Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 7S:576-583

The Effects of Green Tea on Post-Operative Pain and Anxiety in Tibia Surgery: A Randomized Double Blind Clinical Trial

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ABSTRACT

Postoperative pain is always not well controlled by current analgesics. Green tea is supposed to have analgesic and relaxing effect. This study assessed the effect of green tea on post-operative pain and anxiety in tibia surgery. A randomized double blind controlled trial has been conducted from May to September 2015in the north of Iran after being registered in Iranian Registry of Clinical Trials. Sixty eligible patients have randomly been assigned to either green tea (G) or placebo (P) group in quadripartite blocks. Pain severity and anxiety based on visual analogue scale (VAS)and State Trait Anxiety Inventory (STAI)were measured and compared two hours before surgery and drink intake (T0), after recovery filling Aldrete criteria(T1) and eight hours after the end of surgery (T2).Statistical analysis was performed by Chi-square test and repeated measurement in SPSS version 20. In the group of G and P 36 and 32patients remained with mean age of 36.76±10.96 and 41.26±11.44 years (p=0.120). Respectively 69.4% (n=25) and 75% (n=24) of participants were menin groups (p=0.787) and the mean of Body Mass Index (BMI) was 27.81±3.88 and 28.27±5.37 (p=0.706). There was no s ignificant difference in VAS score in each group and also between two groups in three measurement point times. The difference of STAI was significant in each group (p=0.001) and between two groups (p=0.01) in three measurement point times. Green tea could diminish post-operative anxiety but not post-operative pain.

Keywords: Green tea; Post operation; Pain; Anxiety

INTRODUCTION

Patients who have undergone surgery usually report a psychological fear of anesthesia, surgical failure or the other unknown complications of both surgery and anesthesia. This distress has adverse effects on the outcome of surgery and postoperative recovery. In addition, unrelieved post-operative pain, leads to central sensitization and developing of chronic pain. Sympathetic nervous system activation results in immune function down regulation, relating to increased glucocorticoid levels and depressed natural killer T cells. In other word post-operative pain is not only

distressing but also leads to several complications such as delayed recovery and increased hospital stay.[1-4]NSAIDs and opioids have almost always been prescribed to diminish postoperative pain. Concerning the analgesic and opioid dependency and adverse effects of synthetic drugs such as gastrointestinal upset, renal dysfunction and respiratory depression, satisfaction has not been almost achieved by these kinds of pain relieving modalities.[1, 5, 6] Therefore adding the other pain control strategies is demanded.

There is increasing evidence indicating that relaxation can alleviate the sensory and affective components of pain and improves post-operative conditions.[2, 4, 5, 7, 8]Relaxation has several advantages such as patient's satisfaction, reduction the post-operative opioid intake, decreasing the anxiety and mental reactions as well as stabilizing the patient's hemodynamic condition.[9, 10]Today, patient's relaxation has become a significant factor in health care setting which can alleviate post-surgical pain. [2, 4]Various modalities such as midazolam administration, music and relaxation methods have been employed for this purpose; however there are some limitations with mixed results.[2, 5, 7, 8, 11-13]

