International Journal of Communication Networks and Information Security
2024, 16(4)
ISSN: 2073-607X,2076-0930
https://ijcnis.org/

Research Article

Repeated Dexmedetomidine Infusion is a Two-shot Weapon for Pain and Pain-induced Mood Disorders in Chronic Pain Patients: A Placebo-controlled Randomized Prospective Interventional Study

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ARTICLE INFO

Received: 17 Aug 2024
Accepted: 22 sep 2024

ABSTRAT

Objectives: This prospective study examined the effects of 6-sessions of dexmedetomidine (DEX) for patients had chronic musculoskeletal pain (CMSP) on the frequency and severity of pain, and pain-induced depression, anxiety and kinesiophobia.
Patients & Methods: 80 CMSP patients were evaluated using the short-form McGill Pain Questionnaire (SF-MPQ), Pain Anxiety Symptoms Scale (PASS), State-Trait Anxiety Inventory for measuring state and trait anxiety, short-form Tampa Scale of Kinesiophobia and Beck Depression Inventory-II. Patients were randomly divided into Group-C received placebo infusion and Group-S received DEX infusion (0.7 µg/kg for 1-hour) twice weekly for three weeks. Evaluations were re-assessed at the end of infusion (T2), 1-m (T3) and 3-m (T4) in comparison to scores determined before start of infusion therapy (T1).
Results: At T2-T4 the scores of all the evaluated tools decreased significantly in Group-S compared their T1 scores and to scores of patients of Group-C. Moreover, 47.5% of Group-S patients were independent on any analgesia since T2 till T4 with significant difference compared to Group-C patients and to their consumption rate and type of analgesia at T1. Satisfaction scores of Group-S patients by the infusion therapy were significantly higher compared to that of patients of Group-C and to their T1 scores by the usual analgesia. The re-assessed scores were negatively correlated with the administration of DEX infusion and positively correlated with the decrease in pain scores. ROC curve analysis defined decreased kinesiophobia scores as the significant predictor for the decreased depression scores to 0-13.
Conclusion: DEX infusion might break the circle of pain-psychopathy-poor quality of life of CMSP patients. All psychological scorings were improved secondary to improved pain scores but improved kinesiophobia is the significant predictor for alleviation of depression.
Keywords: Dexmedetomidine, Chronic musculoskeletal pain, Kinesiophobia, Depression, Anxiety

Introduction

Chronic primary pain (CPP) is defined as a stress-related chronic pain and often presents as wide-spread pain or comorbid pain conditions in different regions of the body without the presence of tissue injury [(1)]. Chronic musculoskeletal pain asdefined by the International Pain

Association is the persistent or recurrent pain involving spine, bones, joints, and/or musculo-soft tissue [2].

Chronic pain (CP) as a long-lasting stressor might induce disordered mood varying between depression and anxiety with consequent challenge of this combination on treatment outcomes and consumption of health resources [3] and may be of debilitating severity leading to worse quality of life [4].

Dexmedetomidine (DEX) is a centrally selective α_2-adrenoceptor agonist with fast onset of action [5].DEX is widely used for sedation in intensive care units (ICU) [6] and showed the lowest risk for delirium and its administration was associated with decreased psychiatric burden after ICU discharge [7]. Moreover, DEX is used as anesthetic adjunct with promise alleviation of postoperative cognitive function [8].

Hypothesis

These data concerning the effects of DEX on the incidence of delirium and cognitive dysfunction allowed suggestingthe use of repeated DEX infusion for patients with CP to take the advantages of its analgesic and mood modifying effects.

Objectives:

The current study tried to evaluate the effects of repeated DEX infusion sessions on the frequency and severity of the CP-induced mood disorders in patients had chronic musculoskeletal pain (CMSP).

Trial registration

The study protocol was freely discussed with patients before enrolment and those who accepted to participate in the study were asked to sign the written consent The study protocol and intervention was approved by the Research Ethic Committee with the reference number (RC:9-3-2024) and was registered under clinicaltrials.gov ID NCT06402019 on registration date.

Patients

All patients complaining of CMSP and accustomed to attend the pain clinics at the university hospitals sharing in the study and at multiple pain-therapy private centers were evaluated to choose those fulfilling the inclusion criteria and free of exclusion criteria.

