한국 호스피스 · 완화의료학회지
Korean J Hosp Palliat Care Vol. 19, No. 3, 249-255, September 2016
pISSN 1229-1285 · eISSN 2287-6189
http://dx.doi.org/10.14475/kjhpc.2016.19.3.249

Original Article

Factors Associated with Ketamine Use in Pancreatic Cancer Patient in a Single Hospice Center

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Purpose: Up to 90% of pancreatic cancer patients suffer from neuropathic pain. In a palliative care setting, pain control in pancreatic cancer patient is one of the major goals. Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist, effective in neuropathic pain. Additionally, there have been studies about the opioid sparing effect of ketamine. This study was held in the palliative care unit among pancreatic cancer patients to determine the factors related to ketamine use and the opioid sparing effect. **Methods:** The medical records of pancreatic cancer patients admitted to St. Mary's hospital palliative care unit between January, 2013 and December, 2014 were reviewed. Patients were divided into 2 categories according to ketamine use. Also, opioid use before and after ketamine use was compared in the ketamine group. **Results:** Compared to the non-ketamine use group, patients in the ketamine group required a higher dose of opioid. The total opioid dose, daily opioid dose, number of daily rescue medications, and daily average rescue dose were statistically significantly higher in the ketamine group. The opioid requirement was increased after ketamine administration. **Conclusion:** In this retrospective study, ketamine was frequently considered in patients with severe pain, requiring higher amount of opioid. Studies about palliative use of ketamine in a larger number of patients with diverse types of cancer pain are required in the future.

Key Words: Ketamine, Palliative care, Morphine, Cancer pain

INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer related death in the world, and up to 90% of patients suffer from cancer related pain, mostly neuropathic pain (1). The neuropathic character of pancreatic cancer pain is due to neurotrophism and infiltration of nerves, and invasion of the perineurium increasing as the cancer becomes undifferentiated (2-6). Since the major goal of palliative care for pancreatic cancer patients is pain control, strong opioid is recommended as a first line drug for pancreatic cancer pain (7). In addition, adjuvant pain medications are required to control somatic and neuropathic pain of pancreatic cancer pain (8). Among them, ketamine is widely used as adjuvant medication for neuropathic pain (9). Ketamine produces analgesic effects through competitive inhibition of N-methyl-D-aspartate (NMDA) receptor (10). Ketamine is known for its opioid sparing effect in postoperative patients but whether ketamine has an opioid sparing effect in cancer pain is still controversy (11). In a recent randomized control trial study, investigated by Hardy et al., has shown that ketamine did not have opioid sparing effect for chronic uncontrolled cancer pain (12). However, ketamine is still frequently prescribed in palliative practice, especially in patients with high dose opioid or patients with severe neuropathic pain. However, the dosage indications, and routes of

Received May 6, 2016, Revised August 8, 2016, Accepted August 12, 2016

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administration of ketamine differ among studies, and no current published guidelines or dosage nomograms are available (13).

The purpose of this study is to find the variables related to ketamine use in a homogenous population consisting of terminal pancreatic cancer patients and to examine opioid sparing effects of ketamine.

METHODS

1. Study design and data collection

This is a retrospective observational study from a tertiary hospice and palliative care unit inpatients in South Korea from January, 2013 to December, 2014. We collected medical records for the patients who were diagnosed with terminal pancreatic cancer. Some of the patients were admitted several times during 2 years so we reviewed total admission period from 2013 to 2014 of each patient. This study was reviewed with the approval of the Institutional Review Board (IRB) (No.: KC15RISI0720).

2. Opioid and ketamine use, dosage, and monitoring

Opioid administration was available by oral, intravenous, transdermal, and sublingual types. Ketamine administration was carried out only through intravenous injection. All opioid medications for pain control was converted to oral morphine equivalent (OME) dose based on NCCN cancer pain management guidelines (14).

Average pain intensity in the last 24 hours was assessed every morning round, and opioid dose was titrated to balance analgesia and adverse effects with other adjuvant medications. Pain intensity was classified into 3 categories 1) tolerable pain control, 2) moderate pain control with additional pain control required, 3) poor pain control. In patients of category 2) and 3), opioid dose escalation and adjuvant pain medications were considered according to pain type and intensity. Especially when patients were suffering from severe neuropathic pain, we considered ketamine use ahead of opioid escalation. Ketamine dose was started from 25 mg and escalated by 25 mg, according to the daily reassessment of pain.

