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COMPARISON OF THE ANXIOLYTIC EFFECTS

OF BITTER ORANGE (CITRUS AURANTIUM. L) AND DIAZEPAM BEFORE OPHTHALMIC SURGERY: A SINGLE-BLIND RANDOMIZED CLINICAL TRIAL

COMPARACIÓN DE LOS EFECTOS ANTIAPRENSIVOS DE LA NARANJA AMARGA (CÍTRICO AURANTIUM. L) Y EL DIAZEPAM ANTES DE LA CIRUGÍA OFTÁLMICA: UNA PUEBA CLÍNICA PARA LA CEGUERA

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ABSTRACT

Anxiety is an unpleasant feeling that affects the comfort and health of the patient. Surgery-related anxiety is defined as the specific stress, the patient experience when exposed to surgery. The aim of this study is to compare the effects of citrus Aurantium and diazepam on the preoperative anxiety of patients who were candidates for ophthalmic surgery. In this single blind clinical trial study, a total of 67 patients who referred to Bou Ali Sina hospital (Sari, Iran) for ophthalmic surgery were selected and randomly divided into 2 groups. The night before surgery, the patients of group 1 (33 cases) received 100 cc of citrus Aurantium blossom distillate while the patients in group 2 (34 cases) received 1 diazepam pill (5 mg) dissolved in 100cc water. The level of patients' anxiety was measured by using Spielberger Stait-Trait Anxiety Inventory (STAI) before intervention, and the next morning (immediately after entering the operating room).

Keywords: preoperative anxiety, citrus aurantium, diazepam, ophthalmic surgery.

RESUMEN

La ansiedad es una sensación desagradable que afecta la comodidad y la salud del paciente. La ansiedad relacionada con la cirugía se define como el estrés específico, la experiencia del paciente cuando se expone a la cirugía. El objetivo de este estudio es comparar los efectos de los cítricos Aurantium y el diazepam sobre la ansiedad preoperatoria de los pacientes que fueron candidatos para la cirugía oftálmica. En este estudio de ensayo clínico ciego simple, un total de 67 pacientes que remitieron al hospital Bou Ali Sina (Sari, Irán) para cirugía oftálmica fueron seleccionados y divididos al azar en 2 grupos. La noche antes de la cirugía, los pacientes del grupo 1 (33 casos) recibieron 100 cc de destilado de flor de Aurantium de cítricos, mientras que los pacientes del grupo 2 (34 casos) recibieron 1 pastilla de diazepam (5 mg) disuelta en agua de 100 cc. El nivel de ansiedad de los pacientes se midió mediante el uso del Inventario de ansiedad por rasgos estables de Spielberger (STAI) antes de la intervención y a la mañana siguiente (inmediatamente después de ingresar al quirófano).

Palabras clave: ansiedad preoperatoria, citrus aurantium, diazepam, cirugía oftálmica.

INTRODUCTION

Anxiety is an unpleasant feeling that affects the patient comfort and health surgery-related anxiety refers to the specific stress, the patient experience when undergoing surgery. It has been acted as a unique psychological structure which differs from other aspects of patient's well-being and requires a specific and dependent diagnosis which is related to the clinical management. In an observational study of more than 16000 patients, it was found that anxiety is the most common report as the worst aspect of surgery.

Preoperative anxiety has the potential to alter the dynamics of an elective procedure and has been shown to detrimentally affect patients both cognitively and physiologically. If mismanaged, it can lead to essential procedures being postponed or canceled, delay postoperative recovery, and increase patients' requirements for medical intervention postoperatively. Besides, other evidence supported preoperative anxiety and depression as independent predictors of increased rates of persistent postoperative pain and decreased level of health-related quality of life.

Preoperative anxiety was also associated with factors such as difficult access to veins, autonomic changes such as tachycardia, palpitations, perspiration, dry mouth, nausea and vomiting during the post-anesthesia period. Prevalence of preoperative anxiety has been reported in various studies, ranging from 60% to 80% in Western countries, but some researchers have shown that the rate is wider and ranging from 11% to 80% (Cevik, 2018). The stress and anxiety associated with the anesthesia and surgery process may be related to the activity of the hypothalamus and adrenal glands, which may increase adrenocorticotropic hormone (ACTH) circulation.