Exclusion criteria

Patients with other causes for CP, maintained on opioid analgesia, had cardiac lesions, maintained on antihypertensive therapy, or can't attend the clinic to complete the course of DEX infusion sessions were excluded from the study.

Inclusion criteria

Patients with CMSP and maintained on analgesia and/or training exercise, were free of exclusion criteria and signed the written fully informed consent to participate in the study were enrolled in the study.

Evaluation tools

1. **The short-form McGill Pain Questionnaire (SF-MPQ)**for evaluation of present pain intensity and consists of 11 sensory and 4 affective items that are evaluated on 4-point scale with 0 = none, 1 = mild, 2 = moderate or 3 = severe, and total score was calculated [9].
2. **Pain Anxiety Symptoms Scale (PASS)** is 20-item assessment tool for pain-related anxiety with zero (indicates never) and 5 (indicates always) points for a total score range of 0-100. Scores were interpreted as mild, moderate and severe if PASS score was 0-34, 35-67 and >68 [10].
3. **State-Trait Anxiety Inventory** for measuring state anxiety (STAI-S) to determine the anxiety levels induced by stressful procedures and trait anxiety (STAI-T) to evaluate how patients generally feel. Each consisted of 20 statements or questions, respectively and is rated on a 4-point scale; 1= not at all, 2= somewhat, 3= moderately, 4= very much, for a total score range of 20-80 that is classified as 20-37 points indicates “no or low anxiety”; 38-44 indicated moderate and >45 indicated high anxiety[11, 12].
4. **The short-form Tampa Scale of Kinesiophobia (TSK-11)**is an 11-item questionnaire and each item is scored on 4 point scale with 1 indicates strongly disagree and 4 indicates

strongly agree for a total score ranging between 11–44 points and higher score indicates greater fear of pain, movement, and injury[13, 14].

5. **Beck Depression Inventory-II (BDI-II)** consists of 21 questions, the answer of each question is scored on 4-point 0-3 score for a total score ranging from zero to 63 and 0-13 points indicates minimal, 14-19 mild, 20-28 moderate and total score of ≥29 indicates severe depression [15].
6. **Patients' satisfaction** with the applied protocol of analgesia was recorded at the end of infusion sessions using a visual analogue scale of 0-100 with a higher score indicates higher satisfaction[16].

Sample size

The study null hypothesis was receiving repeated sessions of DEX infusion will alleviate the pain-induced mood disorders significantly in comparison to the levels determined before start of infusion and to that reported in patients who received placebo infusion. Sample size was calculated using the G*Power (Version 3.1.9.2)[17]to provide a study power of 80% using α-error 5% with an effect size of 0.20. The calculated sample size was defined by the F test model to be 33 patientsper group to ensure the certainty of the null hypothesis. However, for the possibility of dropout, 40 patients per group were collected.

Randomization & Grouping

Using software (Excel 2007, Microsoft, Redmond, WA, USA) to provide 1:1 sequences with even number dropping, the enrolled patients were categorized into Control (Group-C) and Study (Group-S) groups. The provided sequences were printed and enveloped, patients were asked to choose an envelope and propose it to the pain therapist who was responsible for application of the infusion.

Author contributions

Psychiatric evaluation was performed by junior psychiatrists under supervision of Zakaria A, before intervention, at the end of the sessions, one and three months thereafter. Pain assessment was the duty of Ibrahim SSA, while preparation and administration of infusions was the duty of Shaboob I. Data interpretation was performed by Zakaria A who was blinded about the randomization process and type of the received infusion.

Infusion preparation and administration

The infusions were provided twice weekly for three weeks to receive 6 infusion sessions, each of one hour duration. The enrolled patients were arranged not to meet during the infusion sessions so as to guard against the reciprocal psychological projection. The infusion rate was adjusted to maintain heart rate (HR) in range of 60-80 beats/min and mean arterial pressure (MAP) in range of 65-75 mmHgunder non-invasive monitoring. Patients of Group-C received normal plain saline infusion and were asked to continue their usual analgesia, while patients of Group-S received DEX infusion (Precedex, 100 µg/ml; Rewine Pharmaceutical; Varachha, Seurat, Gujarat) in dose of 0.7 µg/kg/h for one hour according to previousdata provided by **Hayley et al.**[18] and were asked to adjust their usual analgesia according to new requirements.

