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Placebo hypoalgesic and nocebo hyperalgesic effects in post-extraction patients—A cross sectional study

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Abstract

Background and objectives: Pain is an unpleasant sensory and emotional experience that affects people's physical, mental, and social health. Patients at times present with postoperative pain with no clinical signs after the surgical dental procedures and adequate pharmacological management. This can be due to the amplified emotional component of the individual in their postoperative period. Hence, this study aimed to estimate the association between placebo, nocebo effects, and postoperative pain associated with tooth extraction procedures.

Methods: A cross-sectional study was conducted among 301 patients attending the Department of Oral and Maxillofacial Surgery for tooth extraction. Preoperatively, the expected postoperative pain score was recorded using the "Numerical Rating Scale" (NRS), Anxiety and Depression were assessed using the "Hospital Anxiety and Depression Scale" (HADS), and Patients' expectancy regarding the treatment outcome was assessed using the "Credibility Expectancy Questionnaire" (CEQ). Observed postoperative pain scores at the 6th hour, 24th hour, and peak pain score of the day were recorded using the NRS.

Results: There were statistically significant associations ($p < 0.05$) found between expected and observed postoperative pain, preoperative anxiety and observed postoperative pain, preoperative depression and observed postoperative pain, placebo, nocebo effects, and observed postoperative pain.

Interpretation and conclusion: Our study showed a strong association between these variables suggesting that post-extraction pain is a multifaceted condition wherein pain expectation, preoperative anxiety, depression, and expectancy regarding the treatment outcome should be scrutinized before the extraction procedure.

Keywords
Anxiety, depression, expectancy, nocebo effect, placebo effect, postoperative pain, tooth extraction

Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1] The pain of dental origin is of social concern because it can lead to insomnia, poor mental health, declined social activities, and frequent absence from school.[2] Some of the dental procedures that induce postoperative pain are extraction of a completely erupted tooth, impaction, root canal treatment, osseous surgery, periodontal surgery, and surgical implant. Commonly, to relieve postoperative pain analgesics are prescribed after these dental procedures.[3] But we do face patients who never complain of postoperative pain while some complain of

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severe pain, despite adequate pharmacological management with standard dosages of analgesic drugs. Few patients experience enhanced response to the painful stimulation around the area of damaged tissue, which is termed hyperalgesia.[4] It may happen due to inadequate analgesia in some patients, but there are chances for patients' affective components of the brain to augment during the postoperative period.[5] This could be due to the patient's psychological issues during the preoperative period which could significantly influence the postoperative pain.[5] The proposed mechanisms through which psychological factors influence postoperative pain include variations in the action of default mode neuron networks, brain neuroplasticity, and genetic susceptibility.[6,7] In contrast, if there is decreased response to painful stimulation it is called hypoalgesia.[8]

Poorly managed acute postoperative pain is allied with amplified morbidity, extended use of opioids, delayed retrieval time, higher medical management costs, and the development of chronic pain in due time.[9] Psychologically influenced postoperative pain also results in unnecessary consumption of self-medication. Patients follow self-medication in the name of self-care, which leads to a surplus of resources, serious health risks like adverse drug reactions, extended illness, and increased resistance to pathogens.[10]

Placebo and nocebo effects are the positive and negative expectancies regarding the treatment outcome, respectively.[11] In clinical practice, identifying patients with a placebo or nocebo effect is necessary. Highly anxious patients will more likely have nocebo effects which result in harmful postoperative effects.[12] Positively influencing patients' realistic expectations regarding the treatment will induce the placebo effect to avoid discrepancies between realistic and unrealistic treatment outcomes.[11] To minimize the nocebo effect and maximize the placebo effect, a trustful, empathetic, warm clinician–patient relationship and attention to the patient's expectations are required.[13] Gentle positive description of pain in the preoperative period also influences the perception of pain during the intraoperative and postoperative periods. Personalized psychological pain management enhances the efficacy of dental treatments, curtails postprocedural complications, and reduces the extended use of analgesics or opioids, thereby improving overall therapeutic outcomes. With this background, this study was undertaken to estimate the association between expected and observed postoperative pain associated with tooth extraction procedure, to estimate the association between preoperative anxiety, depression, and observed postoperative pain associated with tooth extraction procedure, to estimate the association between placebo and nocebo effects and observed postoperative pain associated with tooth extraction procedure.