On the other hand, Pre-operative anxiety, causes changes in endocrine function, which increases the secretion of insulin antagonists such as growth hormone and cortisol, which may increase blood glucose level and in some cases cause a condition called transient diabetes. Preoperative premedication refers to the use of anesthetic drugs to make the anesthesia and surgery process safer and more enjoyable (Nagendrababu, et al., 2019). Using an appropriate dose of sedation in addition to eliminating the patient's anxiety during surgery have an impact on the metabolic responses to stress and oxygen consumption (Triantafillidis, et al., 2013). various drugs such as benzodiazepines, analgesics, anti-anxiety, anticholinergics and H2 blockers are used for premedication to reduce anxiety (Du, et al., 2019; Gupta, et al., 2019).

Among these cases, diazepam is the most common drug that used as premedication (Rezaei, et al., 2012). Diazepam is a benzodiazepine that binds to the molecular components of the GABA-A receptor present in the neuronal membrane of the central nervous system, leading to the opening of the chlorine channel, thereby exerting its muscular smoothing and relaxing effect (Kalinina, et al., 2016). synthetic drug such as benzodiazepines have the advantage of rapid onset of action, they have the potential to interfere with patient's normal activity and often difficult to stop once started the therapy. These problems and the other side effects of synthetic anxiolytic drugs have enforced more people to seek natural and herbal therapies (Millan, 2003; Nemeroff, 2003). Citrus aurantium L. (Rutaceae), commonly known as bitter orange, is usually utilized as a flavoring and acidifying agent for food (Karabıyıklı, De**ğ**irmenci & Karapınar, 2014). The flowers of this plant in traditional medicine used for the treatment of neurological diseases such as hysteria, epilepsy and neurasthenia. Additionally, this herb is known as sedative, hypotonic, appetizer and lifter palpitations (Suryawanshi, 2011). Regarding to importance of anxiety relief before surgery, due to its role to cause various complication in intra and postoperative (Rodrigues, et al., 2018; Pan, et al., 2019) and popularity of herbal medicine as a premedication in all over the world (Ulbricht et al., 2013; Bent, Padula & Neuhaus, 2004), this study was conducted to compare the effects of citrus Aurantium and diazepam on preoperative anxiety of patients who were candidate for ophthalmic surgery in Bou Ali Sina Hospital (Sari, Iran).

MATERIAL AND METHODS

This single blind randomized clinical trial, upon approval of ethics committee of Mazandaran University of Medical Sciences and registering the search in Iranian Registry Clinical Trial (IRCT20191005044989N1), then 70 candidate patients for ophthalmic surgery aged (18-80) who referred to Bou Ali Sina hospital (Sari, Iran) from 7 October 2019 to 29 November 2019 were included in the study.

Sample size was calculated at 30 participants per group with a significant level of 0.05 (95% confidence interval) and power of β=0.05 selected (statistical power of 95%). By predicting the dropout rate, 35 subjects were allocated to each group.

The inclusion criteria were as follow: 1) expressing desire to do by the participant; 2) age range 18-80 years; 3) no prior history of hypertension and known anxiety disorders, no allergy to plants; 4) being in I and II classes of physical status of American society of anesthesiologist (ASA).

Participants whom were allergic to Citrus Aurantium, its products and tranquilizers expect for those under study were removed from list. Finally, 3 individuals were removed from the list of 70 candidates (2 patients of Citrus Aurantium group because of refusing to complete the study, 1 patient of Diazepam group due to cancelation of their surgery).

The researcher visited the ophthalmic ward of the hospital, night before surgery. After introducing himself to patients were candidate for ophthalmic surgery and explaining the objectives of the study, written consent form was obtained from the selected participants.

Continuous sampling was applied in this study and subjects were randomly assigned to two groups (Citrus aurantium and Diazepam groups) by drawing lots. Letter A and B were written to two identical cards and the aid researcher, who was unaware of the content of each card, was asked to choose one of the cards. The subjects were assigned to two groups as follows: letter A (citrus Aurantium) and letter B (diazepam). Demographic form and Spielberger State-Trait Anxiety Inventory (STAI) questionnaire were first filled by the aid researcher and via interview.

