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Evaluation of the analgesic effects of duloxetine in burn patients: An open-label randomized controlled trial

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ARTICLE INFO

Article history:
Accepted 17 October 2018

ABSTRACT

Objectives: To evaluate efficacy of addition of duloxetine to usual analgesic regimens in management of burn pain.
Methods: In a 3-week open label randomized controlled trial, burn patients were assigned to the intervention (duloxetine 60 mg/day + usual analgesic regimens) or control group (usual analgesic regimens: morphine ± acetaminophen ± gabapentin). Intensity and quality of background pain and severity of procedural pain were evaluated using neuropathic pain scale (NPS) and visual analog scale (VAS), respectively. The primary outcome measure was "intensity" item of the NPS (evaluating intensity of the background pain).
Results: Forty six patients (age: 35.5 ± 6.3 years, TBSA: 36.7 ± 15%) (23 per group) completed the study. At baseline, scores of the "intensity" item were 9.13 ± 1.42 and 9.13 ± 1.86 (P = 1) in the intervention and control group, respectively. Comparison of difference in mean changes from baseline to the end of the study showed that addition of duloxetine only significantly reduced the scores of the "intensity" {1.74 (95% CI: 0.61 to 2.86); P = 0.003}, and "hot" {1.39 (95% CI: 0.166 to 2.614) P = 0.02} items and score of the VAS {2.13 (95% CI: 1.476 to 2.784) P < 0.001}. The most reported adverse effects were nausea and insomnia in the both groups.
Conclusion: Addition of duloxetine may increase efficacy of the other analgesics in reduction of the burn pain.

1. Introduction

Pain is one of nettlesome complications of burn injury. Insufficient control of the pain in burn-injured patients may result in chronic pain syndrome, paresthesia, dysesthesia and psychological disorders such as depression and post-traumatic stress disorder in long term. Despite the extensive use of analgesics such as opioids, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) and anxiolytics, effective management of the burn pain has remained a challenging problem [1].

Acute burn pain has both components of the nociceptive and neuropathic pain [2,3]. Therefore, it can be hypothesized

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https://doi.org/10.1016/j.burns.2018.10.011
0305-4179/

that effective drugs in the reduction of the neuropathic pain, may have good analgesic effects on the burn pain. Reports of successful use of gabapentin [2,4–6], pregabalin [3], intravenous lidocaine [7] and methadone [8] can confirm this hypothesis.

Other effective drugs against the neuropathic pain are serotonin norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and tricyclic antidepressants (TCAs) [9]. Beside more therapeutic effects of TCAs than those of duloxetine in reduction of the neuropathic pain, TCAs have more bothersome adverse effects [10].

Despite the recommendation of duloxetine as the first [10] or second [11] line agent in the management of the neuropathic pain, there has been no study investigated the efficacy of duloxetine in the management of the burn pain up to now. Therefore, we performed a prospective open label randomized controlled trial to test the hypothesis that duloxetine may be effective in reducing the pain intensity and improving the neuropathic characteristics of the burn pain. It should be noted that duloxetine has not been approved by the food and drug administration (FDA[1]) for the management of the burn pain.

2. Methods

The study was approved by the ethics committee of Kerman University of Medical Sciences (KUMS) and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.1. Study design

This study was a three-week open label randomized controlled trial conducted in a 31-bed burn ward of a tertiary referral hospital affiliated to the KUMS. The ward is one of the surgical wards with bed occupancy rate of 36.4% in 2017.

2.2. Patient population

The severity of the background pain [evaluated by the "intensity" item of the neuropathic pain scale (NPS)] and the major neuropathic characteristics of the background pain (evaluated by the "sharp" and "hot" items of the NPS) were evaluated before recruitment of patients in the study. Background pain is a constant mild to moderate pain that burn-injured patients usually experience when they are relatively immobile.

All patients aged 15–75 years who had second or third degree burn and scored 5 or greater on either of the "intensity", "sharp" or "hot" items of the NPS were screened for inclusion in the study. The patients were enrolled during the first 24 h after admission, and patients admitted more than 24 h after the burn injury were excluded. Besides, patients who had any of the following conditions were excluded from the study: history of bipolar mood disorder; using monoamine oxidase inhibitor drugs, tramadol, buspirone, lithium, ondansetron, triptan drugs, TCAs, Selective serotonin reuptake inhibitors, SNRIs, potent inhibitors or inducers of the cytochrome P450 (CYP450) 1A2 and CYP450 2D6; hepatic failure or impaired liver function tests; renal impairment defined as creatinine clearance less than 30 ml/min/1.73 m^2; uncontrolled narrow angle glaucoma; uncontrolled seizure and thrombocytopenia.

2.3. Intervention

Eligible patients were randomly assigned to the duloxetine or control group based on simple block randomization. Since the most reported effective dose of duloxetine as an analgesic has been 60 mg per day [12], duloxetine was prescribed orally at 60 mg single daily dose in addition to routine analgesic regimens mainly containing morphine (3–5 mg, intravenously on a prn basis) ± acetaminophen (325 mg every 6 h or on a prn basis) ± gabapentin (initiated at 100 mg TID and increased based on patient response and tolerance). The recommended time for consumption of duloxetine was after lunch to decrease the adverse effects such as nausea and insomnia. In the control group, patients only received routine analgesic medications, as mentioned above. Patients in the both groups received the intervention for 3 weeks.