Green tea has been historically used for its relaxation effects.[13, 14] It also has various healthful effects such as cardiovascular protection, neuroprotection, anti- oxidant, anti-stress, anti-cancer, anti-inflammatory and anti-thrombogenic effects.[15-26] Although regular dietary of green tea may have valuable effects on health, however drinking too much can lead to an oxidative stress in the liver.[27, 28] L.Theanine [LT], the responsible substance is a unique amino acid, found only in tea plant.[15, 29]This non- protein amino acid has been a focus of attention due to its mental relaxation effect.[12, 13, 30-32]In recent years, evidence indicates that LT targets may include dopamine, serotonin, glutamate and Gama Amino Butyric Acid [GABA]. [14, 30]In addition LT is structurally related to glutamic acid and blocks the binding of L-glutamic acid to the glutamate receptor in the cortical neuronsand influences the secretion and function of neurotransmitters in the central nervous system [CNS]. In fact the increased level of extracellular glutamate in the brain in acute stress leads to facilitation of sympathetic nervous system activity and due to the competitive role of LT against excitation of the glutamatergic phenotype, a relaxation effect of green tea is suggested.[29, 30] Considering the frequency, brain waves have four types of classification including: Alpha, Beta, Delta and Gamma, among which Alpha wave is an index of relaxation.[14]By consumption of 50-200 mg of LT, Alpha wave is generated on the occipital and parietal regions within 40 minutes.[30-32]When green tea is orally administrated, LT passes through brain blood barrier without any metabolic changes, increases by one hour at the latest in serum, liver and brain, thereafter decreases sharply in the serum and liver, however it begins to decrease in brain after five hours.[6, 14, 18]

Several studies have shown the relaxation properties of green tea however to the best our knowledge its efficacy in post-operative pain and anxiety reduction has not been considered. Therefore this study was planned to investigate the efficacy of Iranian green tea for this purpose. The rationale behind this study was provided by several studies.

MATERIALS AND METHODS

This randomized double blind clinical trial took place in an academic hospital in the North of Iran affiliated to Guilan University of Medical Sciences [GUMS]from May to September 2015. Before sampling, its proposal has been approved by Ethics committee of GUMS by reference number of 1930596705 and registered in Iranian Registry of Clinical Trials [IRCT] by number of IRCT201504076186N9.Allpatients scheduled for elective tibia surgery [transverse mid shaft of tibia with displacement], aged between 18-65 years enrolled the study after fulfilling an informed consent by them or their legal responsible. At first in designed protocol only patients in age range of 30-65 years must have been included, but because of mid shaft fracture of tibia occurs almost always among young adults during motor accident so we have entered older than 18 years. The patients were assessed by routine biochemistry tests and 12 leads electrocardiogram and interviewed for a medical history and typical tea consumption pattern. The exclusion criteria included: cognitive impairment in the level which cannot answer the questionnaires, severe heart failure, renal or hepatic failure, pregnancy, breast feeding, the history of dependency or substance abuse, current or past history of psychiatric disorders, and daily intake of more than 3 tea bags or 4cups of diluted tea, any abnormality in ECG result and the recovery time period more than thirty minutes. Thepatients' confidence and anonymity were preserved and they were assured that they could withdraw from the survey at any time, with no impact on their treatment.

They were allocated to one of the two groups using randomized fixed quadripartite blocks; green tea [G] or placebo [P]. A cup of green tea was prepared by leaving a tea bag containing 50 mg LT in 100 ml of 69-87°c water for2- 3 minutes.[33]In group G, a cup of green tea and in group P a cup of hot water was taken 2hours before and 6hours after the end of operation. In both groups an opaque cup with lid and straw was used. In order to mask the bitter taste of green tea, the sweetener and peach flavor were added to both green tea and hot water. Therefore the participants could not detect any discernible taste difference between drinks.

It is needed to mention that the anesthesia method was the same in both groups.

On arrival in the operating room, an intravenous catheter 18 gauge, was inserted into the forearm vein and standard monitoring, including electrocardiography with both leads II and V5 with automated ST-segment analysis to detect ischemia, pulse oximetry, End tidal co2,urine output (UOP) and non-invasive blood pressure(NIBP) with an interval of 3 minutes was applied. Anesthesia was inducted with 0.05 mg/kg midazolam and 2µg/kg sufentanil and etomidate 0.3mg/kg with a pretreatment dose of 0.03mg/kg to suppress myoclonus related to the drug, propofol was also administrated to prevent opioid induced cough (34, 35). After neuromuscular blockade was achieved with 0.2 mg/kg cisatracurium, trachea was intubated. Anesthesia was maintained with continuous infusion of propofol 50-150 mg/kg/min, sufentanil 0.1-0.3 µg/kg/h and cisatracurium 0.6 mg/kg/h. The analgesia protocol was administration of 1gramapotel within the last fifteen minutes of surgery and six hours after. If patients complained of pain they would receive 2 mg of intramuscular morphine but were excluded from survey. The intensity of pain on movement using visual analogue scale (VAS), and State Trait Anxiety Inventory (STAI) -short form- were measured at three measurement point times two hours before surgery and drink intake (T0), when discharging from recovery ward filling Aldrete criteria (T1), and 8 hours after the end of surgery (T2). We also compared two groups according to hemodynamic parameters; heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP) at T0, T1 and T2.

