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Oral Ketamine used as Analgesia in Cancer Patients in Al Forat Al Awsat Oncology Center

Assistant Prof. Dr. Jaafar Hameed Jaafar Mahboba, M.B.Ch.B, F.I.C.M

Consultant of Anesthesia, Medical College/Kufa University, Chief of Iraqi and Arabic Anesthetic Najaf Center, Iraq

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Abstract

Background: *Cancer pain management is complicated and requires assessment, reassessment, and constant vigilance by health care providers. Inadequate pain management has serious consequences for the patient, physician, nurse, and the health care system. Ketamine is commercially available as injection solution. The routes of administration of ketamine include parenteral, oral, topical, intranasal and sublingual. Oral administration of ketamine is preferred in long term use.*

Objective: *To evaluate the effect of the use of oral Ketamine as analgesic in Cancer patients*

Patients and Methods: *This was a randomized single blind controlled clinical trial conducted at Al Forat Al Awsat Oncology center. A total of 112 patients with different types of cancer, aged 18 years or older were included, patients assigned into two groups; 56 patients in each and they were assigned to receive 30 mg ketamine orally three times a day for one month. The second group assigned to receive placebo. The preparation of oral ketamine solution was used by took, 10 ml of 5% ketamine was diluted by 70 ml of 5% glucose water and 20 ml of 20% hypertonic solution. The patients were trained by the researcher how to take the solution by using a disposable 10 ml syringe and to draw 6 ml at each dose. Numeric analogue scale used to assess the intensity of pain among the patients. The patients asked to rate their pain according to the Numeric analogue scale at each visit.*

Results: *The patients age ranged 26 – 65 years, with no significant difference between both groups. All patients in both groups had the higher NAS at baseline. After initiation of treatment with 90 mg/day of oral ketamine in three divided doses , dramatic change had been reported at each visit in ketamine group; the mean NAS score reduced significantly at the last visit; the mean NAS was 9.2 ± 3.1 and 1.6 ± 1.0, respectively, (P<0.001). No similar changes had been found in placebo group. Some patients needed to increase the doses of ketamine and or the interval till reach a mean dose of 163 ± 10 mg in 4 divided doses, 4 patients remained not responding. On the other hand, 4 patients still have severe and very severe pain at the end of study and they were not responding.*

Conclusions: *Oral Ketamine is effective, safe and well tolerated agent for the management of chronic severe pain in cancer patients and it recommended for the cancer patients not respond to conventional treatment, further studies with longer duration are highly suggested.*

Keywords: *Ketamine, oral ketamine as analgesia, cancer*

Introduction

Cancer is a class of diseases characterized by uncontrolled cell growth. Normally, cells grow and divide to produce more cells only when the body needs them. Sometimes, however, cells become abnormal and keep dividing to form more cells without any control or order, creating a mass of excess tissue called a tumor or neoplasm. Approximately one million cases of cancer were reported throughout the world in 1990[(1)], while the figure increased to an astonishing 10 millions in the year 2000[(1)].

Cancer is caused by both internal factors [such as inherited mutations, hormones, and immune conditions] and environmental/acquired factors [such as tobacco, diet, radiation, and infectious organisms. Only 5– 10% of all cancers are due to an inherited gene defect[(3)]. Although all cancers are a result of multiple mutations[(8,9)], these mutations are due to interaction with the environment[(10)].

Epidemiology, surveillance, diagnosis And treatment of cancer cases

Surveillance data and survey data on the incidence and prevalence and of cancer and cancer-related pain indicate that a majority of patients experience pain at one time or another during the course of treatment and that cancer pain impairs quality of life and functionality[(11)].

Pain Assessment and Management

Inadequate pain management has serious consequences for the patient, physician, nurse, and the health care system. Under-treatment of pain in the health care system is at all levels: physician offices,hospitals, and long term care facilities. The results are often needless suffering for patients, complications that can cause further injury or death, and added cost to the healthcare system[(12)]. The societal cost of pain is enormous; pain is responsible for up to 80 % of all doctor visits. The costs arise from emergency room visits, heathcare provider visits, and increased hospital lengths of stay[(13)].

Definition of pain

Pain is defined as —an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[(4)].

Pain Theories

There were several competing theories of pain since the ancient Greeks; Hippocrates believed that pain was caused by an imbalance in the vital fluids of a human[(5,6)].