Study outcomes

1. The primary outcome is the effect of DXM infusions in comparison to placebo on severity of pain, anxiety and depression.
2. The secondary outcomes included
   - The relation between pain scores and anxiety, depression and kinesiophobia scores
   - The best predictor for achieving minimal depression on BDI-II

Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA). The significance of the intergroup differences was assessed using One-way ANOVA test, the intragroup differences was assessed using the paired t-test and Chi-square test was used to assess the significance of the differences in percentage of data. Correlation between the scores determined at the end of infusion sessions was evaluated using the Pearson' correlation analysis. The receiver operating characteristic (ROC) analysis was used to determine the predictor for the decreased BDI-II score to the level of minimum depression at cutoff point of 13 on BDI-II. The optimum cut off point for significance was $P<0.05$.

Results

During case collection, 12 patients were excluded; four patients had CP secondary to other causes; three patients were opioid dependent; two patients were maintained on antihypertensive therapy, one cardiac, one hepatic and another patient had chronic renal disease, while 80 patients fulfilling the inclusion criteria were randomly divided into both study groups (Fig. 1). Patients' enrolment and scores of the applied evaluation tools determined before start of infusions showed insignificant intergroup difference (Table 1).

Table 1: Enrolment data of patients of both groups

Data		Group-C (n=40)	Group-S (n=40)	P value
Age (years)		59.5±5	61.1±6.3	0.209
Gender	Males	13 (32.5%)	16 (40%)	0.485
	Females	27 (67.5%)	24 (60%)	
Body mass index (kg/m²)		32.9±1.36	33.3±1.27	0.194
Pain score (SF-MPQ)		24.5±13.3	24.8±13.4	0.829
Scores of psychological evaluation tools before start of infusions (T1)	PASS	48.6±20.1	46.8±19.4	0.665
	STAI-S	39.9±10.1	41.5±8.6	0.096
	STAI-I	42.5±8.9	40.3±8.5	0.097
	TSK-11	26.5±8.8	26.3±7.7	0.902
	BDI-II	22.3±6.3	23±7.6	0.609

SF-MPQ: The short-form McGill Pain Questionnaire; STAI: State-Trait Anxiety Inventory; TSK-11: The short-form Tampa Scale of Kinesiophobia; BDI-II: Beck Depression Inventory-II; Data are presented as means, standard deviation, numbers and percentages; statistical significance was assessed using One-way ANOVA for intergroup differences (P-value) and Chi-square test for numerical data at $P<0.05$ indicated significant value

At the end of infusions and at 1-m and 3-m of follow-up, SF-MPQ scores were significantly lower in patients of Group-S in comparison to Group-C. Distribution of patients of Group-S among high SF-MPQ scores decreased significantly at T2-4 in comparison to their distribution determined at T1 and was significantly lower in comparison to distribution of patients in Group-C at T2-4. Moreover, 19 patients (47.5%) of Group-S were independent on any analgesia since the end of infusion sessions till 3-m follow-up, with significant difference in comparison to patients of Group-C and to their consumption rate and type of analgesia before start of therapy (T1) as shown in table 2.

Table 2: Data of SF-MPQ and consumption of analgesia by patients of both groups obtained at the end of infusion sessions and at 1-m and 3-m follow-up

Data			Group-C (n=40)				Group-S (n=40)			
SF-MPQ	Score	T2	24±12.4				11.3±12.1			<0.001
		T3	23.3±12.8				12.8±12.5			0.0003
		T4	26.4±13				13.9±13.7			0.0001
	Frequency according to score		T1	T2	T3	T4	T1	T2	T3	T4
		0	4	3	4	3	4	19	17	17
		15	14	17	17	12	12	12	12	10
		30	16	15	15	18	18	9	11	12
		45	6	5	5	7	6	0	0	1
		P1						0.001	0.004	0.0045
		P2					0.965	0.0008	0.0077	0.0013
Analgesia	Type	No	0	0	0	0	0	24	22	19
		NSAIDs	22	23	21	21	24	12	15	13