Interventions were done in 2 groups and as follows:

Group 1) the participants in this group received 100cc of Citrus aurantium blossom distillate

Group 2) the participants in this group received 5 mg oral diazepam dissolved in 100 cc water.

The next morning, the aid research met with the patient again in the operating room environment. In the meantime, try to interview the patient in a quiet room away from commuting, so that the patient answers the researcher's questions accurately.

The Spielberger state-trait anxiety inventory questionnaire, which validity and reliability have been assessed in the Iranian population, has two parts. The first part deals with the state of anxiety (situational anxiety) and includes 20 questions with a rating scale: very low, low, high, very high. Each option was given a score of zero to 3, respectively. The second part of the Spielberger questionnaire also contains 20 questions, each of which has a rating scale: almost never, sometimes, often, almost always, and to measure the individual's trait anxiety (trait anxiety) given to each option. Points are given a score of zero to three, respectively (Khodayari-Fard, et al., 2010).

Following data collection, they were analyzed by SPSS version 20 and chi square, and independent and paired t-tests.

RESULTS AND DISCUSSION

The study was conducted on participants ranging age from 18 to 80 and average age of 56.08±17.41 years (citrus Aurantium group) and 58.11±17.96 years (diazepam group).

There was no significant relation between the two groups regarding to age (p= 0.621), sex (p= 0.872), type of surgery (p=0.752), history of surgery (p=0.241) and study level (p=0.982). Table 1 showed lists demographic data of the two groups.

Table 1. Demographic data of Citrus aurantium and Diazepam groups.

Demographic Data	Citrus aurantium	Diazepam	P value
Sex			**0.621**
Male	13(39.4%)	15(44.1%)	
Female	20(60.6%)	19(55.9%)	
Type of surgery			**0.752**
Cataract	13(39.4%)	14(41.2%)	
Strabismus	5(15.2%)	5(14.7%)	
DCR	7(21.2%)	5(14.7%)	
Petrigyum	4(12.1%)	3(8.8%)	
Belfaroplasty	2(6.1%)	2(5.9%)	
Pelk tumor	1(3%)	2(5.9%)	
Lacrimal probing	0(0%)	1(2.9%)	
Vitrectomy	1(3%)	2(5.9%)	
History of surgery			**0.241**
Yes	16(48.5%)	11(32.4%)	
No	17(51.5%)	23(67.6%)	
Education			**0.982**
Elementary	7(21.2%)	8(23.5%)	
Secondary school	7(21.2%)	6(17.6%)	
High school	6(18.2%)	6(17.6%)	
Higher education	13(39.4%)	14(41.1%)	

There was not significant difference in mean of state anxiety score in pre and post intervention of the citrus Aurantium group (P=0.231) while; there was a significant difference in mean of trait anxiety scores in pre and post intervention of this group (P<0.001) (Table 2).

Table 2. Mean of State and Trait Anxiety in Pre and Post Intervention of Citrus aurantium. Group.

Anxiety / Phase	Pre intervention (mean± SD)	Post intervention (mean± SD)	P value
State	43.6±3.19	43.09±3.88	0.231
Trait	49.12±3.67	46.87±3.87	<0.001

There was a significant difference in mean of state and trait anxiety score in pre and post intervention of diazepam group (p=0.016), (p<0.001) respectively (Table 3).

Table 3. Mean of Sate and Trait Anxiety in Pre and Post Intervention of Diazepam Group.

Anxiety Phase	Pre intervention (mean± SD)	Post intervention (mean± SD)	P value
State	44.23±3.12	43.11±3.33	0.016
Trait	49.26±3.68	46.91±3.26	<0.001

Regarding to state and trait anxiety in pre and post intervention between the two groups; no significant differences were found (p=0.441), (p=0.970) respectively (Table 4).

Table 4. Means of trait and state anxiety in pre and post intervention between the two groups.