Specificity theory

The specificity theory, emerged in the nineteenth century, but had been prefigured by the work of Avicenna and Descartes {Merging Citations}. The Specificity Theory refers to the presence of dedicated pathways for each somatosensory modality.

Intensive theory

Pain is emotional state produced by stronger than normal stimuli such as intense light, pressure or temperature also argued that pain can be generated by any sensory stimulus, provided it is intense enough, and his formulation of the hypothesis became known as the intensive theory[(6)].

Pattern theory

Different cutaneous qualities are the product of different temporal and spatial patterns of stimulation, and ignoring a large body of strong evidence for receptor fiber specificity proposed that all skin fiber endings (with the exception of those innervating hair cells) are identical, and that pain is produced by intense stimulation of these fibers[(8)].

Gate control theory

This is the most accurately accounts for the physical and psychological aspects of pain. Both thin (pain) and large diameter (touch, pressure, vibration) nerve fibers carry information from the site of injury to two destinations in the dorsal horn of the spinal cord: transmission cells that carry the pain signal up to the brain, and inhibitory interneurons that impede transmission cell activity. Activity in both thin and large diameter fibers excites transmission cells. Thin fiber activity impedes the inhibitory cells (tending to allow the transmission cell to fire) and large diameter fiberactivity excites the inhibitory cells (tending to inhibit transmission cell activity)[(10,11)].

Cancer Pain Types

Pain, while highly variable and subjective, has been identified as one of the most common symptoms in patients with cancer [(13)].

Three main types of cancer pain, acute, chronic, and breakthrough pain, are present in 20-75% of adult patients at diagnosis and in 17-57% of the patients undergoing treatment [(14)].

Acute pain is short in duration and typically manifests in ways that can be easily described and observed[(15,17)]. Acute pain does not exceed six months, and it ceases to exist when the underlying cause of pain has been treated or has healed. Unrelieved acute pain, however, may lead to chronic pain refers to pain that lasts for more than three months. Chronic pain may originate from a trauma (car accident) or there may be an ongoing cause of pain (cancer pain)[(16,18)].

According to the American Cancer Society, chronic cancer pain often involves both persistent pain and breakthrough pain, making it difficult to describe and treat [(14)]. The treatment of cancer including surgical procedures, bone marrow biopsies, chemotherapy, radiation, and lengthy x-ray procedures may cause discomfort in addition to the pain associated with the cancer and any other preexisting chronic conditions[(15)].

Assessment and classification of cancer pain

Valid and reliable assessment of pain is essential for both clinical trials and effective pain management. The nature of pain makes objective measurement impossible[(16)].

The well-known visual analogue scale (VAS) and numeric analgesic scale (NAS) for assessment of pain intensity agree well and are equally sensitive in assessing acute pain and they are both superior to a four-point verbal categorical rating scale (VRS). They function best for the patient's subjective feeling of the intensity of pain right now—present pain intensity. They may be used for worst, least, or average pain over the last 24 h, or during the last week[(7)].

The Numeric analogue scale (NAS) is one of the recommended simple tools for the assessment of pain[(11,13)].

The pain NAS is a continuous scale comprised of a horizontal (HNAS) or vertical (VNAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme . Instructions, time period for reporting, and verbal

descriptor anchors have varied widely in depending on intended use of the scale[8,9]. Graphic formats for the NAS may be obtained from Scott & Huskisson. However, the graphic orientation of the NAS can make a difference to the statistical distribution of the data obtained using it[11].

A higher score indicates greater pain intensity. Based on the intensity of pain NAS scores in patients who described their pain intensity as none, mild, moderate, or severe, the following cut points on the pain NAS have been recommended: no pain (0 –0. 4 cm), mild pain (0.5– 4.4cm), moderate pain (4.5–7.4 cm), and severe pain (7.5–10 cm)[16].

Cancer pain Treatment

The experience of pain is a highly complex phenomenon with physical, behavioural, cognitive, emotional, spiritual, and interpersonal aspects. Because of multiple treatments and causes of pain, persistent and undertreated pain is a major concern for cancer patients [18].

Despite these guidelines, cancer pain management is still inadequate Almost 33% of cancer patients with pain had inadequate analgesic prescribing for cancer pain treatment[15]. In addition, physicians reported inadequate training in pain management skills[12]. According to previous studies, the physicians' self-assessment of cancer pain treatment skills was poor[14].

