a minimum intensity of 1 and a maximum of 8. This demonstrates that 96% of patients with the first subcutaneous morphine dose for pain crisis control found it effective, aligning with reports by Afsharimani B et al., where morphine was used, and pain was controlled in 77% of cases, with no difference between subcutaneous and intravenous routes. In patients with intense pain due to advanced cancer, parenteral morphine was shown to be safe and provided better immediate analgesia compared to the oral route. [14]

Yu Sun et al. conducted a study in 2022 where the primary outcome was safety and the number of rescue doses administered as needed in the first 24 hours. They found that the total morphine use per capita was lower in the severe pain group than in the moderate pain group. No differences in opioid-related side effects were found between the two groups. [15] Other research has demonstrated that low-dose morphine (<30mg) has a higher response rate and a faster onset of response compared to weak opioids.

Out of the 590 patients in our study, 566 did not require a second dose. Of these, morphine was considered effective in 555, and only 11 patients did not show effectiveness with the first dose. However, they did not require a second dose as the pain intensity reported after the administration of subcutaneous morphine was <4. In patients who received a second dose (n = 24), only 5 found subcutaneous morphine effective, while in 19, the second dose was deemed not effective based on the criteria of a <30% decrease in NRS after the first dose. However, only one patient remained with severe pain (NRS 8-10), and five had moderate pain (NRS 4-7). The remaining 18 patients reported absent or mild pain (NRS 0-3), indicating that 75% of them had their pain crises adequately controlled, and only 25% (n = 6) did not find the second dose of subcutaneous morphine effective.

Bandieri, E. et al. found that adverse effects related to opioid administration, such as constipation and nausea, were comparable in both treatment groups, and overall well-being/symptom burden was significantly better in the low-dose morphine arm compared to the weak opioid group. [16] This

aligns with our study where less than 1% experienced adverse effects from subcutaneous morphine, with nausea being the only reported symptom.

Using the non-parametric Mann-Whitney U test to compare variables, the U value was 7734 considering the total NRS values (1180), with significance less than 0.05. Therefore, it is concluded that the values recorded in initial NRS and subsequent NRS are different and statistically significant.

CONCLUSION:

Based on the results obtained through our study, we can identify that the use of subcutaneous morphine to alleviate a pain crisis in oncology patients is effective, with minimal adverse events (<1% of the total sample). This is reflected in the fact that out of a total of 590 patients, only 6 persisted with moderate (n=5) or severe (n=1) pain. It is essential to emphasize that many of them had an adequate response with the first dose of subcutaneous morphine (n=566), representing an effective and safe therapeutic option for cancer patients requiring treatment for pain crisis control.

The main limitation of our trial is its retrospective nature, providing an opportunity for the implementation of a prospective clinical protocol to evaluate the response time with the administration of subcutaneous morphine to oncology patients with pain treated in an emergency setting.

Conflicts of interest: All of the authors have stated that no organization provided financial support for the work they submitted

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