Regarding the management of the procedural pain (PP), the pain that patient experiences during or after procedures such as dressing change, physiotherapy and wound debridement, it should be noted that wound debridement and dressing change were done under general anesthesia for all recruited patients. Undergoing general anesthesia for dressing change is voluntary in our ward, and an anesthesiologist evaluates patients' conditions regarding the risks of anesthesia. After recovery from general anesthesia, morphine is prescribed at 3–5 mg, intravenously on a prn basis for the management of the PP.

2.4. Outcome measures

Neuropathic pain scale (NPS) was used to evaluate the intensity and quality of the background pain.

The NPS is a validated tool for assessment of neuropathic pain conditions and identifying response to treatment [3,13,14]. It comprises ten items. Six items (NPS-1 to NPS-5 and NPS-7) characterizing the quality of pain are: intense, sharp, hot, dull, cold, and itchy. The sensitive item (NPS-6) evaluates how the skin is sensitive to light touch or clothing. The eighth (NPS-8) item presents the time quality of the pain (all the time or only sometimes). Overall unpleasantness of the pain is described by the ninth item (NPS-9). Finally the tenth item (NPS-10) presents the severity of deep and surface pain. The score of each item ranges between 0 (no experience of that measured outcome) to 10 (the most severe one) [15].

Visual analog scale (VAS) was used to evaluate the severity of the procedural pain.

The VAS is a continuous scale comprised of a 10- centimeter line. The score of the VAS ranges from 0 "no pain" to 10 "the worst imaginable pain" [16]. It has been shown that the ratio of

[1] FDA: food and drug administration; KUMS: Kerman University of Medical Sciences; NPS: neuropathic pain scale; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; PP: procedural pain; prn: when necessary; RMANOVA: repeated measures analysis of variance; SNRIs: serotonin norepinephrine reuptake inhibitors; TBSA: total body surface area; TID: three times a day; TCAs: tricyclic antidepressants; VAS: visual analog scale.

change in the score of the VAS precisely reflects the ratio of change in the patient's pain intensity. It means that for example when the score of the VAS is halved after an intervention, the magnitude of the perceived pain by the patient has also been halved [17].

The primary outcome measure was change in the intensity of the background pain from baseline to the end of the study, as measured by "Intensity" item of the NPS. The secondary outcome measures were change in score of the other items of the NPS and the VAS from baseline to the end of the study (end of the week 3), difference in cumulative dose of morphine, acetaminophen and gabapentin at the end of the study and frequency of adverse effects between the two groups.

Patients were evaluated by scoring the NPS items and the VAS at baseline and every other day during the study. The procedural pain was evaluated 1-2h after full recovery from general anesthesia. Since the procedures were done in the morning, the patients were asked to complete the NPS in the evening because we could be sure that in the evening hours there was no overlap between the procedural and background pain.

Patients were also asked about the adverse effects in each visit.

2.5. Sample size calculation

The below formula was used to calculate the sample size for comparing the mean change in the score of the "intensity" item of the NPS, primary outcome measure, between the two groups.

$$n = \frac{2\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \delta^2}{d^2}$$

Considering standard deviation (SD) (δ) of 2 in the primary outcome in both groups, valuable group difference (d) of 2, type I error (α) of 0.05 and type II error (β) of 0.1, power of 90%, the calculated sample size was 21 patients in each group.

2.6. Statistical analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) version 20. Assessment of normality of data was done by the Kolmogorov-Smirnov test. Standardized difference was calculated to assess balance of baseline data between the two groups.

The primary statistical test used to analyze results of items of the NPS and VAS was repeated measures analysis of variance (RMANOVA). Whenever results of an outcome measure showed significant time-group interaction, its data in each time point of evaluation were compared between the two groups. The mean change in the score of each item of the NPS and VAS from baseline to the end of the study in the each group was extracted from results of the RMANOVA test. Then independent t-test was used to obtain the overall difference in mean change with 95% confidence interval and related P value between the two groups. This part of analysis was performed by Minitab statistical software version 15.

Difference in the cumulative dose of morphine and other analgesics between the two groups was analyzed by independent t-test.

A P value <0.05 was considered statistically significant.

3. Results

3.1. Patient disposition

Flow of the participants in the trial is illustrated in Fig. 1. Of 200 screened patients, 59 patients enrolled in (34 patients in the duloxetine group and 25 patients in the control group) and 46 patients completed the study (23 patients in each group). Thirteen patients did not complete the entire course of the study. We only analyzed data of the patients that received the interventions for the entire 3 weeks of the study in our center. The study period was from February 2017 to October 2017.

3.2. Baseline clinical and demographic characteristics

The baseline characteristics of the participants are presented in Table 1. Of the forty six patients that completed the study, 36 (78.3%) patients were male. Mean age of the patients was 35.04 $\pm$6.37 and 35.6$\pm$6.34 years in the duloxetine and control group, respectively. All of the patients had a 15% or greater total body surface area (TBSA) burn injury. Moreover, all patients had second or third degree burn due to thermal injury. There was no significant standardized difference regarding the baseline demographic characteristics, laboratory findings and the score of the VAS and the items of the NPS between the two groups at baseline (Table 1).