	Citrus aurantium (mean± SD)	Diazepam (mean± SD)	P value
Pre intervention			
State anxiety	43.6±3.19	44.23±3.12	0.965
Trait anxiety	49.12±3.67	49.26±3.68	0.874
Post intervention			
State anxiety	43.09±3.88	43.11±3.33	0.441
Trait anxiety	46.87±3.87	46.91±3.26	0.970

The result of present study revealed effectiveness of both citrus Aurantium and diazepam on reducing preoperative anxiety.

A closer look at the function of both citrus Aurantium and diazepam can reveal its properties.

Diazepam is a benzodiazepine that binds to the molecular components of the GABA-A receptor present in the neuronal membrane of the central nervous system, leading to the opening of the chlorine channel, thereby exerting its calming and relaxing effect (Kalinina, et al., 2016).

The flower extract of citrus Aurantium has been found to be contain flavonoids include neohesperidin, as they have affinity to bind benzodiazepine receptors (Mannucci, et al., 2018).

In a study by Basiri-Moghadam, et al. (2016), compared the effects of saffron and diazepam on preoperative anxiety in patients undergoing herniorrhaphy surgery, it was shown that the use of 5 mg diazepam 3 hours before herniorrhaphy significantly reduced preoperative anxiety. Hulscher (1987), in their study investigating the role of diazepam as an anxiety-reducing agent, they found that diazepam reduced preoperative anxiety but did not decrease anxiety significantly.

The results of Dehghan & Kalani (2018), studied; aimed to comparison the impact of oxazepam and citrus Aurantium on preoperative anxiety showed that the mean of patients' anxiety, reduced significantly in citrus Aurantium group after intervention; findings of present study are relevant with the result of Dehghan & Kalani (2018), study; but the sample size and the received dosage of citrus Aurantium were the main differences between these two studies.

Study by Lehrner, et al. (2000), indicated that citrus Aurantium essential broadcast in the dental waiting room cause reduction anxiety in referred patients. In spite of the similarity in results and our study, but there was a difference in tools that evaluated anxiety in these two studies.

The results of Sharifipour, Baigi & Mirmohammadali (2015), study aimed to determine the effect of aromatherapy (citrus Aurantium essence) before cesarean section surgery indicated that inhalation aromatherapy is effective in reducing anxiety before surgery and can use this method as complementary medicine therapies in clinical practices. The results of this study are in line with present study while the type of administration was the main difference between these two studies.

CONCLUSIONS

The results of present study reveals that both citrus Aurantium and diazepam almost have the same effect to reduce preoperative anxiety in patients whom were candidate for ophthalmic surgery; therefore we can use citrus Aurantium as a premedication drug.

BIBLIOGRAPHIC REFERENCES

Basiri-Moghadam, M., Hamzei, A., Moslem, A. R., Pasban-Noghabi, S., Ghorbani, N., & Ghenaati, J. (2016). Comparison of the anxiolytic effects of saffron (Crocus sativus. L) and diazepam before herniorrhaphy surgery: a double blind randomized clinical trial. *Zahedan Journal of Research in Medical Sciences*, *18*(3).

Bent, S., Padula, A., & Neuhaus, J. (2004). Safety and efficacy of Citrus aurantium for weight loss. *The American journal of cardiology*, *94*(10), 1359-1361.

Dehghan, K., & Kalani, Z. (2018). Comparison of the effect of Citrus aurantium and oxazepam on the preoperative anxiety of patients candidate for coronary artery implantation operation. *Journal of Research in Medical and Dental Science*, *6*(2), 1-5.

Du, Z., Zhang, X. Y., Qu, S. Q., Song, Z. B., Wei, S. W., Xiang, Z., & Guo, Q. L. (2019). The comparison of dexmedetomidine and midazolam premedication on postoperative anxiety in children for hernia repair surgery: A randomized controlled trial. ***Pediatric Anesthesia***, ***29***(8), 843-849.

Gupta, A., Gunjan, S. S., Gupta, S., & Gupta, A. (2019). Comparison of oral triclofos and oral midazolam as premedication in children undergoing elective surgery. ***Anesthesia, essays and researches***, ***13***(2).

Hulscher, B. E. (1987). Potential use of Buspirone in treatment of dental anxiety. ***Anesthesia progress***, ***34***(3), 90.