Additional physician and patient education about multiple causes of pain, assessment of pain, and pain treatment with pain analgesics could lead to better pain management and fewer reports of underestimated and unresolved cancer related pain[13].

Use of oral ketamine in pain management:

Ketamine is a phencyclidine anaesthetic, increasingly used in subanaesthetic doses as an analgesic in opioid-resistant pain syndromes of different etiologies and in the palliative care setting due to its opioid sparing effects and wide range of pain settings[15]. The analgesic effect of ketamine is primarily based on the antagonism of the N-methyl-D-aspartate (NMDA) receptor[11]. Activation of NMDA receptors results in central sensitization, which may play a crucial role in the pathogenesis of chronic pain. Besides acting on the NMDA receptor, ketamine also acts on nicotinic, muscarinic and opioid receptors[16,17].

Ketamine both has an anti-nociceptive and anti-hyperalgesic effect, the latter especially occurring in the lower dosage ranges. Administration of ketamine is reported to reduce pain in patients with neuropathic pain of various origins, including postherpetic neuralgia , complex regional pain syndrome (CRPS) [14,16]. When used in chronic pain management routes of administration include parenteral (intravenous, subcutaneous, intramuscular, epidural, intraarticular), oral, topical, intranasal and sublingual. In long-term use oral administration is preferred. Orally administered ketamine undergoes extensive first-pass metabolism in the liver, resulting in a bioavailability of approximately 16%. The primary metabole of ketamine is norketamine [14]. The elimination half-life is 2–3 h for ketamine and approximately 4 h for norketamine. Norketamine is thought to contribute to the analgesic effect and the duration of effect after oral administration of ketamine[15]. Although the use of ketamine as an analgesic is now generally accepted, the evidence base remains poor. Little formal research has been performed on the efficacy and safety of ketamine in chronic pain management, especially concerning long-term oral administration. Oral formulations of ketamine are not commercially available. The parenteral formulation is given as an oral solution or an extemporaneous preparation is made. In general, off-label use of medication has to be based on evidence about efficacy and safety[8].

Dosage, dosage form and efficacy of oral ketamine

Two approaches to pain treatment with oral ketamine were described. Either the patient started directly with oral ketamine with a low daily dose which, based on clinical effect and/or adverse effects, is increased. Or, the patient started with parenteral ketamine, either a single test dose or continuous treatment with usually intravenous or subcutaneous ketamine, after which the patient is switched to an equipotent oral dose of ketamine. The effective daily dosages ranged from (approximately) 45 mg to 1000 mg[18,19]. There was no consistent dose–response relation. The number of divided doses necessary for continuous analgesic effect also ranged from once daily up to a frequency of 6 times daily (on average 3–4 times daily). The duration of effect after a single dose (if there was any effect) ranged from a few hours to 24 h or more. Usually the injection fluid was used, in some cases mixed with fruit juice or syrup to mask the bitter taste[20,21].

Adverse effects

The most important adverse effects were effects on the central nervous system, such as sedation, somnolence, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision. The psychotomimetic adverse effects, such as hallucinations, were considered the most disturbing. The cause could be high peak plasma levels of ketamine due to an impaired first-pass metabolism in patient with hepatocellular carcinoma and severe hepatic disease. No adverse effects caused by long-term treatment were described. No effect on blood pressure values and heart rate[11,13].

Aim of the thesis

To evaluate the effect of the use of oral Ketamine as analgesic in Cancer patients

Patients and Methods

Study design, setting and time

This was a randomized single blind controlled clinical trial conducted at AlSader Medical city, Al Forat Al Awsat

Oncology center, Al Najaf Al Ashraf city, during the period from 1st of November 2014 to the end of September 2015.

Patients

A total of 112 patients with proved diagnosed cancer with severe chronic pain not respond to conventional analgesic treatment were enrolled in this study. Patients were randomly divided into two groups; first group consisted of 56 patients and they were assigned to receive 10 mg ketamine orally three times a day for one month, namely, ketamine group, the remaining 56 patients were assigned to receive placebo (similar preparation without ketamine) in similar dose intervals and amount, namely placebo group.

Inclusion criteria

Patients aged 18 years or more were enrolled in the study regardless their gender or duration, type and grade of their cancer.

Exclusion criteria

1) Patients aged less than 18 years.
2) Patients with recent surgical operation.
3) Patients with obvious surgical or medical complication.
4) Patients recently received chemotherapy or radiotherapy.