We calculated each patient's total basal opioid dose and mean opioid dose per day in every admission. In addition, we measured the total rescue opioid dose, the number of rescue opioids per day, and the daily rescue opioid dose. For the ketamine use group, we compared rescue medication requirements and opioid requirements before ketamine use and 24 hours after ketamine was started. To examine the development of delirium by ketamine, we also reviewed medical records and haloperidol prescriptions on the assumption that haloperidol is usually administrated for delirium management (15). We could not exclude haloperidol dose for other uses, such as nausea and insomnia.

3. Statistical analysis

Descriptive analysis was used to evaluate the general characteristics of the study population. Independent t-test, Mann-Whitney test, and chi square tests were used to compare the ketamine and non-ketamine group. Univariate and multivariate logistic regression analysis was performed to examine the variables related to ketamine use. The difference between morphine dose before and during ketamine use was evaluated by paired t-test. We used Statistical Analysis System (SAS) version 9.3 for statistical analysis.

RESULTS

1. General characteristics of the study population

The total number of inpatients in the Palliative care unit from 2013 to 2014 was 1,600. Among them, the total number of patients diagnosed with pancreatic cancer was 111 and total number of patients who were administrated with ketamine was 34. The average age of patients in this study was 71.0±10.7. 54 patients were female while 57 patients were male. Patients unable to intake orally were 24 (21.6%) and those with a PPS (Palliative Performance Scale) score of less than 30 were 25, 40～50 was 59, ＞60 was 27. The most common metastasis site was the liver, with 27 patients. Opioid requirements were assessed by total basal opioid dose (0～5080.0), opioid dose per day (0～148.8), total rescue opioid dose (0～1846.7), number of rescue opioid uses per day, rescue opioid dose per day (0～113.8). Also, ketamine use was assessed by total ketamine dose, and mean ketamine dose per day. Delirium, one of the most common psychotomimetic effects of ketamine, was observed in 7 (20%) of patients in the ketamine group. Haloperidol was used to control ketamine side effect such as delirium, vivid hallucination etc. (0～960.0). Not all of the patients reviewed in

this study expired while receiving inpatient care and survival time was estimated among the ones who expired. The mean survival time was 25 days.

2. Comparison of clinical variables, opioid use, and haloperidol use between ketamine and non-ketamine use patients

We compared the variables related to ketamine and non-ketamine use. The average age of the ketamine group was 66.9±11.0 and the non-ketamine group was 72.9±10.1, which was not statistically significant. Among the variables, the ones related to opioid were significantly different between the 2 groups. The total basal opioid dose was 465.5 (5, 5080) in the ketamine group and 120.0 (0, 1846) in the non-ketamine group. The opioid dose per day was higher (46.9±37.5) in the ketamine group when compared to the non-ketamine group (18.4±17.6). The total rescue opioid dose was 158.0 (8, 1846) in the ketamine group and 48.0 (0, 1706.7) in the non-ketamine group. The number of rescue opioids per day was 4.5±0.6 and the non-ketamine group was 2.6±1.4. The rescue opioid dose per day was 17.1 (2.0, 113.8) in the ketamine group and 6.9 (0, 77.5) in the non-ketamine group. The total haloperidol dose per day did not show a significant difference among the 2 groups. The survival time of the patients who expired during the observation period was 24.5 (6, 389) in the ketamine group and 25.0 (0, 450) in the non-ketamine group, which was not statistically significant (Table 1).

3. Clinical factors associated with ketamine use

The relevant factors associated with ketamine use were

Table 1. Comparison between Ketamine and Non-Ketamine Group.