3.3. Efficacy

All patients received the interventions for three weeks. However, because the changes in the scores of the NPS items and the VAS reached a plateau at the end of the second week of the study, only the results of the first two weeks of the study are presented.

Data analysis showed that there was significant group-time interaction for the "intensity" ($P<0.0001$) (Fig. 2), "sharp" ($P=0.007$) (Fig. 2), "hot" ($P<0.0001$) (Fig. 2), "surface pain of the upper half of the body" ($P=0.001$) (Fig. 4)and "surface pain of the lower limbs" ($P=0.004$) (Fig. 4) items of the NPS as well as the VAS, representing PP intensity ($P<0.0001$) (Fig. 5). Therefore, results of these outcome measures in each time point of the evaluation were analyzed to compare the two groups (Table 2).

In contrast, data analysis showed no significant group-time interaction for the other items of the NPS (Table 2, Figs. 3 and 4). Since a few number of patients had very mild pruritus and feeling of cold along with feeling of pain, results of the "itch" and "cold" items of the NPS were not analyzed.

Comparison of the two groups in each time point of evaluation showed that the difference in the scores of the "intensity" and "hot" items of the NPS between the two groups reached a statistical significance after six days and eight days, respectively. Surprisingly, difference in the scores of the VAS, representative of the PP intensity, between the two groups reached a statistical significance two days after the initiation of the study (Table 2, Fig. 5).

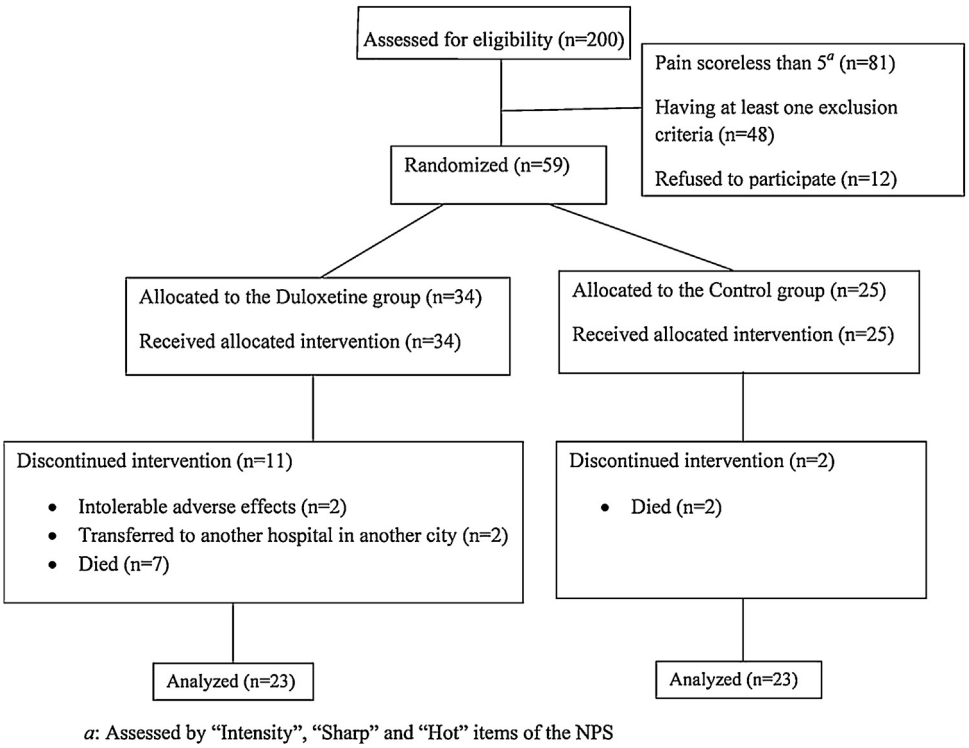

Fig. 1 – Flow chart of participants in the study.

Table 1 – Baseline clinical and demographic characteristics of participants.

Demographic and laboratory variables	Duloxetine group (n=23)	Control group (n=23)	Standardized[a] difference
Age (year)	35.04±6.37	35.6±6.34	0.08
Number of males/females	18/5	18/5	0
BUN (mg/dl)	31.74±15.18	31.52±16.16	0.01
Creatinine (mg/dl)	0.96±0.23	0.99±0.37	0.09
Sodium (mEq/l)	136.91±3.34	136.54±3.94	0.1
Potassium (mEql))	3.76±0.32	3.8±0.61	0.08
White Blood Cells (cells/μl) × 10^3	14.89±7.11	14.17±7.03	0.1
Hemoglobin (g/dl)	16.15±2.13	16.39±2.78	0.09
Platelet (cells/μl) × 10^3	263.94±115	257.43±84.35	0.06
Albumin (g/dl)	3.28±0.64	3.5±0.4	0.09
TBSA (percent)	36.41±17.31	38.04±12.49	0.1
number of patients with second degree burn/third degree burn	10/13	11/12	0.08
NPS items[b]			
Intensity	9.13±1.42	9.13±1.86	0
Sharp	8.48±1.72	8.7±2.1	0.11
Hot	8.52±1.72	8.3±2.324	0.10
Dull	6.37±1.74	6.53±2.4	−0.07
Sensitive	5.36±2.15	5.72±2.86	−0.14
Unpleasant	8.87±0.75	9.04±1.33	−0.15
Deep pain (upper limbs, Face, chest or abdomen)	7.57±2.79	8±2.73	−0.15
Deep pain (lower limbs)	7.48±2.79	7.83±2.57	0.13
Surface pain (upper limbs, Face, chest or abdomen)	8.43±1.47	8.57±1.3	0.1
Surface pain (lower limbs)	8.39±1.5	8.65±1.46	0.17
Procedural pain intensity (VAS)	9.61±0.65	9.7±0.63	−0.14