		Others	18	17	19	19	16	4	3	8
		P1						<0.001	<0.001	<0.001
		P2					0.859	<0.001	<0.001	<0.001
	Frequency	No	0	0	0	0	0	24	22	19
		Occasionally	5	6	6	5	7	10	9	6
		Sometimes	23	22	20	21	22	6	8	12
		Always	12	12	14	14	11	0	1	3
		P1						<0.001	<0.001	<0.001
		P2					0.941	<0.001	<0.001	<0.001

SF-MPQ: The short-form McGill Pain Questionnaire; NSAID: Non-steroidal anti-inflammatory drugs; T1: start of infusion sessions; T2: end of infusion sessions; T3: at 1-m of follow-up; T4: at 3-m of follow-up;; Data are presented as means, standard deviation and numbers; statistical significance was assessed using One-way ANOVA for intergroup differences (P-value), paired t-Test for intragroup differences (P1 value) and Chi-square test for numerical data (P1 & P2) at P<0.05 indicated significant value

Re-assessment of scores for evaluation of patients' psychological status showed significant improvements at the end of infusion sessions and through follow-up of patients of Group-S in comparison to data obtained on assessment before start of infusions and to corresponding data of patients of Group-C(Table 3).

Table 3: Follow-up patients' data concerning evaluation tools for patients' psychological status

Data			**Group-C (n=40)**				**Group-S (n=40)**			
PASS	Score	T2	47.3±20.1				26.5±21.6			<0.001
		T3	46.7±19.6				26.9±18.5			<0.001
		T4	47.8±19.4				28.8±18.7			<0.001
	Frequency according to score		T1	T2	T3	T4	T1	T2	T3	T4
		0-34	14	14	17	13	14	31	34	31
		35-67	16	16	11	17	17	7	4	6
		≥68	10	10	12	10	9	2	2	3
		P1						0.0005	0.0003	0.0006
		P2					0.959	0.0005	0.0023	0.0003
STAI-S	Score	T2	36.9±9.2				33.3±9			0.033
		T3	37.9±9.5				33.9±8.8			0.017
		T4	39.2±10				34.6±8.9			0.0086
	Frequency according to score		T1	T2	T3	T4	T1	T2	T3	T4
		20-37	13	12	14	13	11	29	26	24
		38-44	14	17	16	15	17	8	10	12
		≥45	13	11	10	12	12	3	4	4
		P1						0.0002	0.0026	0.0079
		P2					0.779	0.0006	0.023	0.022
STAI-I	Score	T2	39.6±10.2				26±5.4			<0.001
		T3	39.4±10.1				27.6±5.8			<0.001
		T4	40.1±9.9				30±7			<0.001
	Frequency according to score		T1	T2	T3	T4	T1	T2	T3	T4
		20-37	7	9	10	8	5	26	28	25
		38-44	21	20	19	21	22	10	8	9
		≥45	12	11	11	11	13	4	4	6
		P1						<0.001	<0.001	<0.001
		P2					0.820	0.0006	0.0003	0.0055
TSK-11	Score	T2	26±7.9				14.1±3.7			<0.001
		T3	26.2±7.4				15.4±4			<0.001

		T4	25.6±7.6				16.9±4.5			<0.001
BDI-II	Score	T2	20.9±6.1				13.2±4.7			<0.001
		T3	21.5±5.7				14.3±4.9			<0.001
		T4	22±6.1				15.5±5.3			<0.001
	Frequency according to score		T1	T2	T3	T4	T1	T2	T3	T4
		0-13	1	3	3	1	3	25	19	14
		14-19	13	11	12	13	12	10	15	18
		20-28	20	22	25	20	14	5	6	8
		≥29	6	4	0	6	11	0	0	0
		P1						<0.001	<0.001	0.0004
		P2					0.312	<0.001	<0.001	0.0001

PASS: Pain Anxiety Symptoms Scale; STAI: State-Trait Anxiety Inventory; TSK-11: Short-form Tampa Scale of Kinesiophobia; BDI-II: Beck Depression inventory-II; T1: start of infusion sessions; T2: end of infusion sessions; T3: at 1-m of follow-up; T4: at 3-m of follow-up; Data are presented as means, standard deviation and numbers; statistical significance was assessed using One-way ANOVA for intergroup differences (P-value), paired t-Test for intragroup differences (P1 value) and Chi-square test for numerical data (P1 & P2) at P<0.05 indicated significant value

Patients' satisfaction scores by using the usual analgesia before the start of infusion therapy were insignificantly (P=0.387) higher for patients of Group-S (33±14.2) than for patients of Group-C (30±12.8). At the end of infusion therapy, the satisfaction scores of patients of Group-S (63±17.6)were significantly (P<0.001) higher in comparison to the corresponding scores of patients of Group-C and to their scores by the usual analgesia before the start of infusion therapy, while for patients of Group-C (33±10.4) was insignificantly (P=0.150) higher than their baseline score (Fig. 2).

