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Atorvastatin calcium tablets effectively alleviated the morphine tolerance in the management of cancer pain

LF. Quan[1,2] and J. Fan[1*]

[1]Department of Oncology, the Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, China
[2]Department of Oncology, Zigong First People's Hospital, Zigong, Sichuan 643000, China

► ***Short report***

***Corresponding author:**
Juan Fan, Ph.D.,
E-mail:
fanjuan_edu@hotmail.com

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ABSTRACT

Background: The aim of this study was to elucidate the efficacy of atorvastatin calcium tablets to relieve morphine tolerance in cancer pain patients. ***Materials and Methods:*** Cancer patients were randomized into the control and observational groups. The morphine dose increment time (T2), the onset time of morphine (T1), the titration dose and pain management rate in the two groups were evaluated and compared. Adverse events such as nausea, vomiting, constipation and respiratory depression were recorded. The impact of different treatments on the life quality of patients was assessed with Karnofsky performance status (KPS) score. Liver function and hematologic toxicities of different treatment was evaluated and examined. ***Results:*** The duration of T2 was significantly prolonged in the observational group (P=0.04), while the time of T1 as well as the titration dose showed no significant difference between the two groups (P>0.05). The adverse effects were slighter in the observational group (P>0.05). There was no respiratory depression case in either group. The life quality in two groups of patients showed no difference (P>0.05). Liver function and hematologic toxicitie results indicated that the combined treatment showed no extra damage to liver function and had no severe haematologic toxicity compared with the control. ***Conclusion:*** The combined treatment of atorvastatin calcium tablets and morphine effectively prolonged the time between morphine dose increments, alleviating the morphine tolerance with high safety in cancer pain patients, which may provide clues for morphine tolerance treatment in cancer pain management.

INTRODUCTION

Pain is a common symptom in cancer patients, affecting the life quality of patients from both the physical and emotional aspects. Both cancer and anti-cancer therapy can cause pain of patients [1, 2]. Therefore, it is imperative to optimize the treatment strategies and improve the cancer pain management.

Opioids are the leading drugs of cancer pain treatment, and morphine as a first-line opioid is available in multiple formulations [1, 3]. However, due to the opioid tolerance, higher dose of morphine is required to sustain the satisfactory effect, which reduces the analgesic efficacy, increases the side effects such as nausea, constipation and respiratory depression, and economic burden to the patients [4, 5]. The mechanism of opioid tolerance is complex and multifactorial. Factors such as down-regulation of receptors, interactions between the drug and the opioid receptors, desensitization of receptor signaling may contribute to this tolerance [6, 7]. Therefore, novel strategies are urgently to be developed for the improvement of the treatment effects.

Accumulating studies have also reported the anti-tumor properties of statins, and suggested the application of statins in the combined cancer therapy [8, 9]. Additionally, statins are revealed to suppress the phosphorylation of ERK in a number of disease such as renal cell carcinoma, Marfan syndrome and multiple myeloma [10-12], which may attenuate opioid tolerance. Atorvastatin is a frequently prescribed statins with low adverse effects, and can alleviate neuropathic pain [13, 14]. Thus, we assumed that the combined treatment of Atorvastatin and morphine may improve the antinociceptive effect of morphine and attenuate the morphine tolerance in the treatment of cancer pain.

In this study, we aimed to explore the effects of Atorvastatin Calcium Tablets in combination with morphine, which might provide novel clues for the attenuation of morphine tolerance and increment morphine consumption of cancer patients.

MATERIALS AND METHODS

Participants

The Ethics Committee of The Affiliated Hospital of Southwest Medical University has approved the protocol ((M) 2022-008). All participants signed the informed consent. Inclusion criteria: 1) aged 18 or

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older; 2) diagnosed with malignant cancers by pathologic biopsy. 3) With cancer pain, numerical rating scale (NRS) ≥3. 4) Expected life span > 6 months; 5) No known contraindications of morphine hydrochloric sustained release tablets, morphine hydrochloride tablets as well as Atorvastatin Calcium Tablets. The exclusion criteria: 1) received radiotherapy, chemotherapy, targeted therapy, immunotherapy during the study. 2) Received anti-tumor treatment that affected the pain symptoms. 3) Adverse drug reaction required to stop taking relevant drugs; 4) consciousness disorder and poor compliance, reduction of Karnofsky performance status (KPS)≥60. Totally 55 cancer patients were enrolled in this study, with 5 patients excluded, and finally 50 patients finished this research. The participants were randomly allocated into the control and observational group (n=25 per group).