Ketamine and placebo solution preparation and doses

A ketamine solution was used for preparation of oral ketamine solution, a vial of 10 ml, 5% ketamine was diluted by 1 in 10 with 70 ml of 5% glucose water and 20 ml of 20% hypertonic solution to get the desired solution with 0.5% ketamine with 5 mg ketamine per ml. Then the patients asked to take 2 ml of this solution orally three times a day. The patients were trained by the researcher how to take the solution by using a disposable 5 ml syringe and to draw 2 ml at each dose. Similar technique was used for receiving the placebo solution which composed of 80 ml glucose water 5% and 20 ml of 20% hypertonic solution. The glucose solutions were used in preparation to overcome the undesirable taste of the ketamine solution, while in placebo solution it was used to approximate the taste of ketamine solution.

Tools of the study

Data collection sheet

Which gathered the demographic and clinical data of the patients?

Numeric analgesic scale

NAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations. The pain NAS is a continuous scale comprised of a horizontal (HNAS) or vertical (VNAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme.

The pain NAS is self- completed by the respondent. The respondent is asked to place a line perpendicular to the NAS line at the point that represents their pain intensity. Scoring. Using a ruler, the score is determined by mea suring the distance on the 10-cm line between the —no pain anchor and the patient‘s mark, providing a range of scores from 0 –10.

Score interpretation

A higher score indicates greater pain intensity. Based on the distribution of pain NAS scores in postsurgical patients (knee replacement, hyster- ectomy, or laparoscopic myomectomy) who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the pain NAS have been recommended: no pain (0 – 0.4 cm), mild pain (0.5–4. 4cm).

Assessment of patients and follow up

At baseline all patients were interviewed and their demographic and clinical data were reported and they asked to rate their pain according to the Numeric analogue scale at each visit.

Statistical Analysis

Data were entered and analyzed by using the statistical package for social sciences (SPSS) software for windows, version 22, IBM, Chicago, 2014. Descriptive statistics were presented as mean, standard deviation , frequencies (no.) and proportions (%). Appropriate statistical tests were applied accordingly and the level of significance (P.value) set at ≤ 0.05. The results then presented in tables and or figures.

Results

A total patients 112 with different types of cancers and had pain of a high grade and failed to respond to traditional analgesia. They were divided into two groups, with 56 patients in each group. First group, namely, ketamine group and they received ketamine 10 mg 3 times a day. The second group assigned to receive placebo substance 4 patients in group one and 7 patients in group two were missed to follow up after initiation of treatment, and the remaining patients who complete the study were 52 in ketamine group and 49 patients in Placebo group.

Demographic characteristics

The baseline demographic characteristics of the studied groups are shown in table 1. In both groups, the majority

of patients aged more than 40 years. The mean age of patients was 53.5 ± 7.3 (range: 28 – 65) years in ketamine group and it ranged (26 – 63) years in placebo group, furthermore distribution of the age into age groups is shown in the same table. Males and females about equally distributed in both groups.

The mean body mass index (BMI) was 27.4 ± 3.7 (range: 24.6 – 39.1) kg/m2. in ketamine group and 28.6 ± 5.2 (range: 23.7 – 41.3). The distribution of BMI into three categories, revealed that in ketamine group, 22 patients had normal BMI (24.6, 24.8 kg/m2), 17 patients(32.7%) were overweight (BMI>25 kg/m2) and 13 patients were obese (25%), the corresponding numbers in placebo group were 40.8%, 28.6% and 30.6% , respectively. The mean disease duration of the patients was 1.3 ± 0.8 year (range: 13) years in ketamine group and 1.26± 1.1 in placebo group.