Materials and methods

Study design

A descriptive cross-sectional study was conducted after obtaining ethical committee clearance (no: EC/2020/2408/CR/84) and informed consent from the study subjects. The study was conducted over 2 months between July 2021 and September 2021 with patients attending the Department of Oral and Maxillofacial Surgery for the extraction of teeth. The sample size was estimated as 301 based on the previous study with the prevalence of anxiety and depression at 43% and 27%, respectively, among the study population.[5] As literature reviews showed a strong relationship among the variables, the effect size was fixed at 1 and the (p-value) level of significance was fixed at 0.05 to estimate the sample size.

Eligibility criteria

Patients aged 18–80 years who consented to participate in the study and had undergone intra-alveolar extraction in the Department of Oral and Maxillofacial Surgery were included through convenience sampling. Patients already under analgesics for other systemic diseases and tooth pain, patients with impacted teeth, and patients under psychiatric medicine were excluded from the study.

Data collection

A total of 301 patients in their pre- and postoperative period were recruited for the study. Sociodemographic data of the patients were recorded, and questionnaires were used to collect the data by a single trained investigator to avoid interviewer bias. Preoperatively, the expected postoperative pain score was recorded using the "Numerical Rating Scale" (NRS).[14] It is an 11-item self-report scale widely used for pain assessment, in which 0 was considered as "no pain" and 10 was considered "worst pain". Preoperative anxiety and depression were assessed using the "Hospital Anxiety and Depression Scale"(HADS).[15] It is a 14-item self-report scale widely used for the assessment of anxiety and depression, in which there are 7 questions for anxiety and 7 questions for depression. In the assessment of anxiety, scores 0–7 were considered normal, scores 8–10 were considered borderline abnormal, and scores 11–21 were considered abnormal. The same approach has been taken with depression assessment as well. Patients' expectancy regarding the treatment outcome was assessed using the "Credibility Expectancy Questionnaire"(CEQ) in their preoperative period.[16] According to Smeets et al.,

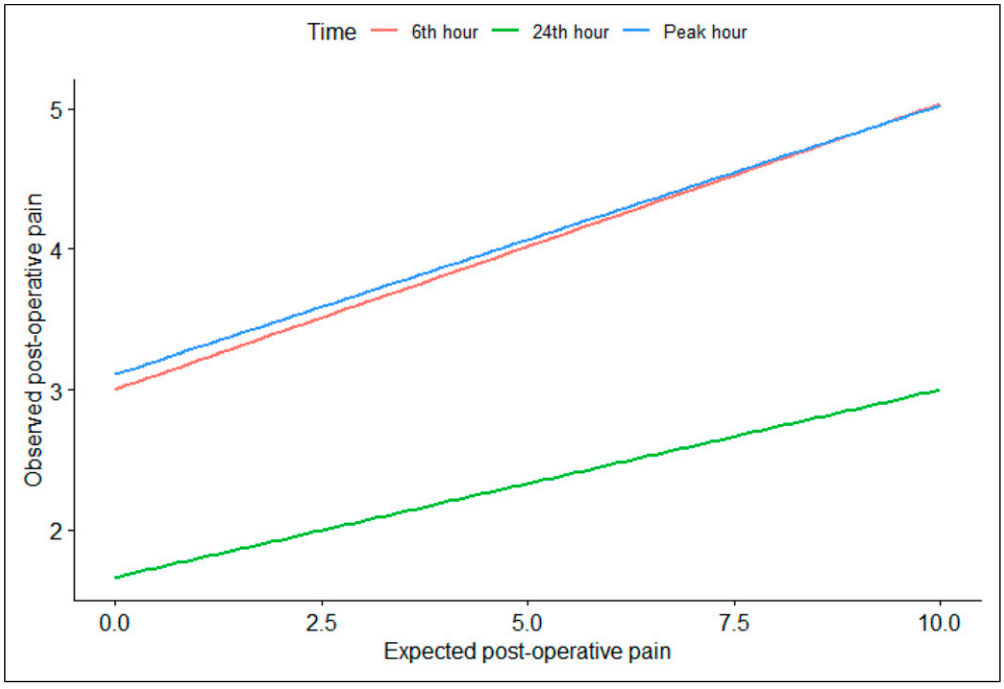

Figure 1. Regression line showing the correlation between expected postoperative pain and observed postoperative pain in the 6th hour, 24th hour, and peak hour.

questions 4 and 6 in CEQ were transformed with a minimum score of 1 and a maximum score of 9.[17] The original scorings of the CEQ are in the range of 6–54; in the present study, we have categorized the patients with nocebo effects (scores—6–30) and placebo effects (scores—31–54) based on the scores obtained from CEQ.[16] Observed postoperative pain scores at the 6th hour, 24th hour, and peak pain score of the day were recorded using the Numerical Rating Scale.