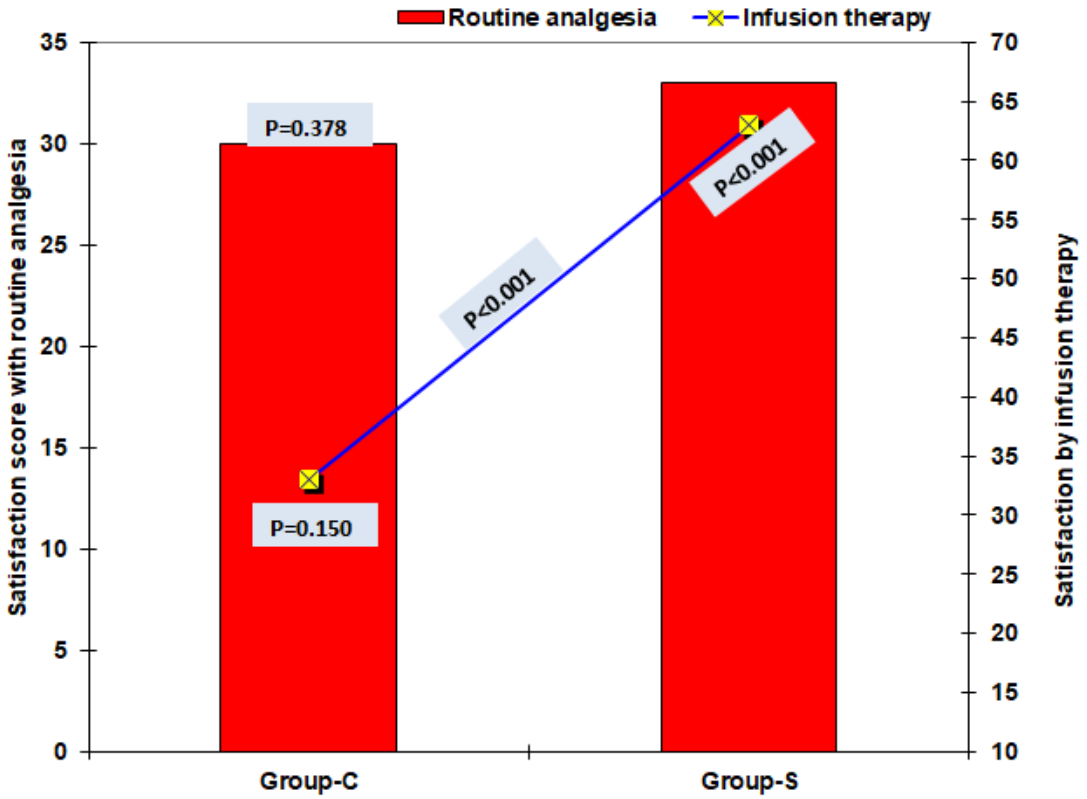

Fig. 2: Satisfaction scorings at the end compared to before start of infusion sessions

The assessed SF-MPQ, PASS, TSK-11 and BDI-II scores at the end infusion sessions negatively correlated with the administration of DEX infusion. Also, decreased scores of anxiety, depression and the fear of movement or physical activity positively correlated with the decrease in pain scores. ROC curve analysis for the predictors for decreased depression scores to minimal depression (BDI-II = 0-13) defined decreased kinesiophobia scores as the significant predictor,

while decreased anxiety and pain scores were insignificant predictors for improved depressive mood to minimal level (Table 5, Fig. 3).