Data are presented as mean ± SD or number.
NPS: Neuropathic Pain Scale; TBSA: Total body surface area; VAS: Visual Analog Scale.
[a] Standardized difference=difference in means or proportions divided by pooled SD; imbalance defined as absolute value >0.20.
[b] Since a few patients had "cold" or "itch" sensation at baseline, these items of the NPS were not evaluated in the study.

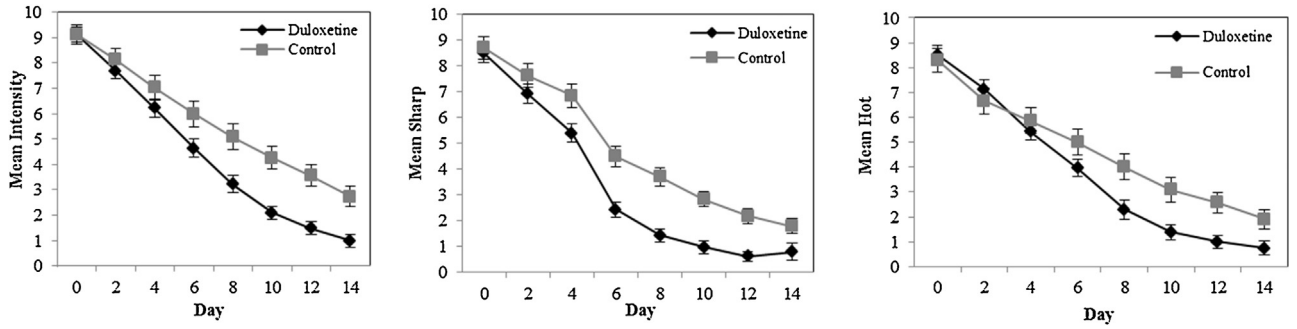

Fig. 2 – Changes in the average score of the "intensity", "sharp" and "hot" items of the NPS over the first two weeks of the study. Error bars represent SEM. NPS: Neuropathic pain scale.

The overall difference in mean changes from baseline to the end of the second week in the score of "intensity" (1.74 (0.614–2.866); P=0.003) and "hot" (1.39 (0.166–2.614); P=0.02) items of the NPS and VAS (PP intensity) (2.13 (1.476–2.784); P<0.0001) was in favor of duloxetine (Table 3).

Although the scores of the "sharp pain" and "surface pain" items of the two groups reached a significant difference on the fourth day of the study, the overall difference in mean changes from baseline to the end of the second week was not significantly different between the groups (Table 3).

Scores of the other items of the NPS showed no significant difference in mean changes from baseline to the end of the second week between group duloxetine and control (Table 3).

At the end of the study, the cumulative dose of acetaminophen in the duloxetine group (4.28±4.53 g) was lower than that of the control group (6.63±3.83 g); however, the difference was not statistically significant (P=0.064). The difference between the cumulative dose of morphine in the duloxetine group (22.57±17.82 mg) and control group (26.3±21.76 mg) also did not reach a statistical significance (P=0.52). The cumulative dose of gabapentin during the study was 2.86±2.85 g in the duloxetine group and 4.25±2.37 g in the control group and the difference was not statistically significant (P=0.25).

3.4. *Safety*

The reported adverse effects were nausea (four patients (12%) in the duloxetine group) and insomnia (three (8%) and two (8%) patients in the duloxetine and control group, respectively). Two patients in the duloxetine group (5.8%) left the study due to adverse effects; one patient could not tolerate the nausea and insomnia and the other patient experienced serotonin syndrome.

4. Discussion

For the first time our study showed that addition of duloxetine to the routine analgesic regimens (morphine±acetaminophen ±gabapentin) was effective in reducing the severity of the background pain, assessed by the "intensity" item of the NPS as the primary outcome measure, and hot or burning sensation of the pain, assessed by the "hot" item of the NPS as one of the secondary outcome measures, as well as the severity of the procedural pain in the burn-injured patients. The "intensity" item measures the severity of pain irrespective of its nociceptive or neuropathic nature while the "hot" item measures one of the most prevalent characteristics of the neuropathic pain, the burning sensation. Considerable effects of duloxetine on these outcome measures approximately initiated during the first week of the study. One of the considerable results of the study is the early onset analgesic effect of duloxetine on the procedural pain, two days after the initiation of the study. However, addition of duloxetine to the other analgesics did not significantly reduce the score of the other items of the NPS as well as the cumulative dose of acetaminophen, morphine and gabapentin.