Statistical Methodology

To test all scale variables normality, Kolmogorov-Smirnov test has been used. Based on the normality of variables the appropriate statistic tests were chosen. To compare patients' characteristics variables, Chi-square test was used. Repeated Measurement has been applied to determine the trend of changes. The differences of VAS and STAI between the two groups at baseline were compared by using paired-t-test. Also Mann Whitney U test has been used to compare the changes of VAS and STAI from T0 until T2. The values were estimated as mean ± standard deviation (SD). P value of <0.05 was considered significant in all analysis. The data analysis was performed in SPSS software version 20.

RESULTS

The subjects were selected from a 155 patients with tibia fracture (transverse mid shaft of tibia with displacement) during the study period. Among them, 51 did not meet the inclusion criteria and 15 of them refused to enter the study for personal reasons. The remaining 89 patients were enrolled in this clinical trial and were divided into Green tea and Placebo groups. Two patients allocated to G group and 2 patients allocated to P group had the recovery time more than thirty minutes and were excluded. Six patients of group G and 11 of group P lost the follow up for receiving intravenous morphine because of inadequate pain control and therefore were deleted from the study. Finally a total of 68 patients (36 in group G and 32 in group P) completed the survey and their data has been analyzed.

There was no significant difference between two groups regarding to the base line characteristics. The means age of the subjects in groups G and P were 36.76±10.96 and 41.26±11.44 years respectively (P=0.120). In group G, 69.4% (n=25) and in group P 75% (n= 24) of participants were men (P=0.787). The mean of BMI of participants in green tea and placebo groups were 27.81± 3.88 and 28.27±5.37 (p= 0.706). No important harm or unintended effect has been reported in each group.

Based on VAS there was no significant difference in each group and also between two groups in three measurement point times(table2).According to STAI the difference was significant in each group (P=0.001) and between two groups(P=0.01) in three measurement point times(table3). Comparing two groups as the mean of VAS at T0, T1 and T2,although the results were better at T0 and T2 in group G but it was not significant (P=0.355 and 1.000), however the STAI was significantly lower at T1 among green tea consumers (P=0.048).

Regarding to HR, the difference between two groups at T0 (P=0.947, t=0.067),T1(P=0.152,t=1.45) and T2(P=0.32,t=1.0) and the trend of changes(P=0.139) were not significant. However the results were significantly different in group G(P=0.0001, F=24.8) and group P(P=0.001, F=10.7) at three measurement point times. Regarding to SBP, the difference between two groups at T0 (P=0.915,Z=0.1),T1(P=0.79,Z=0.26) and T2(P=0.97,Z=0.038) and the trend of changes(P=0.633,F=0.23) were not significant. However the results were significantly different in group P (P=0.001,F=5.63) but not in group G(P=1.0,F=0) at three measurement point times. Regarding to DBP, the difference between two groups at T0 (P=0.724,Z=0.353), T1 (P=0.722,Z=0.356) and T2 (P=0.751,Z=0.318) and the trend of changes(P=0.142,F=2.03) were not significant. However the results were significantly different in group G(P=0.0001,F=66.68) and group P(P=0.326,F=1.01) at three measurement point times.

