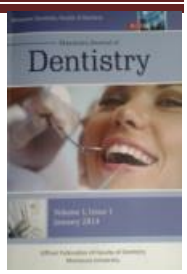

Efficacy of Adjunctive Use of Diacerein Local Delivery in Management of Moderate Chronic Periodontitis

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Abstract:
Introduction: Chronic periodontitis is a common public health concern characterized by a progressive gingival inflammation.
Objective: The aim of this study was to assess the clinical and laboratory effect of diacerein as an adjunctive therapeutic management to conventional periodontal therapy (SRP) of moderate chronic periodontitis.
Subjects and Methods: Thirty patients (n=30) suffering from moderate chronic periodontitis were involved based on specific criteria. These were divided into control and study group and subjected to SRP. The study group was administered diacerein in the form of a gel-formula into the periodontal pocket using the local delivery system. Clinical parameters were collected and compared between and after treatment any analysed by descriptive and non-descriptive statistical analysis using the Chi-square test.
Results: Our analysis showed that age and gender was not found significantly different between the two studied groups. However, there was a statistically significant higher median values of clinical indices after treatment among control than study group as well as significant decrease of median values of clinical indices after treatment as compared to pre-treatment results among the study group ($p<0.05$). Interestingly, a significant decrease of mean IL-β1 after treatment among both groups with more significant decrease among the study group comparing to control group ($p<0.05$).
Conclusion: Diacerein can provide alternative and promising therapeutic option as well as safe, and effective drug particularly along the non-surgical SRP procedure for the management and control of chronic periodontitis.

Introduction

Chronic periodontitis is a common periodontal condition mainly affecting adults and clinically characterized by a progressive gingival inflammation.[1] Various plaque-causing organisms are responsible for the initiation and progression of the disease.[2] In addition, several systemic and non-systemic diseases, and numerous factors play contributing-role in the progression of the diseases (e.g. oral hygiene, smoking, diabetes mellitus and genetic susceptibility).[3]

The inflammatory process of chronic periodontitis leads to elevated localized inflammatory reaction accompanied with over-expression of several pro-inflammatory cytokines and chemokines (e.g. Interleukin IL-1β, tumour necrosis prostaglandins (PGE2), IFNγ, IL-6 and IL-8.[4] These play important role in bone, collagen destruction and degradation of connective tissues and osteoclast activation.[5] Therefore, Regulation and controlling of the host responses is the concept that is largely adopted in the treatment of periodontal conditions.[6]

In addition, local delivery system is considered a key element for the management of chronic periodontal conditions and can be used as an extension to SRP and/or as supporting therapy along systemic therapies.[7] Such option has recently generated interests through the application of various anti-inflammatory drugs (e.g. non-steroidal drugs (NSAIDs)) showing better treatment outcomes and less undesirable effects.[8]Recently, diacerein was proposed as potential and promising candidate for the therapy of periodontal diseases.[9] Diacerein (DCN) is a anthraquinone symptomatic drug provides high permeability, low solubility and typically prescribed to treat osteoarthritis.[10] The aim of the study is to assess the clinical and laboratory effect of diacerein as an adjunctive therapeutic management to conventional periodontal therapy (SRP) of moderate chronic periodontitis.

PATIENTS AND METHODS

Selection of Patients

Thirty patients (n=30) were involved in the study of patients attending the department of oral medicine and periodontology clinic. Patients were included based on clinical and diagnostic criteria of moderate chronic periodontitis.[11] and were selected based on the following criteria; age from 35-45years; probing depth ≥3- 4mm; attachment loss ≥ 3 mm and a minimum of 20 teeth. Patients that had any previous treatment for periodontal diseases or given antibiotic drugs 3 months prior to the study were excluded. Also, any systemic disease, pregnancy or smoking habit were also adopted as exclusion criteria.

Design of Study

Patients were divided into two groups, each contain fifteen patients (n=15) as follows:

Group-I Control patients: These were treated with scaling and root planing (SRP) using ultrasonic scaler and hand instrument once per week. Periodontal indices were taken before treatment and after six weeks of treatment. Samples of gingival crevicular fluids were also collected at the base line as well as at six weeks after the initiation of the treatment for the purpose of IL-1ß assessment.

Group-II (study patients): Patients of this group were initially treated with SRP once per week using ultrasonic scaler and hand instrument. Patients were then given diacerine into the periodontal pocket adopting as local delivery using a syringe with blunt cannula. Patients were subjected for the treatment and followed for consecutive six weeks; in the first visit and the following five visits. Periodontal indices were taken before treatment and throughout the six weeks. Sample of GCF fluids were collected at the base line and throughout the six weeks for IL-1ß assessment.