The use of duloxetine in the burn-injured patients has not been reported, yet. So we compared results of our study with results of studies of duloxetine in the diabetic peripheral neuropathy, fibromyalgia and chronic musculoskeletal pain due to osteoarthritis (OA) [18]. Results of several studies examined effects of duloxetine on symptoms of the diabetic peripheral neuropathy showed that duloxetine 60 mg once daily had significant therapeutic effects in comparison to placebo and less adverse effects in comparison to duloxetine 60 mg two times per day. Besides, significant analgesic effects of duloxetine began after one week in these studies [19–21]. Bradley et al. performed a pooled analysis of results of a 12-week period of four double blind placebo controlled trials of duloxetine in patients with fibromyalgia. The compared arms were duloxetine 60 mg per day, duloxetine 120 mg per day and placebo. The analysis showed that at the end point, the percentage of patients showed ≥ 30% reduction (defined as a clinically significant treatment response) in brief pain inventory (BPI) average pain score in the duloxetine groups (60 mg (46.9%) and 120 mg (48.6%)) were significantly higher than that of the placebo group (32.1%) (P<0.001). Moreover, 27% and 35% of patients received duloxetine 60 mg daily and 120 mg daily, respectively, achieved ≥ 30% reduction in the BPI score at the end of the first week of the study [22]. Results of two 13-week, randomized, double-blind, placebo-controlled trial of duloxetine 60 mg per day [23] or 60–120 mg per day [24] in patients with OA of knee showed that in the duloxetine group, significant reduction in weekly mean of the 24-h average pain severity began at the end of the first week of the study and progressively continued to the end of the study [23,24]. Similar to the results of the above mentioned studies, the significant analgesic effects of duloxetine began almost at the end of the

Table 2 – Scores on the rating scales at baseline and during the study.

	Time	Group				
		Doluxetine[a] n=23	Control[a] n=23	P value[b]	Interaction Factor (P value)[b]	
NPS items[c]						
Intensity	Baseline	9.13±1.42	9.13±1.86	1	8.875 (<0.0001)	
	2nd day	7.7±1.55	8.13±2.09	0.42		
	4th day	6.22±1.67	7.04±2.32	0.17		
	6th day	4.65±1.69	6±2.43	0.03		
	8th day	3.22±1.6	5.09±2.41	0.004		
	10th day	2.09±1.31	4.26±2.15	<0.0001		
	12th day	1.48±1.23	3.57±2.12	<0.0001		
	14th day	1±1.2	2.74±1.98	0.001		
Sharp	Baseline	8.48±1.72	8.7±2.1	0.71	5.21 (0.007)	
	2nd day	6.91±1.83	7.61±2.16	0.24		
	4th day	5.39±1.64	6.83±2.14	0.01		
	6th day	2.43±1.4	4.48±1.97	<0.0001		
	8th day	1.43±1.19	3.7±1.69	<0.0001		
	10th day	0.96±1.14	2.83±1.46	<0.0001		
	12th day	0.61±0.94	2.17±1.37	<0.0001		
	14th day	0.78±1.62	1.78±1.44	0.03		
Hot	Baseline	8.52±1.72	8.3±2.32	0.72	8.35 (<0.0001)	
	2nd day	7.13±1.74	6.65±2.51	0.45		
	4th day	5.43±1.72	5.87±2.52	0.49		
	6th day	3.96±1.71	5±2.46	0.1		
	8th day	2.3±1.86	4±2.52	0.01		
	10th day	1.39±1.43	3.09±2.39	0.006		
	12th day	1±1.27	2.57±2.01	0.003		
	14th day	0.74±1.32	1.91±1.88	0.01		
Dull	Baseline	6.37±1.74	6.53±2.4	0.83	2.61(0.07)	
	2nd day	4.68±1.7	5.38±2.9	–		
	4th day	3.62±1.82	4.46±2.4	–		
	6th day	2.18±1.55	3.69±2.52	–		
	8th day	1.31±1.44	3.15±2.3	–	Within subjects effects factor[d] (P value)	Between subjects effects factor[e] (P value)
	10th day	0.62±0.88	2.15±2.11	–		
	12th day	0.37±0.61	1.38±1.75	–	141.82 (<0.0001)	2.89 (0.1)
	14th day	0.25±0.57	0.76±1.23	–		
Sensitive	Baseline	4.45±2.46	5.72±2.86	0.27	0.48 (0.61)	
	2nd day	4±2.6	4.72±3.31	–		
	4th day	2.72±2.1	3.81±3.02	–		
	6th day	1.81±1.4	2.9±2.7	–		
	8th day	0.9±1	2.36±2.54	—	Within subjects effects factor (P value)	Between subjects effects factor (P value)
	10th day	0.54±0.93	1.63±1.74	–		
	12th day	0.45±0.93	1.27±1.19	–	64.44(<0.001)	0.14 (0.7)
	14th day	0.41±0.89	0.72±1	–		

(continued on next page)

Table 2 (*continued*)