DISCUSSION

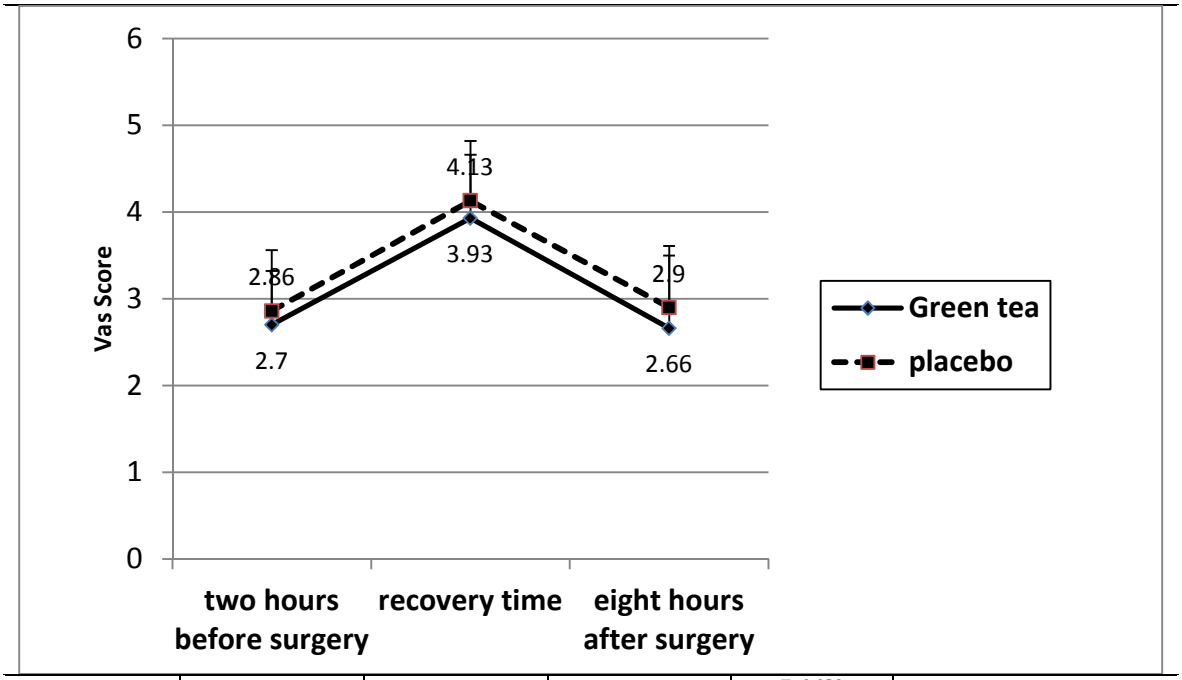
Several studies have indicated that relaxation is in correlation with post-operative pain reduction and much more ones have examined different modalities to blunt the stress response due to surgery and pain control.[2, 4, 7, 8, 36-39]. However no study has been designed to evaluate the effects of green tea as a relaxation agent on post-operative pain. It might be the special feature of the present study. Postoperative pain includes distress which is described as the amount of emotional upset associated with the sensation of pain, and if not well controlled, results in chronic pain, physical and psychological injury. The amount of emotional tension, worry and nervousness experienced by operated patients was defined as anxiety. Relaxation response is characterized by a quiet mind and a reduced sympathetic stimulation of the hypothalamus, increases endogenous opioid secretion and consequently moderates pain in central nervous system.[2]