Variables	Ketamine group (N=34)	Non-Ketamine group (N=77)	P value
Age*	66.9±11.0	72.9±10.1	0.006
Sex‡			0.506
Female	17 (50%)	37 (48%)	
Male	17 (50%)	40 (52%)	
Oral intake‡			0.458
None	8 (23%)	16 (21%)	
Liquid diet	20 (59%)	43 (56%)	
Regular diet	6 (18%)	18 (23%)	
Palliative performance scale‡			0.269
≤30	5 (15%)	20 (26%)	
40～50	18 (53%)	41 (53%)	
≥60	11 (32%)	16 (21%)	
Metastasis‡			
Bone	5 (15%)	8 (10%)	0.514
Peritoneum	10 (29%)	25 (32%)	0.749
Liver	21 (62%)	46 (60%)	0.841
Opioid/Ketamine use			
Total basal opioid dose (mg)†	465.5 (5, 5080)	120.0 (0, 1846)	0.001
Opioid dose per day (mg)*	46.9±37.5	18.4±17.6	<0.001
Total rescue opioid dose (mg)†	158.0 (8, 1846)	48.0 (0, 1706.7)	<0.001
Number of rescue opioid per day*	4.5±0.6	2.6±1.4	<0.001
Rescue opioid dose (mg) per day†	17.1 (2.0, 113.8)	6.9 (0, 77.5)	<0.001
Total haloperidol dose (mg)†	15.0 (0, 960)	12.5 (0, 732.5)	0.211
Haloperidol dose per day (mg)*	8.3±7.8		
Survival time from first referred to PCU (days)†	24.5 (6, 389)	25.0 (0, 450)	0.671

Values are presented as mean±SD, number (%), or median (Q1, Q3).
Opioid dose was adjusted by oral morphine equivalent (OME).
Total Haloperidol dose includes both basal and rescue administration.
PCU: Palliative Care Unit.
*Statistic analysis by independent t-test, †Statistic analysis by Mann-Whitney test, ‡Statistic analysis by Chi square test.

Table 2. Clinical Factors Associated with Ketamine Use.

Variable	Univariate (95% CI)	P value	Multivariate (95% CI)	P value
Age	0.95 (0.910～0.987)	0.010	0.951 (0.897～1.009)	0.096
Sex (male)	0.92 (0.413～2.074)	0.835		
PPS	1.05 (0.994～1.064)	0.110		
Presence of metastasis	1.67 (0.505～5.496)	0.401		
Oral intake (able)	0.85 (0.325～2.237)	0.746		
Total basal opioid dose (mg)	1.00 (1.001～1.003)	0.001	1.00 (0.999～1.002)	0.324
Opioid dose per day (mg)	1.05 (1.022～1.072)	<0.001	1.10 (1.037～1.164)	0.001
Number of rescue opioid per day	1.62 (1.220～2.145)	<0.001	1.83 (1.267～2.653)	0.001
Rescue opioid dose per day (mg)	1.04 (1.013～1.071)	0.004	0.89 (0.827～0.962)	0.003
Total haloperidol dose (mg)	1.00 (0.999～1.005)	0.237		
Haloperidol dose per day (mg)	1.06 (0.997～1.121)	0.064		

PPS: Palliative Performance Scale was standardized.
Standardized scale=(raw scaleaverage)/standard deviation.
Binary logistic regression analysis.
P<0.01, P<0.001.

Table 3. Comparison of Mean Morphine Dose before and after Ketamine Use.

Variable	Mean opioid dose before ketamine use	Mean opioid dose during ketamine use	P value
Morphine dose (mg)	76.1 (±64.5)	89.6 (±80.9)	0.039

Morphine dose based on intravenous morphine.

based on a univariate and multivariate binary logistic regression model (Table 2). Age showed a significant association with ketamine use (OR: 0.95, 95% CI: 0.910～0.987) with total basal opioid dose (OR: 1.00, 95% CI: 1.001～1.003), opioid dose per day (OR: 1.05, 95% CI: 1.022～1.072), number of rescue opioid per day (OR: 1.62, 95% CI: 1.220～2.145), and rescue opioid dose per day (OR: 1.04, 95% CI: 1.013～1.071). Sex (male), PPS, presence of metastasis, possible oral intake, total haloperidol dose, and haloperidol dose per day showed no significant relationship with ketamine use. In multivariate analysis, only opioid dose per day (OR: 1.10, 95% CI: 1.037～1.164), number of rescue opioids per day (OR: 1.83, 95% CI: 1.267～2.653), and rescue opioid dose per day OR: 0.89, 95% CI: 0.827～0.962), showed significant association. Particularly, the rescue opioid dose per day showed reverse OR in multivariate analysis.