	Time	Group				
		Doluxetine[a] n=23	Control[a] n=23	P value[b]	Interaction Factor (P value)[b]	
Unpleasant	Baseline	8.87±0.75	9.04±1.33	0.56	1.85 (0.15)	
	2nd day	7.61±0.89	7.87±1.45	–		
	4th day	6.26±1.09	6.87±1.63	–		
	6th day	4.91±1.44	5.7±1.63	–		
	8th day	3.61±1.61	4.65±1.82	–	Within subjects effects factor (P value)	Between subjects effects factor (P value)
	10th day	2.57±1.77	3.61±1.85	–		
	12th day	1.74±1.48	2.87±1.57	–	387.75(<0.001)	4.13 (0.04)
	14th day	1.26±1.54	2.13±1.51	–		
Deep 1[f]	Baseline	7.57±2.79	8±2.73	0.6	2.17 (0.12)	
	2nd day	6.3±2.49	6.96±2.54	–		
	4th day	5.04±2.22	6.04±2.38	–		
	6th day	3.52±2.04	4.96±2.28	–		
	8th day	2.39±2.03	4±2.19	–	Within subjects effects factor (P value)	Between subjects effects factor (P value)
	10th day	1.39±1.61	3.13±1.93	–		
	12th day	0.91±1.27	2.48±1.72	–	224.38 (<0.001)	4.8 (0.03)
	14th day	0.57±0.84	1.61±1.4	–		
Deep 2[g]	Baseline	7.48±2.79	7.83±2.57	0.66	3.26 (0.053)	
	2nd day	6.04±2.47	6.78±2.61	–		
	4th day	4.61±1.99	5.57±2.37	–		
	6th day	3.26±1.65	4.78±2.29	–		
	8th day	1.74±1.32	3.78±2.19	–	Within subjects effects factor (P value)	Between subjects effects factor (P value)
	10th day	0.96±1.18	2.87±2.13	–		
	12th day	0.61±0.94	2.26±1.81	–	220.9 (<0.0001)	6.5 (0.01)
	14th day	0.39±0.94	1.61±1.55	–		
Surface 1[f]	Baseline	8.43±1.47	8.57±1.3	0.75	6.32 (0.001)	
	2nd day	6.78±1.53	7.43±1.83	0.19		
	4th day	4.96±1.77	6.39±1.64	0.007		
	6th day	3.3±1.84	5.13±1.76	0.001		
	8th day	2.09±1.34	4.17±1.77	<0.0001		
	10th day	1.13±0.96	3.04±1.66	<0.0001		
	12th day	0.83±0.98	2.3±1.71	0.001		
	14th day	0.65±0.83	1.52±1.72	0.035		
Surface 2[g]	Baseline	8.39±1.5	8.65±1.46	0.55	4.68 (0.004)	
	2nd day	6.91±1.56	7.57±1.7	0.18		
	4th day	5.22±1.73	6.35±2.16	0.05		
	6th day	3.57±1.53	5.3±2.09	0.002		
	8th day	2.43±1.4	4.22±2.02	0.001		
	10th day	1.3±1.18	3.09±1.99	0.001		
	12th day	0.91±1.16	2.48±1.72	0.001		
	14th day	0.74±1.13	1.74±1.54	0.01		

Table 2 *(continued)*

	Time	Group			
		Doluxetine[a]	Control[a]	P value[b]	Interaction Factor (P value)[b]
		n=23	n=23		
VAS					
Procedural pain intensity	Baseline	9.61±0.65	9.7±0.63	0.65	12.36 (<0.001)
	2nd day	8.3±0.87	9.13±0.81	0.002	
	4th day	7.48±0.84	8.48±0.89	0.001	
	6th day	6.89±0.85	7.96±1.14	0.001	
	8th day	6.22±0.73	7.35±1.07	<0.001	
	10th day	5.48±0.99	6.87±1.14	<0.0001	
	12th day	4.52±0.89	6.26±0.91	<0.001	
	14th day	3.7±0.92	5.91±1.16	<0.001	

NPS: neuropathic Pain scale; VAS: Visual Analog scale.

[a] Data are mean±SD.

[b] Repeated measure ANOVA.

[c] Since a few patients had “cold” or “itch” sensation at baseline, these items of the NPS were not evaluated in the study.

[d] Time is within subject variable.

[e] Group is between subject variable.

[f] upper limbs, Face, chest or abdomen.

[g] lower limbs.

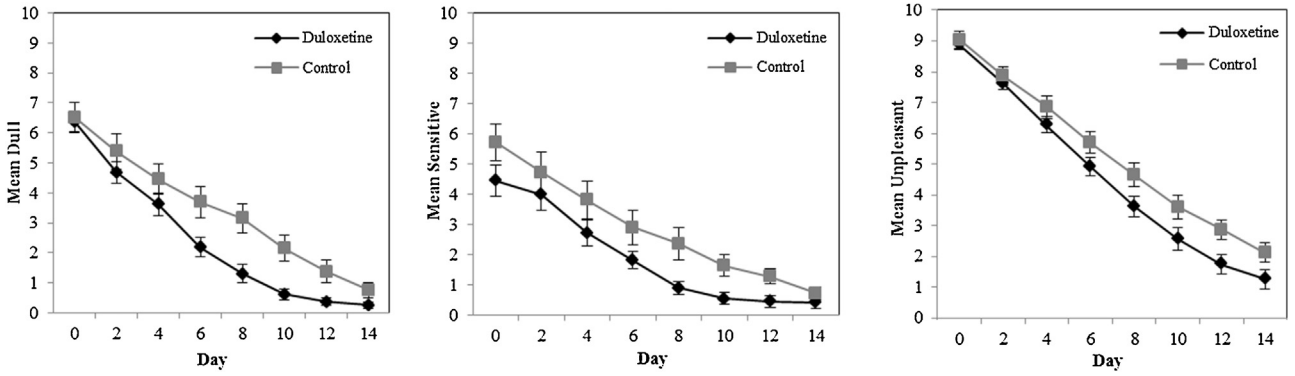

Fig. 3 – Changes in the average score of the "dull", "sensitive" and "unpleasant" items of the NPS over the first two weeks of the study. Error bars represent SEM. NPS: Neuropathic pain scale NPS: Neuropathic pain scale.