Statistical analysis

RStudio Version 1.2.1093 was used for statistical analysis. Descriptive analysis was carried out by frequency and proportion to study relevant variables. The Pearson correlation test was used to assess the correlation between continuous explanatory variables. The association between categorical variables was assessed by cross-tabulation, and a comparison of percentages and a chi-square test was used to test statistical significance. p-Value <0.05 was considered statistically significant.

Results

On analysis of demographic details, most of the patients in the study population belonged to the age group of 45–54 years (23.9%); there was a female gender prediction of 52.8%; the urban population was higher in number(55.1%) when compared to their counterparts; 49.5% had completed elementary level of education. 76% of the study population had a previous history of extraction; 35.9% of the patients were diagnosed with acute apical periodontitis, and 36.9% of extraction was done in the lower posterior region as shown in Table 1.

Analysis to estimate the association between expected and observed postoperative pain associated with tooth extraction procedure in the 6th hour, 24th hour, and peak hour of the day revealed that the data were low, positive ($p < 0.05$), and statistically significant as shown in Table 2.

Analysis to estimate the association between preoperative anxiety and observed postoperative pain revealed that the data were statistically significant in the spread of NRS score in the 6th hour, 24th hour, and peak hour according to anxiety status as shown in Table 3.

Figure 2 shows the correlation between preoperative anxiety status and observed postoperative pain in the 6th hour, 24th hour, and peak hour according to the HADS score and NRS score, respectively

Analysis to estimate the association between preoperative depression and observed postoperative pain revealed that the data were statistically significant in the spread of NRS score in the 6th hour, 24th hour, and peak hour according to depression status as shown in Table 4.

Figure 3 shows the correlation between preoperative depression status and observed postoperative pain in the 6th hour, 24th hour, and peak hour according to the HADS score and NRS score, respectively.

Table 1. Demographic characteristics of the study population (*N* = 301).

Background characteristics		Frequency	Percentage
Age group	18–24 years	18	6.00%
	25–34 years	49	16.30%
	35–44 years	51	16.90%
	45–54 years	72	23.90%
	55–64 years	61	20.30%
	≥65 years	50	16.60%
Gender	Female	159	52.80%
	Male	142	47.20%
Area of residence	Rural	20	6.60%
	Semi-urban	115	38.20%
	Urban	166	55.10%
Education	Illiterate	28	9.30%
	Elementary level	149	49.50%
	Higher secondary level	59	19.60%
	The third level of education	65	21.60%
Past dental history	First dental visit	72	23.90%
	H/O extraction	229	76.10%
Diagnosis	Acute apical periodontitis	108	35.90%
	Chronic pulpitis	81	26.90%
	Chronic generalized periodontitis	41	13.60%
	Chronic localized periodontitis	52	17.30%
	Aggressive periodontitis	12	4.00%
	Others	29	9.60%
Segment	Lower anterior	22	7.30%
	Lower posterior	111	36.90%
	Upper anterior	18	6.00%
	Upper posterior	95	31.60%
	Multiple extractions	55	18.30%

Table 2. Association between expected postoperative pain and observed postoperative pain.

Observed postoperative pain in:	Correlation coefficient (95%CI)	*p*-Value
6th hour	0.178 (0.066,0.285)	0.002
24th hour	0.137 (0.025,0.247)	0.017
Peak hour	0.166 (0.054,0.274)	0.004

Analysis to estimate the association between placebo and nocebo effects and observed postoperative pain revealed that the correlation of CEQ scores with observed postoperative pain in the 6th hour, 24th hour, and peak hour was low, negative ($p < 0.05$), and statistically significant as shown in Table 5.

Discussion

In the past, studies have focused on the relationship between preoperative psychological status and postoperative pain after various surgical procedures in the field of medicine, whereas we focused on the relationship between preoperative psychological status and postoperative pain after the tooth extraction procedure.

The findings of the existing study revealed that patients in the age group of 45–54 years (23.9%) were higher in the number who had undergone extraction, and this is similar to the previous study carried out by Jafarian et al.[18] This might be probably because the adult age group is susceptible for both caries and periodontitis which contributes to more extraction. In our study, there was a female predilection of 52.8% who had undergone extractions, and this finding is as per a similar study conducted by Alesia et al. where females were more prone to extraction may be because of their higher importance given to managing the dental problems than males.[19] This finding is contrary to the previous studies conducted by Jafarian et al. and Passarelli et al. where males were more

Table 3. NRS score (observed postoperative pain) according to anxiety status.