4. Comparison of mean morphine dose before and after ketamine use

We compared daily mean opioid requirements before and during 24 hours after ketamine administration. The mean morphine dose was significantly increased from 76.1 (±64.5) to 89.6 (±80.9) after ketamine administration (P value: 0.039) (Table 3).

DISCUSSION

In this study, ketamine use in pancreatic cancer patients was positively correlated with variables related to opioid use, such as opioid dose per day, number of rescue opioids per day, and rescue opioid dose per day in multivariate logistic regression. This can be understood in a way that patients requiring a high amount of opioid were more likely to use ketamine. Also PPS had a significant positive correlation with ketamine use, and age had a significant negative correlation with ketamine use. It can be referred that in younger pancreatic cancer patients with higher PPS, ketamine is considered frequently in controlling neuropathic pain compared with older patients with lower PPS.

There are many previous studies on opioid sparing effect of ketamine. One of the latest randomized double blind study in 2012 with 185 participants, carried out by Hardy, ketamine

was injected subcutaneously with dose titration in refractory chronic pain secondary to cancer or its treatment (12). There was no statistically significant difference in pain intensity after 5 days of subcutaneous ketamine and placebo injections. We did not have a placebo in our study since it is a retrospective study carried out by reviewing medical charts. In our study, to determine whether ketamine has an opioid sparing effect, the opioid requirements before and after ketamine use were compared since we could not compare the daily pain intensity score due to several missing records. The result of our study showed that opioid usage was increased after ketamine use. This could be due to the fact that this study was conducted among terminal patients receiving inpatient care. Most of the patients requiring admission are suffering from severe ongoing pain due to symptom progression and analgesics are likely to increase to control pain. In this circumstance the use of ketamine could have decreased the amount of additionally required opioid, relatively speaking. The study by Hardy used subcutaneous injection of ketamine, 100, 300, 500 mg, and in this study ketamine was started in a relatively small dose of 25 mg/24 hrs continuous infusion and was increased by 25 mg with at least 24 hrs interval. Also in the study by Hardy, ketamine was titrated during 5 days. In our study, we did not restrict the use of ketamine so many patients on ketamine used it more than 5 days. This study has its strength as a first study done in Korea with ketamine use in continuous intravenous infusion in a single hospice inpatient center.

Another randomized control study in 1999 carried out by Lauretti was conducted to evaluate oral ketamine as an adjuvant to oral morphine therapy in 60 cancer patients in outpatient setting (16) The goal was to keep visual analog scale scores at less than 4 and the ketamine group received 0.5 mg/kg oral ketamine at 12-h intervals while control group received additional 10 mg of morphine in 12-h intervals. In the study by Lauretti, ketamine group had lesser opioid consumption compared to the control group but there was no difference in pain intensity. Since control group received additional morphine instead of ketamine, comparison between ketamine group and control groups may be inappropriate to compare opioid sparing effect of ketamine. On the contrary, our current study was conducted among admitted patients with intravenous ketamine, and did not limit dose of opioid. Also, our study was conducted in homogenous population consisting of pancreatic cancer patients with neuropathic pain.

Salas conducted a study to compare the effect of ketamine-morphine combination to morphine alone among 20 patients (11 ketamine, 9 placebo) admitted in several palliative care units. This study has similarities with ours in a way that it was held among hospitalized patients. In study of Salas, ketamine was intravenously injected 0.5 mg/kg/day with addition of 1 mg/kg/day (17). This previous study showed no difference in pain intensity between ketamine and control group and they proposed the hypothesis that terminal cancer patients have been previously exposed to analgesics for a long period which alters the metabolism of ketamine. Ketamine is mostly metabolized by cytochrome P450 enzymes, primarily by CYP2B6 (18) We agree on this hypothesis and our study also started ketamine on relatively safe, low dose and increased it with small amounts and this also could have been a cause of lack of effectiveness.