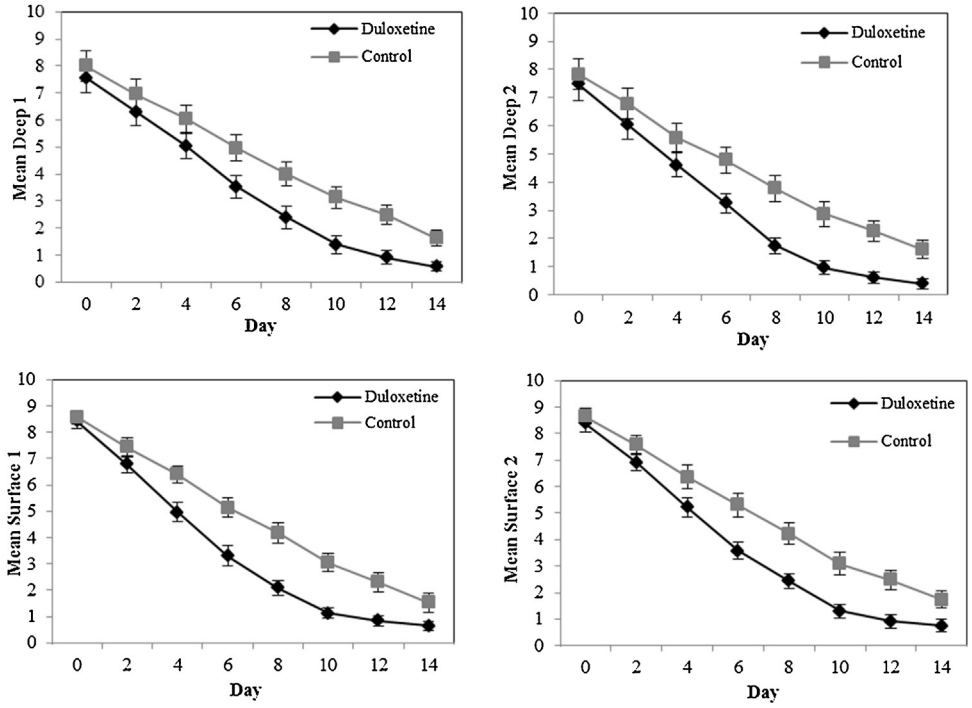

Fig. 4 – Changes in the average score of the "deep 1: deep pain of the upper limbs, face, chest or abdomen", "deep 2: deep pain of the lower limbs", "surface 1: surface pain of the upper limbs, face, chest or abdomen" and "surface 2: surface pain of the lower limbs" items of the NPS over the first two weeks of the study. Error bars represent SEM. NPS: Neuropathic pain scale.

first week of our study. In contrast, the response rate reached a plateau at the end of the second week in our study while the other studies showed a continued response through the study period.

From 13 patients who left the study, seven patients in the duloxetine group and two patients in the control group died before completion of the 3-week study period. They had extensive TBSA involvement (more than 75%) and the cause of death was severe sepsis in all of them. So we believe that duloxetine had no effect on the mortality rate. Furthermore, one patient left the study because of the suspected serotonin syndrome one week after the initiation of duloxetine. The patient had only drowsiness and lethargy without other symptoms of the serotonin syndrome. However, only after discontinuation of duloxetine, his mental status became normal. In the literature, there are some case reports of serotonin syndrome in patients consuming duloxetine [25–28]. All cases had the triad symptoms of the serotonin syndrome [29], neuromuscular hyperactivity, excitation of autonomic nervous system, and altered mental state. In the most cases the syndrome manifested during the 6h after initiation or increasing dosage of duloxetine [25,26] or an interacting drug (linezolid [28]) that increases the risk of serotonin syndrome in combination with duloxetine. However, in one case, the syndrome initiated several days after increasing dosage of methadone in a patient who had been consuming stable doses

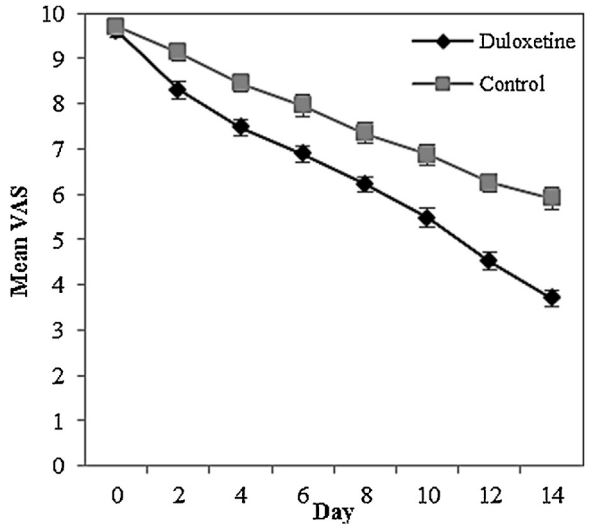

Fig. 5 – Changes in the average score of VAS (procedural pain intensity) over the first two weeks of the study. Error bars represent SEM. VAS: visual analog scale.

of duloxetine and methadone before that [27]. Therefore, we cannot definitely confirm that the changes in the mental status of our 33-year old patient which manifested seven days after the initiation of duloxetine were due to serotonin syndrome.