Table 5: Statistical analysis for the relation between the studied scores

Pearson' correlation analysis				
Variates	Administration of DEX infusion		Pain scores	
	"r"	P	"r"	P
Pain scores (SF-MPQ)	-0.472	<0.001	-	-
Anxiety scores (PASS)	-0.462	<0.001	0.369	<0.001
Kinesiophobia (TSK-11)	-0.750	<0.001	0.489	<0.001
Depression (BDI-II)	-0.633	<0.001	0.371	<0.001
Receiver Operating Characteristic (ROC) curve analysis				
	AUC (±SE)	P	95% Confidence interval	
DEX infusion	0.368 (±0.135)	0.377	0.104-0.633	
Anxiety scores (PASS)	0.553 (±0.129)	0.724	0.300-0.805	
Kinesiophobia (TSK-11)	0.801 (±0.110)	0.043	0.585-1.000	

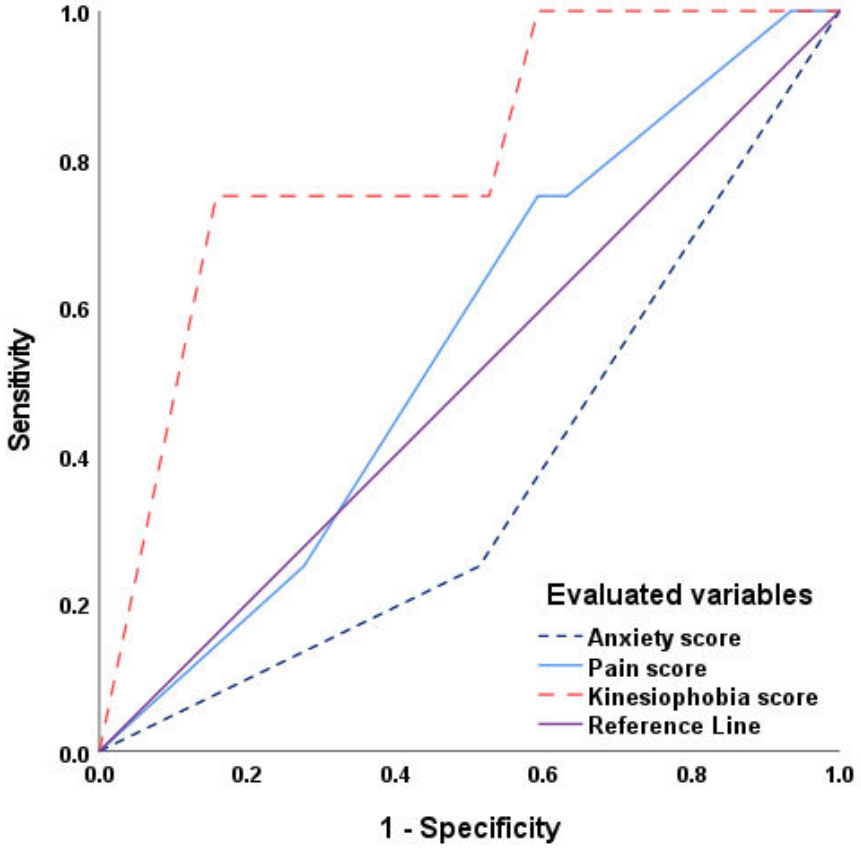

Fig. 3: ROC curve analysis for the predictors of decreased depression scores to minimum scores

Discussion

The infusion sessions of DEX significantly improved both pain scores and pain-related psychological manifestations thus the obtained results assured the reality of the null hypothesis that repeated DEX infusions might improve the performance of patients had chronic primary pain that was documented to be related to stress and aggravate these stress [1]. Thus, DEX infusions can break the vicious cycle of stress, pain, stress and this significantly improved

patients' quality of life mostly through improved mood and ability to move with improved ability to carry on daily life activities as evidenced by positive significant correlation between kinesiophobia and pain scorings and ROC curve analysis defined decreased kinesiophobia scores as significant predictor for alleviation of depression.

In accordance with the study hypothesis, **Li et al.**[1] experimentally found chronic stress induced anxiety- and depression-like behaviors, and resulted in long-lasting wide-spread hyperalgesia over several body regions due to chronic stress-induced upregulation of spinal CCK1 receptors with subsequent development of central mechanisms that initiate and maintain the reported wide-spread hyperalgesia, and documented that antagonism of these central mechanism may provide a potential for clinical treatment of CPP.