Delirium was observed in 7 patients in the ketamine group and the incidence of delirium was about 20%. However, since this study is a retrospective observational study, other possible cause of delirium, such as morphine or other adjuvant medication or an underlying condition, were not fully considered (19).

There are limitations to our study. This study is a retrospective observational study with a relatively small number of patients and pain score assessments were not included. A prospective study with large population considering other types of cancer is required. Furthermore, the effect of adjuvant medications, other than opioid, was not excluded in the analysis. In cancer pain control, adjuvant medications, besides opioid, play an important role. In this study, of the 34 patients in the ketamine group, 10 patients were on adjuvant medications other than ketamine, such as NSAIDS (N=9) or gabapentin (N=2) or TCA (N=2) and these medications could have created a bias in the analysis of the opioid sparing effect of ketamine. Also, there were 6 patients who received nerve block treatment prior to admission, which could have affected opioid requirements. The effects of adjuvant medication and subsequent nerve blocks should be considered in future larger studies on ketamine effects.

Despite these limitations, this study has the strength as a first domestic study conducted with inpatients in a single palliative care unit. All patients were monitored under the

same circumstances with continuous intravenous ketamine infusion during 24 hours with dose modification with at least 24 hourly intervals except for patients with severe side effects. Since there are no current guidelines regarding ketamine dose for cancer pain, we started ketamine from 25 mg/day, escalating by 25 mg according to our experience in the palliative care unit, which is a relatively safe dose in terms of palliative care. A guideline for ketamine use is needed in the future.

Although patients did not have the benefit of using lesser amount of opioid to control pain with the administration of ketamine, this does not mean that ketamine has no opioid sparing effect. Opioid sparing effect of ketamine is still debatable and further randomized studies on larger number of patients with more sophisticated method of ketamine administration are required.

요 약

목적: 췌장암 환자의 90% 이상이 신경성 통증을 앓는 것으로 알려져 있으며 말기 췌장암 환자에서는 통증조절이 매우 중요한 목적 중 하나이다. 케타민은 NMDA 수용체 길항제로서 신경통에 효과가 있는 것으로 알려져 있으며 마약성 진통제의 요구를 감소시켜주는 효과에 대한 연구들이 앞서 진행된 바 있는 약물이다. 본 연구에서는 완화병동에 입원한 췌장암 환자들을 대상으로 케타민의 사용과 관련된 항목들을 알아보고 마약성 진통제를 줄여주는 효과를 나타내는지에 대해 진행한 연구이다.

방법: 2013년 1월부터 2014년 12월까지 서울성모병원 완화의학과에 입원한 췌장암 환자 111명에 대한 의무기록을 통하여 케타민을 사용한 그룹(34명)과 사용하지 않은 그룹(77명)에 대해 케타민 사용과 관련된 요인 및 사용 후 모르핀을 포함한 마약성 진통제의 용량 변화를 분석하였다.

결과: 케타민을 사용한 군에서 사용하지 않은 군에 비하여 총 기본 마약성 진통제 사용량(P value 0.001), 하루에 사용한 마약성 진통제의 용량(P value＜0.001), 평균 구제 약물의 용량(P value 0.001), 하루 평균 구제 약물 사용 횟수(P value 0.001), 하루 평균 구제 약물을 용량(P value＜0.001)이 더 높게 나타났다. 케타민 사용 전후를 비교한 결과 마약성 진통제는 케타민 사용 전(76.1 (±64.5))에 비하여 후(89.6 (±80.9))에 유의하게 증가한 것으로 확인되었다.

결론: 후향적으로 의무기록 분석을 통해 이루어진 본 연구에서는 더 많은 용량의 마약성 진통제를 요한 환자들이 케타민을 사용한 경향이 확인되었다. 이와 더불어 케타민을 사용함으로 인해 마약성 진통제 요구량이 감소하는 경향은 확인할 수 없었다. 차후 더 많은 환자들과 다양한 종류의 암성 통증을 대상으로 한 완화의료적 목적의 케타민 사용에 대한 연구가 요할 것으로 생각되며 케타민의 사용에 관련된 가이드라인에 대한 논의가 요할 것으로 생각된다.

중심단어: 케타민, 완화의료, 모르핀, 암성통증

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