Given the importance of the issue, several studies have been performed to investigate the efficacy of different relaxation modalities that can contribute to reduce post-operative pain and anxiety; on the other hand researches have shown the relaxation properties of green tea. Firoozabadi *et al.* investigated the effects of relaxation on post-operative pain and hemodynamic parameters in coronary arteries bypass graft [CABG] surgery. They reported that relaxation could be effective in post-operative hemodynamic status with no significant effect on pain reduction.[5]Kimura *et al.* showed that the results in LT group were better than control group. They measured subjective and physiologic response to acute stress and reported that LT intake could alleviate the sympathetic activity during acute stress challenge, reflected in heart rate and saliva- IgA.[30]Lu *et al.* reported that although LT induces some relaxation effect under resting condition, however it has not any anti-anxiety effects in acute increased stress conditions.[29] Haskell*et al.* claimed that LT could block the reduced sleep efficacy induced by caffeine.[13] Wise *et al.* suggested that LT might be a potential candidate to reduce withdrawal signs in opioid- dependent patients.[32] Seers *et al.* found that relaxation techniques could reduce post-operative pain in elective orthopedic surgeries without a sustained effect.[7]Roykulcharoen *et al.* showed that relaxation had beneficial effects on post-operative pain and distress in abdominal surgery.[2] Juneja *et al.* confirmed that drinking the green tea induces a noticeable relaxation effect and could make people who are exposed to many kinds of mental pressure feel relaxed.[14]Topcu *et al.* suggested that relaxation exercises are non- pharmacological and effective methods in postoperative pain reduction in upper abdominal surgery.[8]Vazquez *et al.* studied the effects of cybertherapy on postoperative patient's condition admitted to the intensive care unit. Their findings supported the positive relation between relaxation and postoperative discomfort reduction.[4]

In the present study the authors tested the hypothesis that Iranian green tea might reduce postoperative pain and anxiety reflected in VAS and STAI scores and hemodynamic parameters including heart rate [HR], systolic [SBP] and diastolic blood pressure [DBP]. VAS is the gold standard for pain measurement with acceptable validity and reliability.[40]STAI a psychological inventory is a commonly used measure of two types of anxiety; state anxiety or anxiety about an event, and trait anxiety or anxiety level as a personal characteristic. Higher scores are indicated as higher levels of anxiety. In clinical settings it can diagnose anxiety and distinguish it from depression.[41, 42]Our finding did not reveal any significant difference between two groups regarding to VAS score and hemodynamic parameters, but in agreement to previous studies have reported encouraging results about green tea relaxation effects, we also found that STAI which represents the level of anxiety diminished in green tea group comparing to placebo, although this reduction was only significant at T1.As green tea effects on alpha waves generation begins within 40 minutes after oral administration and starts to decrease in brain after five hours, it would be predictable that at T1 that represents almost 3:30 hours after receiving green tea, it might be the peak levels of LT. It was found that in both groups STAI significantly diminished at T2 comparing to T0, on the other hand although the results in group G were better at T1 and T2, but it was only significant at T1. The reason might be due to that with the passage of 8 hours of operation and receiving analgesics, the patients in both groups could cope with the stress and anxiety related to the surgery therefore the difference was not significant at T2 although they received green tea also in at 6 hours after surgery.