Table 1 Baseline demographic characteristics of the studied group

		Ketamine group (n= 52)		Placebo group (n = 49)		*P. value*
		No.	%	No.	%	
Age (year)	< 40	11	21.2	10	20.4%	0.54
	41 - 50	18	34.6	15	30.6%	
	51 - 60	13	25.0	11	22.4%	
	> 60	10	19.2	13	26.5%	
	Mean ± SD	53.5 ± 7.3		54.4 ± 8.2		0.68
	range	28 - 65		26 -63		
Gender	Male	25	48.1	26	53.1	0.76
	Female	27	51.9	23	46.9	
BMI (kg/m^2)	Normal	22	42.3	20	40.8	0.45
	Overweight	17	32.7	14	28.6	
	Obese	13	25.0	15	30.6	
	Mean ± SD	27.4 ± 3.7		28.6 ± 5.2		0.77
	range	24.6 – 39.1		23.7 – 41.3		
Disease duration (year)	*Mean ± SD*	1.3 ± 0.8		1.26 ± 1.1		0.82
	Range	1 – 3 year		1 - 3		

Assessment of the patients and follow up

In Placebo group all patients at baseline had the higher NAS of 10, so as the ketamine group after initiation of treatment dramatic change had been reported at each visit in ketamine group. After initiation of 30 mg of ketamine three times a day the NAS assessed at each visit, it had been found that the mean NAS score reduced to 9.2 ± 3.1at first visit, and there was dramatic continuous reduction in mean NAS score at the subsequent visits to reach 1.6 at the 7 th visit, the mean reduction in NAS score at initiation of treatment was only (0.8) at first visit to reach 8.4/10 at the 7th visit and fixed at this level in the subsequent 3 visits (to the end of follow up period) with highly significant change (P<0.001) in the 3rd visit to the last visit, while the change at the first two visits was statistically insignificant (P>0.05), (table 2 and figure 1) No similar changes had been found in placebo group where no obvious change reported in NAS at each visit, and the mean NAS still fluctuated between the maximum score of 10 and 9.3 leading to highly significant difference between groups after the 2nd visit. From other point of view, the change in mean NAS of patients in ketamine group reported at each visit was significantly lower than that of previous visit, while not significant change in placebo group, table 1 figure 1 demonstrates these findings.

Table 2 Change in mean VAS score of the patients at the subsequent visits

Visit	No. of patients	Ketamine group (n= 52)	Placebo group (n = 49)	*P.value*
		VAS/ Mean ± SD	VAS/ Mean ± SD	
		10.0 ± 0.0	10.0 ± 0.0	1.0
1st visit	48	9.2 ± 3.1	9.8 ± 0.0	0.32
2nd visit	52	7.1 ± 4.5	10.0 ± 0.0	< **0.001**
3rd visit	52	6.4 ± 4.5	9.7 ± 0.3	< **0.001**
4 th visit	47	3.2 ± 4.5	9.6 ± 0.4	< **0.001**
5 th visit	46	2.1 ± 4.5	10.0 ± 0.0	< **0.001**
6 th visit	52	1.7 ± 4.5	9.3 ± 0.6	< **0.001**
7 th visit *	52	1.6 ± 1.0	9.4 ± 0.8	< **0.001**
** The values approximately fixed in the next 3 visits 8-10*				

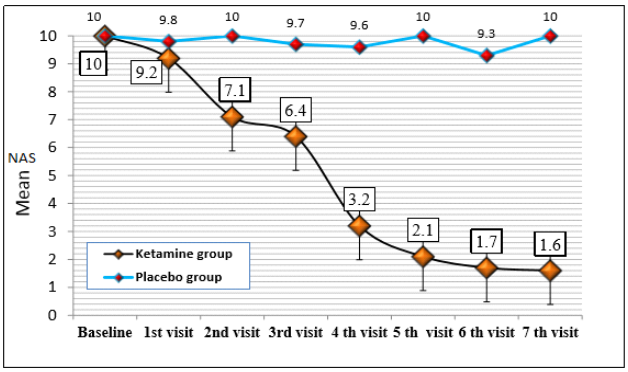

Figure 1 Comparison of changes in mean NAS score of the studied groups

Changes in doses of Ketamine

Out of the 52 patients who received Ketamine, 39 patients not respond to treatment till the 3rd visit and they needed to increase the interval or the dose of treatment so that the mean doses needed was 112.5 ± 30 mg/day; in 7 of those patients (3 males and 4 females) the dose interval reduced and the patients received ketamine 6 hourly until reached no pain status in the next two visits and the dose fixed at this level, other 32 patients still suffering severe pain despite the increase in the number of doses to 4 times a day and therefore the

dose increased accordingly with a mean dose reached to 129.4 ± 40 mg/day at the 4th visit. In the next visits as it shown in table 3 the mean dose of ketamine ranged 129.4 ± 40 to 163.0 ± 10 mg/day depending on the number of patients who needed to increase the number of doses or amount per each dose.