Study design

Patients in the control group received morphine hydrochloric sustained release tablets (Southwest pharmaceutical co., ltd, China) and/or morphine hydrochloride tablets via titration. Patients in the observational group received Atorvastatin Calcium Tabletsin (Qilu pharmaceutical (hainan) co., ltd, China) combination with morphine hydrochloric sustained release tablets and/or morphine hydrochloride tablets.

For morphine titration, patients were administrated with 10-30 mg morphine hydrochloric sustained release tablets (fixed dose) per 12 h and/or 5-15 mg rescue dose of morphine hydrochloride tablets were received if breakthrough pain occurred at day 1 (D1). At day 2, patients were administrated with the fixed and rescue dose of day 1 (fixed) per 12 h and the rescue dose of morphine hydrochloride tablets were 10%-20% of fixed dose of day 2. The dose was accordingly adjusted to reach NRS≤ 3. The morphine titration was finished within 72 h. For Atorvastatin Calcium Tabletsin treatment, patient were orally taken with 10 mg Atorvastatin Calcium Tablets per day.

The cancer pain was assessed with NRS every 6 h during the morphine administration, and at least once a day after controlling the pain. The morphine was administrated at the same dose until the pain was relieved. The cancer pain was considered to be controlled when the NRS score was ≤ 3 and episodes of breakthrough pain in 24 h were ≤ 2, otherwise, it was regarded as exacerbated pain.

Efficacy and safety measurements

Pain management efficacy

T1 indicated the time to relieve the pain since day 1 until the day when the NRS score was ≤ 3 and less than 2 times of breakthrough pain in 24 h. T2 indicated the interval from the time when pain was considered to be controlled to the time point when pain was exacerbated and administration of increased morphine dose. The T2 was recorded by hospital, out-patient visits or telephone follow-ups (no longer than 30 days). The efficacy of pain management was calculated as the ratio of the pain controlled cases to the total cases in each group.

Relevant adverse events

All these adverse events and indexes, etc. were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [15]. Besides, for respiratory depression, respiratory rate≥12 times/min was regarded as no respiratory depression, while those <12 times/min and lower than baseline respiratory frequency was considered as respiratory depression. The life quality of patients was evaluated with the KPS scores.

Statistical analysis

The SPSS 24.0 software (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Results were shown as the mean ± standard deviation (SD). Statistical difference between two groups was analyzed by Student's t test. P< 0.05 indicated statistical significance.

RESULTS

Interval from pain control to pain exaggeration (T2), onset time of morphine (T1) and Dose of morphine treatment in each group

At the end of the follow-up, the T2 and T1 value in the control and observational groups were evaluated. The results showed that T2 in the observational group was significantly longer than that in the control group (*P*=0.04) (table 1).

Table 1 showed that the T1 value and dose of morphine titration was very close without statistical significance.

Table 1. T2, T1 and dose of morphine titration in each group.

	Control group	Observational group	*P* value
T2 (days)	10.92±6.15	15.28±8.32	0.04
T1 (days)	1.60±0.65	1.56±0.82	0.85
Dose of morphine titration (mg)	21.20±14.81	31.2±33.83	0.18

Adverse events in each group

For nausea, vomiting and constipation, the observational group showed a lower incidence compared with the control group, with no statistical difference. Additionally, both the cases were at the mild or moderate grade, no severe cases, no respiratory depression cases were found in both groups (table 2).

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Table 2. Adverse events in each group.

	Control group	Observational group	*P* value
Nausea cases (%)			0.37
Yes	10 (40%)	7 (28%)	
No	15 (60%)	18 (72%)	
Nausea Grades			
Mild or moderate cases	10	7	
Severe cases	0	0	
Vomiting cases (%)			0.37
Yes	10 (40%)	7 (28%)	
No	15 (60%)	18 (72%)	
Vomiting Grades			
Mild or moderate cases	10	7	
Severe cases	0	0	
Constipation cases (%)			0.51
Yes	7 (28%)	5 (20%)	
No	18 (72%)	20 (80%)	
Constipation Grades			
Mild or moderate cases	7	5	
Severe cases	0	0	
Respiratory depression cases (%)			
Yes	0 (0%)	0 (0%)	
No	25 (100%)	25 (100%)	

Evaluation of Karnofsky performance status (KPS) in each group

We found that KPS score reduction rate was lower in the observation group relative to the control group but with no statistical significance (table 3).

Table 3. KPS score reduction rate in each group.