Anxiety	NRS (6th hour) median (IQR)	*p*-Value
Abnormal	5.5 (3,9)	<0.05
Borderline abnormal	4 (2,8)	
Normal	3 (1,4)	
Anxiety	**NRS (24th hour) median(IQR)**	***p*-Value**
Abnormal	3 (2,7)	<0.05
Borderline abnormal	4 (2,4)	
Normal	1 (0,2)	
Anxiety	**NRS (peak hour) median (IQR)**	***p*-Value**
Abnormal	5.5 (3,9)	<0.05
Borderline abnormal	5 (4,8)	
Normal	3 (1,4)	

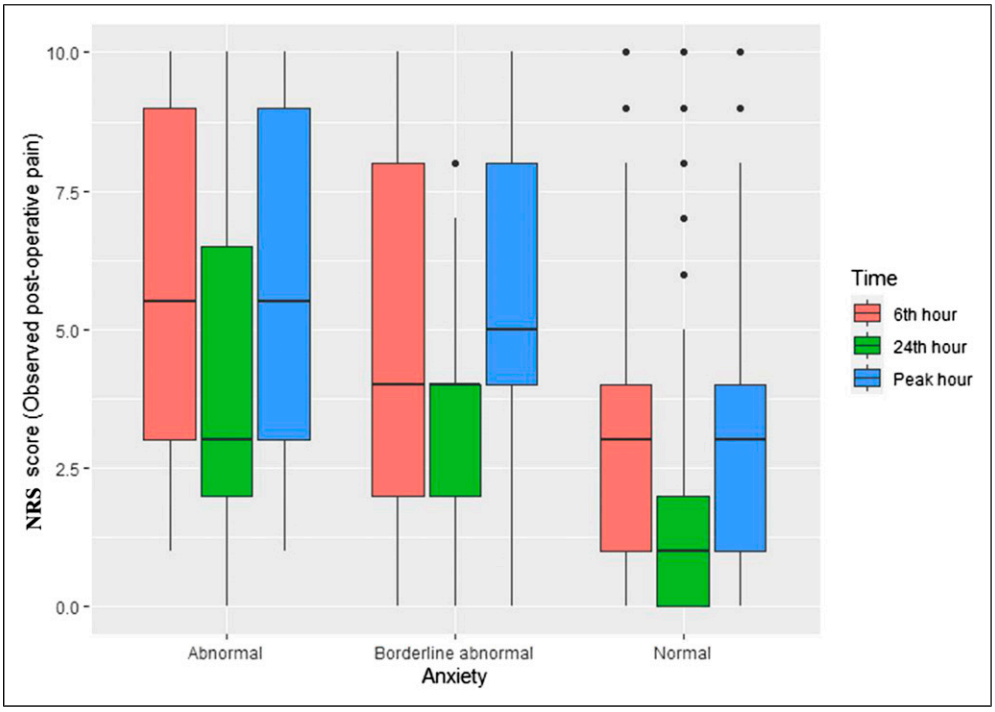

Figure 2. Boxplot depicting NRS score (observed postoperative pain) in the 6th hour, 24th hour, and peak hour.

prone to extraction may be due to their deleterious habits.[18,20] Patients hailing from the urban residential area (55.1%) had undergone more extractions than their counterparts following the previous study performed by Spalj et al., and they suggested that the urban population is more prone to periodontal disease which might be probably because of their unhealthy lifestyle behaviors and it contributes to more extractions.[21,22] Patients who had completed elementary level of education (49.5%) had undergone more extractions, and this followed the previous study conducted by Jafarian et al. and Passarelli et al.[18,20] This might be probably due to less awareness of oral health among low-level education groups. 35.9% of the patients with acute apical periodontitis have undergone more extractions, and it could be because in its chronic form it is left unnoticed and untreated and during exacerbations produce severe pain which contributes to more extractions.[23] In our study, 36.9% of extractions were

Table 4. NRS score (observed postoperative pain) according to depression status.