Clinically, **Åström Reitan et al.**[4] found ratings of depression in patients with long-termed chronic pain were positively and significantly related to ratings of sickness behavior and anxiety and also found insomnia was positively and significantly related to sickness behavior. Also, **Shaker et al.**[19] reported that 8-week of simple sequence of mental exercises to induce a relaxed state appears effective in significantly improving anxiety, stress, depression, pain and insomnia with enhancement of patients' overall well-being. Moreover, **Ferguson et al.**[20] detected positive association between avoidance/rumination among people living with HIV with anxiety, anger and pain interference and at time points with greater avoidance/rumination these patients reported increased pain severity and anxiety and anger symptoms that correspond with long-termed poorer health outcomes.

DEX infusions significantly reduced pain scores for 3–m after the end of infusions and this finding go in hand with previous studies used DEX as adjuvant to various analgesic modalities used for alleviation of CP as continuous erector spinae plane block for post-thoracotomy pain syndrome [21] and stellate ganglion block for patients with complex regional pain syndrome [22] and as the sole therapy for chronicincisional pain after elective brain tumor resections [23].

Unfortunately, literature review failed to find similar studies evaluating the effect of DEX infusion sessions on CP-induced mood disturbances; however, multiple previous experimental studies detected such outcomes and tried to elucidate the underlying mechanisms for the effect of DXM infusions on CP-induced mood disturbances, where **Gao et al.** [24] found DXM alleviated anxiety-like behaviors due to mechanical allodynia and attributed DXM-elicited anxiolysis in CP to decreasing the excitability of glutamatergic neurons in anterior cingulate cortex. Also, **Zhou et al.**[25] reported that DXM could alleviate anxiety-like behaviors secondary to CMSP mostly through blocking the decline of activity of Sirtuin 1 with downregulation of the expression levels of acetyl-p53 in the medial prefrontal cortex, and suggested that DXM may have a potential therapeutic role in CMSP-induced anxiety. Further, **Li et al.,** [26] found DEX can improve sleep deprivation-induced anxiety by inhibiting the activation of the p38/ Mitogen- and stress-activated kinase 1/nuclear factor-κB (NFκB) pathway, thus attenuating SD-induced inflammatory responses and oxidative stress in the cerebral cortex of mice.

A recent animal study showed that DEX anxiolytic effect might be attributed to reduction of the excitability of corticotropin-releasing hormone-producing hypothalamic para-ventricular nucleus via α_2-adrenergic receptor-triggered inhibition of these hypothalamic neurons [27]. Clinically, **Fu et al.**[28] found intraoperative DEX infusion significantly improved postoperative (PO) emergence agitation, anxiety and depression with attenuation of plasma levels of S-100β and neuron-specific enolase in older patients.

Regarding depressive disorders, **Xu et al.**[29] reported a success rate of 62.5% for once daily DXM intra-peritoneal injections for 7-days as management of animal with CP-induced depression and concluded that DXM alleviates CP-induced depression dose-dependently through neurogenesis promotion in the dentate gyrus region of the hippocampus. Also, **Zhou et al.**[30] found DEX injection might protect against depression-like behaviors through upregulation of the expression levels of microRNA -146a-5p and inactivation of NFκB pathway.

Clinically, recent prospective study documented the ability of early postpartum DEX infusion to significantly reduce the incidence of postpartum depression at 7 and 42 days postpartum in comparison to placebo and was found to provide such effect with maintained favorable safety profile [31]. Also, a recent systemic review and meta-analysis documented the prophylactic effect of DEX against the incidence of postpartum depression for women undergoing operative delivery [32]. Moreover, **Liu et al.**[33] found that DEX exhibits rapid and durable antidepressant properties that were evident after 2 infusion sessions in comparison to 6 sessions of ECT for patients had treatment-resistant depression with fewer side effects and no serious adverse events.

Conclusion

Chronic pain is psychologically stressful condition with wide variability range between anxiety and depression and results in kinesiophobia with poor social life and activity. DEX infusion according to the provided protocol might break the circle of pain-psychopathy-poor quality of life. All psychological scorings positively and significantly correlated with pain scores but improved kinesiophobia is the significant predictor for alleviation of depression.

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