Further distribution of the number of patients who needed to further ketamine doses or to increase dosage is shown in table 4, while details of number of patients who get benefit of the same doses of previous visit are shown in tables 4 and 5.

Table 3 Doses of Ketamine used at subsequent visits

Visits	No. of patients	Dose Mean ± SD mg/day	mean Number of doses/day
Baseline (pretreatment)	52	-	-
1st visit	48	90.0 ± 0.0	3.0
2nd visit	52	112.5 ± 30	3.0
3rd visit	52	129.4 ± 40	3.2 ± 0.4
4 th visit	47	140.6 ± 35	3.2 ± 0.4
5 th visit	46	142.4 ± 42	3.2 ± 0.4
6 th visit	52	139.4 ± 28	3.2 ± 0.4
7 th visit	52	139.4 ± 32	3.2 ± 0.4
8 th visit	44	145.0 ± 12	3.2 ± 0.4
9 th visit	41	141.2 ± 10	3.2 ± 0.4
10 th visit	23	163.0 ± 10	3.2 ± 0.4

Table 4 Number of patients received different doses of Ketamine used at subsequent visits

Visit	Dose/day (mg)					Total No. of patients
	90	120	160	200	240	
Baseline (pretreatment)	52	0	0	0	0	52
1st visit	48	0	0	0	0	48
2nd visit	13	39	0	0	0	52
3rd visit	13	17	22	0	0	52
4 th visit	9	16	13	9	0	47
5 th visit	11	14	12	5	4	46
6 th visit	13	17	13	5	4	52
7 th visit	13	17	13	5	4	52
8 th visit	10	12	13	5	4	44
9 th visit	11	12	10	4	4	41
10 th visit	3	5	7	4	4	23

Table 5 Number of patients who get benefit on the same previous doses of ketamine

	Total number of patients on the current dose	No. of patients get benefit on that dose
90 mg	52	13
120 mg	39	17
160 mg	22	5
200 mg	9	5
240 mg	4	4

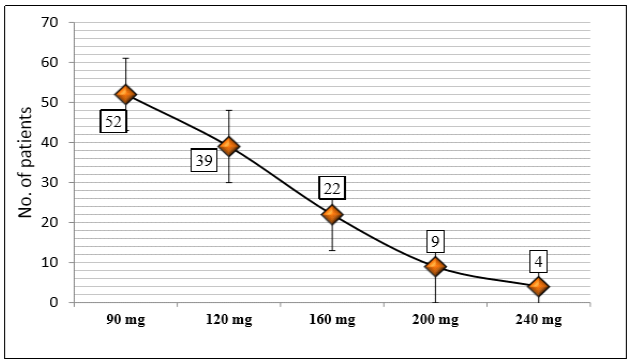

Figure 2 Number of patients who needed specific doses of ketamine

Table 6 Changes in the severity of pain according to NAS score rated by patients

NAS scale	Total No. of patients	Severe and very severe	Moderate	Mild	No pain
Baseline	52	52	0	0	0
1st visit	48	43	4	1	0
2nd visit	52	22	18	10	2
3rd visit	52	10	9	22	11
4 th visit	47	6	6	22	16
5 th visit	46	4	2	6	38
6 th visit	52	4	0	0	52
7 th visit	52	4	0	0	52
8 th visit	44	4	0	0	40
9 th visit	41	4	0	0	37
10 th visit	23	4	0	0	19

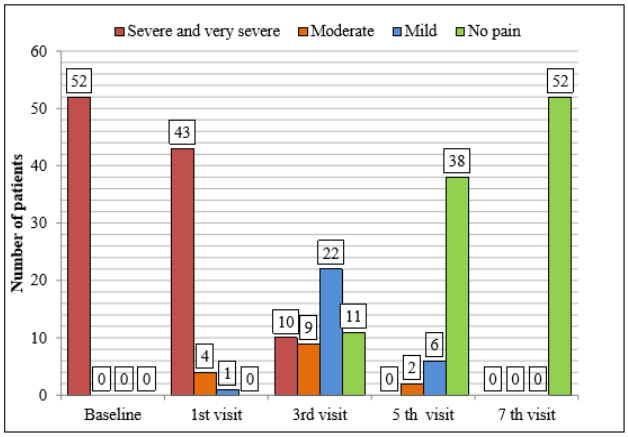

Figure 3 Comparison of numbers of patients according to severity of pain rated at subsequent visits