Depression	NRS (6th hour) median (IQR)	*p*-Value
Abnormal	7 (3,9)	<0.05
Borderline abnormal	4 (2,7)	
Normal	3 (2,4)	
Depression	**NRS (24th hour) median (IQR)**	***p*-Value**
Abnormal	4 (2,6)	<0.05
Borderline abnormal	2 (0,4)	
Normal	1 (0,3)	
Depression	**NRS (peak hour) median (IQR)**	***p*-Value**
Abnormal	7 (3,9)	<0.05
Borderline abnormal	4 (2,7)	
Normal	3 (2,4)	

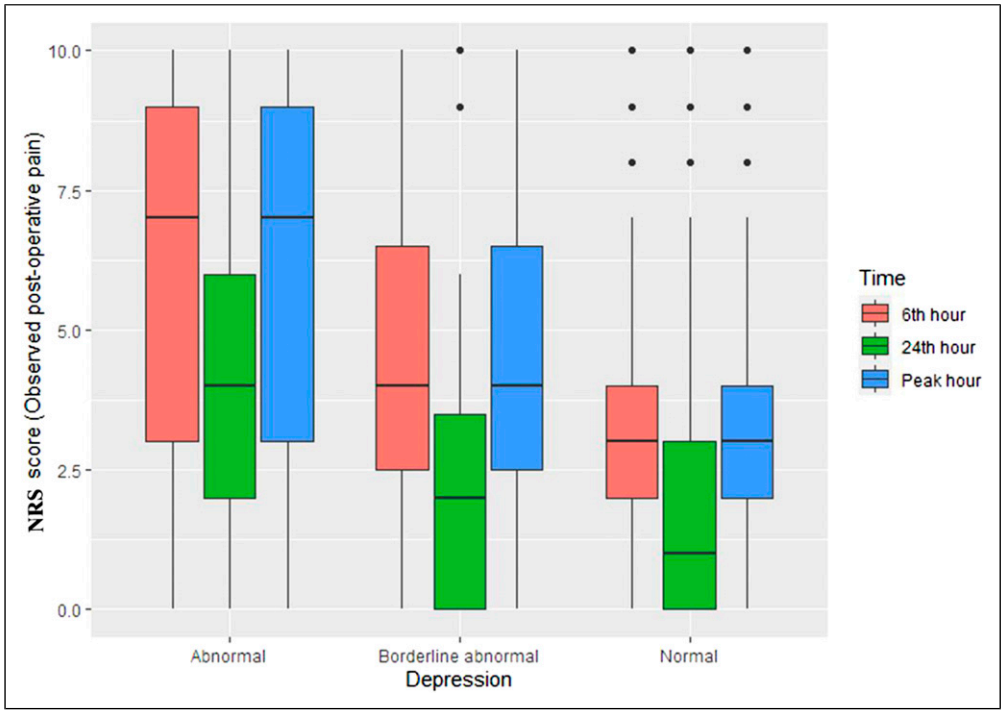

Figure 3. Boxplot depicting NRS score (observed postoperative pain) in the 6th hour, 24th hour, and peak hour.

Table 5. Association of CEQ score and observed postoperative pain.

Observed postoperative pain in:	Correlation coefficient (95%CI)	*p*-Value
6th hour	−0.166 (−0.274,−0.054)	0.004
24th hour	−0.147 (−0.256,−0.034)	0.011
Peak hour	−0.173 (−0.280,−0.061)	0.003