Groups	KPS score reduction (%)		*P* value
	Yes	No	
Control group	7 (28%)	18 (72%)	0.50
Observational group	4 (16%)	21 (84%)	

The impact of combined treatment on liver function

We found that the AST, ALT and TBIL increase rate was the same in the observational and control groups, with no statistical significance. AST and ALT at higher grades was not found in both groups. In addition, there was a grade IV TBIL increase case in the control group, while the observational group had no TBIL increase case cases at grade II or higher. The other two TBIL increase cases were both at grade I (table 4).

The impact of combined treatment on haematologic toxicity

The changes in WBC, PLT and Hb indexes showed no significant difference between the two groups. The one case of grade IV PLT count reduction in the control group was diagnosed with advanced esophageal squamous cell carcinoma with multiple metastasis (Table 5).

Table 4. Liver function in each group.

	Control group	Observational group	*P* value
AST increase cases (%)			1.00
Yes	5 (20%)	5 (20%)	
No	20 (80%)	20 (80%)	
AST Grade			
III	1	1	
IV	0	0	
ALT increase cases (%)			1.00
Yes	2 (8%)	3(12%)	
No	23 (92%)	22 (88%)	
ALT Grade			
II	0	0	
III	0	0	
IV	0	0	
TBIL increase cases (%)			1.00
Yes	2 (8%)	1 (4%)	
No	23 (92%)	24 (96%)	
TBIL Grade			
II	0	0	
III	0	0	
IV	1	0	

Table 5. The haematologic toxicity in each group.

	Control group	Observational group	*P* value
WBC reduction cases (%)			1.00
Yes	4 (16%)	21 (84%)	
No	4 (16%)	21 (84%)	
Grade			
II	0	2	
III	3	2	
IV	1	0	
Hb reduction cases (%)			0.39
Yes	12 (48%)	9 (36%)	
No	13 (52%)	16 (64%)	
Grade			
II	4	1	
III	2	1	
IV	0	0	
V	0	0	
PLT reduction cases (%)			1.00
Yes	2 (8%)	1 (4%)	
No	23 (92%)	24 (96%)	
Grade			
II	0	1	
III	1	0	
IV	1	0	

DISCUSSION

A previous study has indicated that statins including atorvastatin calcium might be helpful in the treatment of patients with neuropathic pain [16, 17]. In this study, we used atorvastatin calcium tablets in combination with morphine tolerance for cancer pain management.

Our work found that the combined treatment of

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atorvastatin significantly attenuated the continuous increment in the dose of morphine for cancer pain management. The combined treatment increased the time interval for between two different doses of morphine administration, contributing to attenuate the morphine tolerance in cancer patients. Nausea, vomiting, constipation and respiratory depression are common side effects induced by opioid drugs in cancer pain management [5, 18]. In our study, we analyzed that no severe adverse events and poor life quality were found in the two groups, suggesting that the combined therapy with atorvastatin calcium tablets and morphine was of high safety in cancer pain management.

The changes of liver function index and hematologic toxicity showed no significant difference between the two groups. The TBIL increase grade IV case was at the advance stage of colorectal adenocarcinoma with liver metastases. Considering the liver function injury was closely related to the primary colorectal adenocarcinoma, there is little association between the liver function with the medication administrated in the two groups. Above of these suggesting that the drugs used in this study showed no evident effects on the liver function of patients. For the evaluation of hematologic toxicities, it found that the one case of grade IV PLT count reduction in the control group was diagnosed with advanced esophageal squamous cell carcinoma with multiple metastasis. The severe PLT count reduction was considered to be related to the bone narrow depression caused by bone metastasis in esophageal squamous cell carcinoma. There was no evident association with the administration of opioids with the severe PLT count reduction in this case. The results suggested that the combined treatment has no effect in hematologic toxicity compared with opioid treatment alone.

CONCLUSION

The combined treatment of atorvastatin calcium tablets effectively prolonged the time of morphine dose increment and alleviated the morphine tolerance with high safety and no adverse impact to the life quality of cancer patients compared with morphine treatment alone. The findings of this study may provide novel therapeutic strategies against morphine tolerance in cancer pain management.

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Ethical consideration: All patients signed a documented, voluntarily informed consent form. All methods were carried out in compliance with the Helsinki Declaration criteria, and the Ethics Committee of The Affiliated Hospital of Southwest Medical University has approved the protocol ((M) 2022-008).

Author contribution: Juan Fan conceived and designed the experiments. Lifeng Quan contributed significantly to the experiments and arranging data. Juan Fan and Lifeng Quan performed data analyses. Lifeng Quan wrote the draft manuscript. Juan Fan revised the manuscript. All authors read and approved the final manuscript.

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