Change in severity of pain it is worth mentioning that no change in severity of pain had been reported in placebo group till the end of study the patients suffered the worst and very severe pain. From other point of view, table 6 shows the change in severity of pain at each visit and the number of patients with each category of pain scale in ketamine group; at baseline all the patients had the worst pain, at the first visit after initiation of treatment, where 48 patients attend this visit, 43 had severe and very severe pain scores, 4 had rated their pain as moderate and only one patient rated as mild pain, with

the subsequent visits it had been noticed that the number of patients with severe or very severe pain reduced dramatically with regard to those with less severe rates, and the 5 th visit none of the patients rated his/her pain as severe or very severe, 2 patients with moderate pain and 6 with mild pain, while majority of the patients (38/52) reported no pain. At the 6 th visit till the end of the study only 4 patients still have severe pain despite the maximum dose of ketamine they were received, and get no benefit.

Discussion

The treatment goal of cancer pain is to try to balance the analgesic effects with the adverse effects. The addition of adjuvant therapies to the armamentarium in pain management has allowed clinicians to treat pain in a multimodal approach incorporating medications with different mechanisms of action in order to improve its efficacy, thus minimizing side effects[(22)]. Although, the use of ketamine as an analgesic is now generally accepted. Oral formulations of ketamine are not commercially available, therefore the parenteral formulation is given as an oral solution or an extemporaneous preparation is made[(23)].

The current clinical trial tried to present the available clinical data as a basis for defining the potential role of the use of oral ketamine in chronic pain management in patients with different types of cancer who were not respond to conventional treatment. For this purpose a total of 112 patients with different cancer types were enrolled and randomly allocated in two groups either to receive oral ketamine or not (placebo). Only 101 patients were completed the study while 52 in ketamine group and 49 in placebo group, the missed patients were excluded from the study. The demographic characteristics of the patients including the age gender, BMI and disease duration were not statistically significantly different between both groups indicated the well randomization of the studied groups. The current study found that at baseline assessment all patients in both groups had the higher pain score according to the NAS with a score of 10. After initiation of treatment a dramatic change had been reported at each visit in ketamine group with 10 mg of ketamine orally three times a day. In ketamine group the mean NAS score reported to be continuously reduced at each subsequent visit to reach 1.6 at the 7 th visit and fixed at this level in the subsequent 3 visits (to the end of follow up period) with highly significant change ($P<0.001$). While no significant change in NAS of the patients of the placebo group and the mean NAS still fluctuated between the maximum score of 10 and 9.3, leading to highly significant difference between groups after the 2nd visit. From other point of view, the change in mean NAS of patients in ketamine group reported at each visit was significantly lower than that of previous visit, while no similar change reported in the placebo group.

From other point of view, some patients in ketamine group not respond to the initial dose of oral ketamine, thus the interval increased to 4 times a day and in some other patients the doses were increased as they not respond even after increasing the interval, and the dose reached to 60 mg/day and fixed at that level, however, no other patients needed more increase neither in the dose nor in the interval. The patients then re assessed in the subsequent visits and all were at NAS of zero till the end of study. From other point of view, at baseline all patients had the worst pain after initiation of ketamine and at the subsequent visits there were significant change in the severity of pain from severe and very severe toward the mild grades or no pain. Findings of the current study no doubt proved that oral ketamine had a significant ameliorating effect in the management of severe cancer pain. It is worth mentioning that no adverse effect or intolerance reported in our patients in ketamine group. To best of our knowledge this the first study concerned with the use of injectable ketamine as an oral administration in the management of cancer pain, at least in Najaf city. However, findings of the current study are supported by previous clinical trials. An earlier study was conducted by Hoking et al in 2003 (UK) [(24)] reported similar findings and proved the effectiveness of oral ketamine in management of severe chronic pain, additionally, Hoking et al confirmed that effective oral doses are often less than parenteral doses of ketamine. As a result of the higher doses needed in parenteral routes that need hospitalization the need for oral dosing has arisen [(25)].

Conclusion

- Oral Ketamine of 30 mg three times a day is effective agent for the management of chronic severe pain in cancer patients.
- Oral ketamine was well tolerated and no obvious adverse effect reported among the patients.

Recommendation

- Oral ketamine 30 mg three times a day is suggested for the management of severe pain in cancer patients not respond to conventional treatment.

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