Diacerein Local Drug Delivery

Initially, diacerein capsules (500mg hard gelatin) (EvaPharma) (1.2% w/w) were dissolved in both propylene glycol and glycerin as described by Ahmad et al.[12] Diacerine gel was then locally delivered into the pocket using a syringe with blunt cannula once per week for 6 weeks. Patients were asked to self-performed oral hygiene, refrain from chewing any food or drink materials or brushing close to the treated area, at least 30 minutes after the therapy. Anti-inflammatory and/or antibiotics agents were not given after treatment.

Assessment of Clinical parameters

Clinical and periodontal parameters were performed following frequent and typical procedure and were: Plaque index (PI), Gingival Bleeding Index, Probing pocket depth (PPD) and Clinical attachment level (CAL)**.**

Laboratory analysis of IL-1ß

The ELISA of IL-1ß was performed using ELISA Kit uses sandwich-ELISA method (Elabscience Biotechnology, China). Gingival crevicular fluids were initially collected from each pocket using sterile paper strips at the baseline and after 6 weeks of SRP. Optimum clean strips were placed in sterile Eppendorf tubes and stored at -80°C for further analysis. The ELISA was performed following the manufacturer instruction and in duplicate for each sample.

Statistical analysis

Data were introduced into a Microsoft Excel programme and the analyses was processed using IBM SPSS software (Ver. 20.0). Description of qualitative data was performed using descriptive statistical analysis. Chi-square test was used for categorical variables and for comparison purposes between both groups. In addition, student t-test, paired t-test, Mann Whitney test, wilcoxon signed rank test were performed.

Results

The mean for age in study and control groups was found to be 41.2 & 38.8 respectively (P<0.05) (Table1). The median clinical indices for each index were estimated before treatment for the control and studies patients and no statistically significant variation between both groups (p>0.05) (Table2).

Table (1): The Mean±SD estimates of age and sex between both groups

	Study Group	Control Group	Test Significance
Age (years)	41.2±2.93	38.8±3.8	t=1.94 (p=0.06)
Gender	N (%)	N (%)	FET (P=0.59)
Male	1(6.7)	3(20.0)	
Female	14(93.3)	12(80.0)	

Footnote; t, Student t test; FET, Fischer exact test; p, probability

Table (2): Median of clinical indices before treatment between groups

Before-treatment	Study Group Median*	Control Group Median*	Test Significance
PI	2.83(1.95-3.0)	2.66(1.91-3.0)	Z=0.59 (P=0.55)
GI	2.66(2.16-3.0)	2.66(1.91-3.0)	Z=0.02 (P=0.98)
GBI %	44.33(36.0-50.0)	44.33(36.0-50.0)	Z=0.04 (P=0.97)
PD	3.71(2.63-5.02)	3.61(2.36-4.64)	Z=1.78 (P=0.07)
CL	3.71(2.63-5.02)	3.61(2.36-4.64)	Z=1.54 (P=0.13)

Footnote: Median* estimates are presented as minimum to maximum values; z, Mann Whitney U test; p, probability

The median clinical indices for each index were estimated post-treatment option for both groups. There is significant higher median values of clinical indices after treatment among control than study group (1.5, 1.85, 27.66, 1.22 & 1.22) versus (0.33, 0.33, 8.33, 1.01 &1.01) for PI, GI, GBI, PD and CL, respectively (p<0.05). (Table (3) and figure (3))

Table (3): Median of clinical indices after treatment between groups

After-treatment	Study Group Median*	Control Group Median*	Test Significance
PI	0.33(0.0-0.83)	1.5(0.5-2.5)	Z=4.52 (P<0.001†)
GI	0.33(0.0-1.33)	1.85(1.0-2.33)	Z=4.56 (P<0.001†)
GBI %	8.33(0.0-33.3)	27.66(8.33-40.66)	Z=3.49 (P<0.001†)
PD	1.01(0.01-1.20)	1.22(1.0-2.84)	Z=3.76 (P<0.001†)
CL	1.01(0.01-1.20)	1.22(1.0-2.84)	Z=3.76 (P<0.001†)

Footnote: Median* estimates are presented as minimum to maximum values; †, statistically significant (p<0.05); z, Mann Whitney U test; p, probability.