Nausea (12%) and insomnia (8%) were the most reported adverse effects of duloxetine in our study. In contrast, the most reported adverse effects of duloxetine 60 mg per day in the studies of patients with diabetic neuropathy were nausea (16.7% and 28.1%), somnolence (7.9% and 20.2%), dizziness (9.6% and 15.8%), fatigue (12.3%) and constipation (5.2% and 7%) [19,21]. While fatigue (8%), insomnia (5%) and nausea (5%) were the most reported adverse effects of duloxetine (60 mg daily) in a study in chemotherapy induced painful peripheral neuropathy [30], nausea (29.3%), headache (20.0%), dry mouth (18.2%), insomnia (14.5%), constipation (14.5%) and fatigue (13.5%) were the most prevalent short term adverse effects of duloxetine (60 mg and 120 mg per day, collectively) in five studies conducted in patients with fibromyalgia [31]. The most reported adverse effects of duloxetine in clinical trials in patients with knee OA were Nausea (8.4%), constipation (5.9%), erectile dysfunction (5%) and fatigue (4.2%) [32].

The difference in the prevalence and type of adverse effects of duloxetine between our study and the above mentioned studies may be explained by the younger age of our patients (mean age of 35 years in our study vs mean age of 50-59 years in the other studies), different races of patients in different studies (Asian in all the participants of our study versus Caucasian (white) in most patients of the other studies) [19–22,30,32], negative past medical history and drug history in the most of our patients, different natures of the underlying disease (burn injury versus diabetes mellitus, fibromyalgia, malignancy and osteoarthritis), and shorter duration of our study, 3 weeks versus 12 weeks, 6 weeks, 13 weeks and 6 months in the diabetic peripheral neuropathy, chemotherapy induced neuropathy, OA of knee and fibromyalgia studies, respectively.

4.1. *Limitations of the study*

The main limitations of the present study are relative small sample size, short duration, using fixed dose schedule (some patients with more severe pain may respond to higher doses of duloxetine) and open label design without using placebo. Moreover, none of the patients had less than 15% TBSA burn, so results of this study may not be extrapolated to patients with less than 15% TBSA involvement.

Finally, a long term large scale double blind placebo controlled trial should be conducted to confirm the results of the present study.

Table 3 – Changes of score of the NPS items and VAS Between the baseline and the end of the study.

	Mean decrease from baseline to the end of the study		Overall difference between the duloxetine and control groups	
	Duloxetine, n=23 Mean±SD	Control, n=23 Mean±SD	Difference in means (95% CI)	P value[a]
NPS items				
Intensity	8.13±1.88	6.39±1.91	1.74 (0.614 to 2.866)	0.003
Sharp	7.69±2.32	6.91±2.34	0.78 (−0.605 to 2.165)	0.26
Hot	7.78±2.06	6.39±2.06	1.39 (0.166 to 2.614)	0.02
Dull	6.12±1.82	5.76±1.82	0.36 (−0.722 to 1.442)	0.5
Sensitive	4.72±2.02	5±2.02	−0.28 (−1.480 to 0.920)	0.64
Unpleasant	7.6±1.72	6.91±1.74	0.69 (−0.338 to 1.718)	0.18
Deep pain (upper limbs or Face or chest or abdomen)	7±2.58	6.39±2.58	0.61 (−0.923 to 2.143)	0.42
Deep pain (lower limbs)	7.08±2.58	6.21±2.58	0.87 (−0.663 to 2.403)	0.25
Surface pain (upper limbs or Face or chest or abdomen)	7.78±1.64	7.04±1.64	0.74 (−0.235 to 1.715)	0.13
Surface pain (lower limbs)	7.78±1.64	6.85±1.64	0.93 (−0.045 to 1.905)	0.061
VAS				
Procedural pain intensity	5.91±1.1	3.78±1.1	2.13 (1.476 to 2.784)	< 0.001

NPS: Neuropathic pain scale; VAS: Visual analog scale.
[a] Two tailed Independent t-test.

5. Conclusion

Results of the present study showed that addition of duloxetine to the other analgesic medications, morphine, acetaminophen and gabapentin, was well tolerated and effectively reduced both nociceptive and neuropathic (burn sensation) components of the background pain as well as the severity of the procedural pain. Although the addition of duloxetine did not decrease the cumulative dose of the other analgesics, it can be considered as an add-on medication in the burn-injured patients who do not satisfactorily respond to these analgesic drugs.

Author's contribution

Ali Najafi: This author helped conduct the study, collect data and draft the manuscript.

Hamid Zeinaly Nejad: This author helped design and conduct the study and draft the manuscript.

Naemeh Nikvarz: This author helped design and conduct the study, analyze the data and draft the manuscript.

All authors have approved the final version of the manuscript.

Trial registration

The trial has been registered at IRCT.ir (IRCTID: IRCT2017051422637N4).

Funding

The study was supported by Kerman University of Medical Sciences (KUMS) (grant number: 95000039). The ethics committee of the KUMS reviewed the study protocol. The KUMS has had no role in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest

All authors declare that they have no conflict of interest.

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