Kalinina, T. S., Shimshirt, A. A., Volkova, A. V., Korolev, A. O., & Voronina, T. A. (2016). Anxiolytic effects of diazepam and afobazole on the anxiety response evoked by gaba (a) receptor blockade in wistar rats and inbred mice of balb/c and c57bi/6 strains. ***Eksperimental'naia i klinicheskaia farmakologiia***, ***79***(10), 3-7.

Karabıyıklı, β., Deβirmenci, H., & Karapınar, M. (2014). Inhibitory effect of sour orange (Citrus aurantium) juice on Salmonella Typhimurium and Listeria monocytogenes. ***LWT-Food Science and Technology***, ***55***(2), 421-425.

Khodayari-Fard, M., Lavasani, M., Akbari_Zardkhane, S. E., & Liaghat, S. (2010). Psychomertic properties spielberger's state-trait anger expression inventory-2 among of Iranian students. ***Archives of Rehabilitation***, ***11***(1), 47-56.

Lehrner, J., Eckersberger, C., Walla, P., Pötsch, G., & Deecke, L. (2000). Ambient odor of orange in a dental office reduces anxiety and improves mood in female patients. ***Physiology & behavior***, ***71***(1-2), 83-86.

Mannucci, C., Calapai, F., Cardia, L., Inferrera, G., D'Arena, G., Di Pietro, M., ... & Calapai, G. (2018). Clinical Pharmacology of Citrus aurantium and Citrus sinensis for the Treatment of Anxiety. ***Evidence-Based Complementary and Alternative Medicine***, ***2018***.

Millan, M. J. (2003). The neurobiology and control of anxious states. ***Progress in neurobiology***, ***70***(2), 83-244.

Nagendrababu, V., Pulikkotil, S. J., Jinatongthai, P., Veettil, S. K., Teerawattanapong, N., & Gutmann, J. L. (2019). Efficacy and Safety of Oral Premedication on Pain after Nonsurgical Root Canal Treatment: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. Endodontic ***Journal***, 52, 1096–1107.

Nemeroff, C. B. (2003). The role of GABA in the pathophysiology and treatment of anxiety disorders. ***Psychopharmacology bulletin***, ***37***(4), 133-146.

Pan, X., Wang, J., Lin, Z., Dai, W., & Shi, Z. (2019). Depression and anxiety are risk factors for postoperative pain-related symptoms and complications in patients undergoing primary total knee arthroplasty in the United States. ***The Journal of arthroplasty***, ***34***(10), 2337-2346.

Rezaei, A., Rezaei-Dorostkar, K., Ahmadizadeh, C., & Jafari, B. (2012). A comparative study of sedative and anxiolytic effects of the Hypericum perforatumin and diazepam on rats. ***Zahedan Journal of Research in Medical Sciences***, ***13***(8).

Rodrigues, H. F., Furuya, R. K., Dantas, R. A. S., Rodrigues, A. J., & Dessotte, C. A. M. (2018). Association of preoperative anxiety and depression symptoms with postoperative complications of cardiac surgeries. ***Revista Latino-americana de Enfermagem***, ***26***.

Sharifipour, F., Baigi, S., & Mirmohammadali, M. (2015). The aromatic effect of Citrus arantium on pain and vital signs after cesarean section. ***International Journal of Biology, Pharmacy, and Allied Sciencies***, ***4***(7), 5063-5072.

Suryawanshi, J. A. S. (2011). An overview of Citrus aurantium used in treatment of various diseases. ***African Journal of Plant Science***, ***5***(7), 390-395.

Triantafillidis, J. K., Merikas, E., Nikolakis, D., & Papalois, A. E. (2013). Sedation in gastrointestinal endoscopy: current issues. ***World Journal of Gastroenterology: WJG***, ***19***(4), 463-481.

Ulbricht, C., Costa, D., Giese, N., Isaac, R., Liu, A., Liu, Y., ... & Weissner, W. (2013). An evidence-based systematic review of bitter orange (Citrus aurantium) by the Natural Standard Research Collaboration. ***Journal of dietary supplements***, ***10***(4), 391-431.