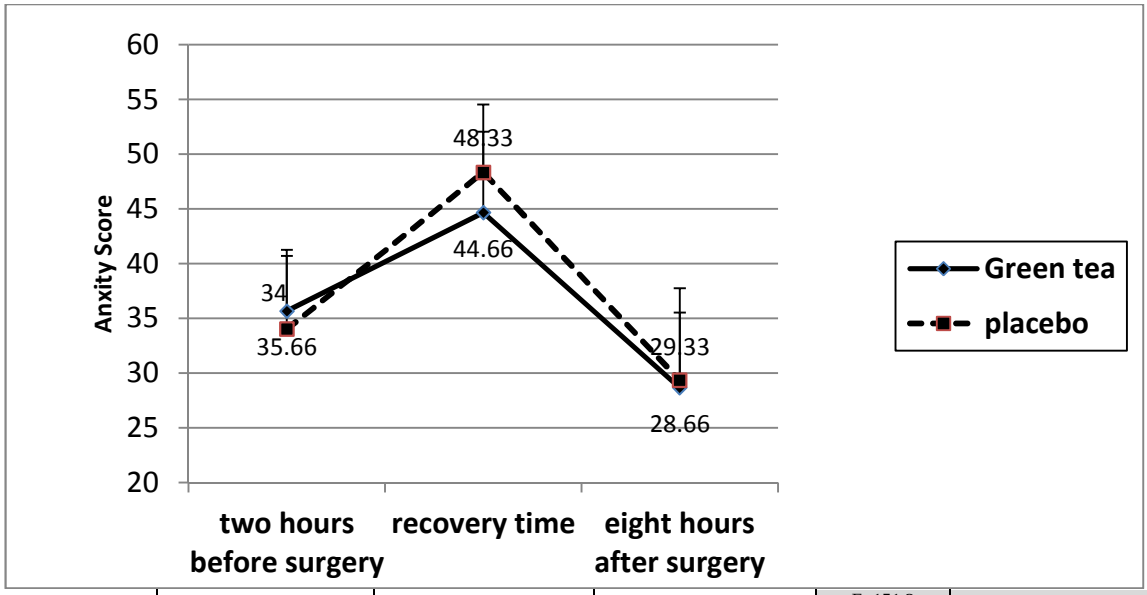
In the current study, several limitation factors may be responsible for green tea not being able to diminish postoperative VAS score; timing and dosage of green tea LT contain may not have been optimal. It is noticeable that different styles of surgery induce different stress degrees.

Table 2: The trend of changes of VAS score in measurement time points in green tea and placebo groups



Green tea	2.7±0.7	3.93±0.69	2.66±0.71	F=0.039 P=0.84	P-value Between groups F=0.067 P=0.79
Placebo	2.86±0.62	4.13±0.73	2.9±0.84	F=0.029 P=0.86	
	P=0.288	P=0.274	P=0.27		

Table 3: The trend of changes of anxiety score by STAI in measurement time points in green tea and placebo groups



Green tea	35.66±6.78	44.66±6.28	28.66±6.28	F=151.2 P=0.0001	P-value Between groups F=5.85 P=0.01
placebo	34±5.63	48.33±7.46	29.33±9.07	F=123.2 P=0.0001	
	P=0.355	P=0.048	P=0.99		

Table 1: The demographic data of patients in green tea and placebo groups

Variable		Groups		P-value
		Green tea	Placebo	
Gender	Male	25(69.4%)	24(75.0%)	P=0.787
	Female	11(30.6%)	8(25.0%)	
Age(year)		36.76±10.96	41.26±11.44	P=0.120
Weight(kg)		82.36±13.1	77.03±12.17	P=0.1
Height(Cm)		171.9±5.79	165.6±4.23	P=0.001
BMI(Kg/m2)		27.81±3.88	28.27±5.37	P=0.706

The other reason could be inner personal factors that show patients belief and trust about efficacy of the type of treatment that influences on pain relief outcomes. It is believed that the positive attitude towards a treatment method plays a powerful role in induced analgesia. It is important to give the patients right and intelligent information and adequate explanation.[43, 44]

CONCLUSION

Our finding although did not feature any decrease in pain score and hemodynamic parameters, but resulted in relaxation effect and diminishing of anxiety by green tea.

Suggestions

Considering to several positive impacts of green tea on health in addition to its relaxation effects, easy preparation, cost benefit, and safe in defined doses, it is worth to design further studies with larger sample sizes, in different styles of surgeries and employing higher doses of LT. In addition, more measured parameters are needed to generalize the findings. Considering the limited data, large and well planned trials are still needed before any recommendations for pre, peri or postoperative dosage of LT that might be effective in relieving of pain and anxiety due to the surgery, also in order to compare the relaxation effects of green tea with other relaxant agents.

Conflict of interest

The authors had no conflict of interests to report.

Acknowledgment:

Activities related with this work have been supported, in part, by Anesthesiology Research Center of Guilan University of Medical Sciences. The authors would like to acknowledge the collaboration of medical doctors and residents, nurses, and administration staff of the orthopedic ward of Poursina Hospital, Guilan, Iran.

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