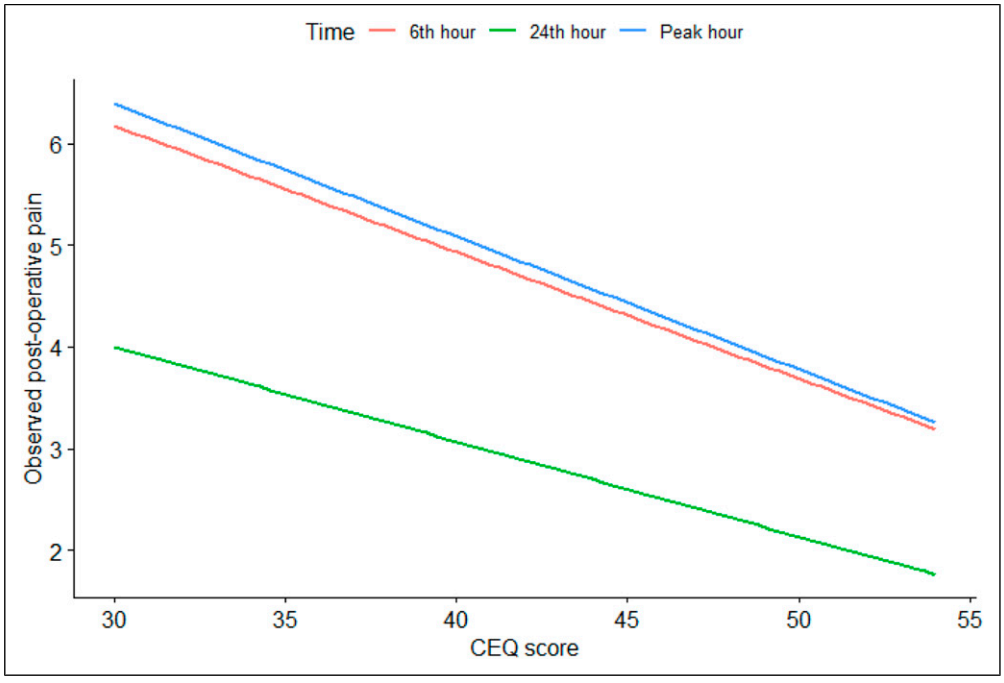

Figure 4. Regression line showing the correlation between CEQ score and observed postoperative pain in 6th hour, 24th hour, and peak hour.

carried out in lower posteriors, which is similar to a previous study conducted by Passarelli et al. which could be due to the presence of occlusal pits, fissures, and anatomic grooves in molars which contributes significantly to caries frequency.[20]

The prominent finding of our study is the strong association between expected postoperative pain scores and their observed postoperative pain scores in the 6th hour, 24th hour, and peak hour of the day, (Figure 1) and these findings are following the previous report by Bradshaw et al.[5] The possible reasons would be patient's mental representation of impending sensation of pain which changes the neural processes and impacted on the actual perception of pain.[24] This is in contrast to the previous report by Ene et al. where more patients expected severe pain than perceived.[25] This would be because of their retrospective estimation of postoperative pain where patients may catastrophize into more or less pain.

In the present study, there was a significant correlation between preoperative anxiety and postoperative pain, and this finding is consistent with the previous study conducted by Pinto et al.[26] The possible reasons could be that the more anxious the patient is, the more changes take place in the neurotransmitters mainly in dopamine, serotonin, and norepinephrine and turn leads to lower pain threshold and also patients tend to be more attentive to the pain which results in increased perception of pain.[27,28]

The present study also found a strong correlation between preoperative depression and postoperative pain which is following the previous study performed by Bradshaw et al.[5] The proposed mechanisms through which psychological factors influence postoperative pain include variations in the action of default mode neuron networks, brain neuroplasticity, and genetic susceptibility.[6,7]

The current study revealed that patients with positive expectancy regarding the treatment outcome (placebo effect) had reported less pain and patients with negative expectancy regarding the treatment outcome (nocebo effect) had reported more pain.(-Figure 4) These findings were consistent with the previous study conducted by Smeets et al.[17] Patients' experience with the past treatment influences patients' expectation regarding the present treatment outcome. Patients with a history of negative treatment experience decreased placebo analgesia due to expectation-induced pain modulation in the bilateral posterior insulae with high stimulation of the nociceptive process and low stimulation of the right dorsolateral prefrontal cortex by which placebo and nocebo effects are formed and maintained.[29]

In this extant study, extraction was not carried out by a single dentist because of which there could be operator bias, and due to social influence on patients regarding extractions, there could be subjective bias. Difficulty in interpreting some of the terminologies in

the HADS questionnaire such as "wound up" would have influenced patients' responses. Pain measurements were done for a shorter duration. Long-term effects were not followed up. These could be the possible limitations of the study.

Our study reveals that preoperative assessment of emotionally deteriorated patients is one of the important aspects in decreasing the probability of the development of negative notions. Dentists and psychologists have a pivotal role in identifying and intercepting underlying mood disorders. This would arrest the progression of the acute inflammatory state to chronicity and promote early wound repair, thereby enhancing patients' surgical experience.

In the future, clinical trials could be conducted on patients with preoperative psychological distress by treating them with non-pharmacological management like brain wave music, cognitive therapy, and relaxation techniques through which the placebo effect can be induced in dental practices. Further studies could be performed to analyze the factors influencing a patient's mental state in various dental treatments for achieving a good prognosis.

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Author contributions

Ms. Suchithra Sampath Kumar: Research idea, conduction of study, and manuscript writing. Dr. Sidra Bano: Modifications made in the study design and guidance for manuscript writing. Dr. P. Jagan: Statistical analysis and guidance in results interpretation.

Declaration of conflicting interests

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