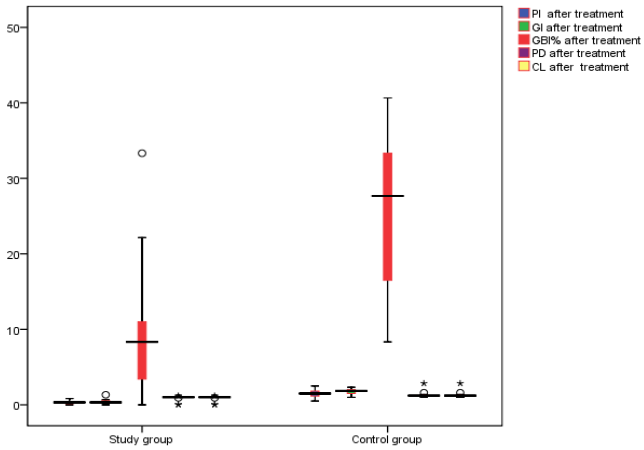

Figure (1): The median of clinical indices after treatment in both groups.

The median of clinical indices for each index were compared between pre and post-treatment for the studied patients. There is statistically significant decrease of median values of clinical indices after treatment as compared to pre-treatment results among the study group (2.83, 2.66, 44.33, 3.71 &3.71) versus (0.33, 0.33, 8.33, 1.01 & 1.01) for PI, GI, GBI, PD and CL, respectively (Table 4) & figure (4).

Table (4): Median of clinical indices before and after treatment among the study group

Study group	Before treatment Median*	After treatment Median*	Test Significance
PI	2.83(1.95-3.0)	0.33(0.0-0.83)	Z=3.41 (P=0.001†)
GI	2.66(2.16-3.0)	0.33(0.0-1.33)	Z=3.4 (P=0.001†)
GBI %	44.33(36.0-50.0)	8.33(0.0-33.3)	Z=3.41 (P=0.001†)
PD	3.71(2.63-5.02)	1.01(0.01-1.20)	Z=3.40 (P=0.001†)
CL	3.71(2.63-5.02)	1.01(0.01-1.20)	Z=3.41 (P=0.001†)

Footnote: Median* estimates are presented as minimum to maximum values; †, statistically significant (p<0.05); z, Wilcoxon signed rank test; p, probability.

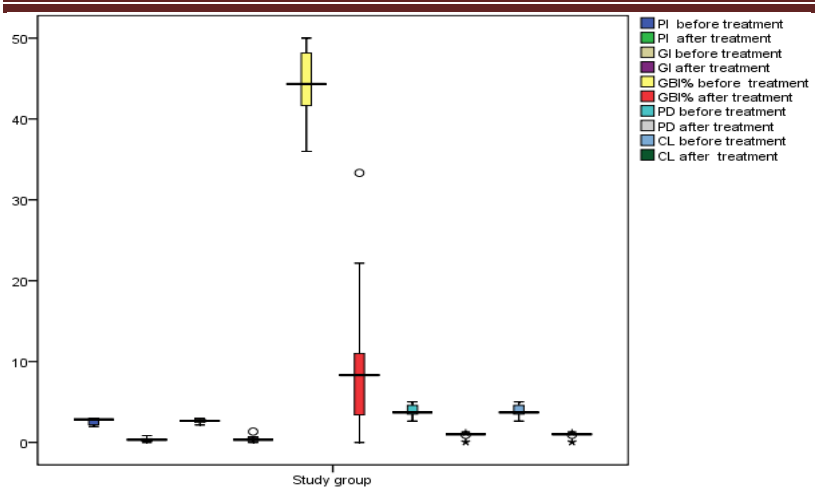

Figure (2): Median clinical indices before and after treatment among study group.

The median of clinical indices for each index were compared between pre and post-treatment for the studies patients. There is statistically significant decrease of median values of clinical indices after treatment as compared to pre-treatment results among the control group (2.66, 2.66, 44.33, 3.61 &3.61) versus (1.5, 1.85, 8.33 27.66,1.22 & 1.22) for PI, GI, GBI, PD and CL, respectively (Table (5) & figure (3)).

Table (5): The median of clinical indices before and after treatment among the control group

Control Group	Before treatment Median*	After treatment Median*	Test Significance
PI	2.66(1.91-3.0)	1.5(0.5-2.5)	Z=3.43 (P=0.001†)
GI	2.66(1.91-3.0)	1.85(1.0-2.33)	Z=3.42 (P=0.001†)
GBI %	44.33(36.0-50.0)	27.66(8.33-40.66)	Z=3.42 (P=0.001†)
PD	3.61(2.36-4.64)	1.22(1.0-2.84)	Z=3.41 (P=0.001†)
CL	3.61(2.36-4.64)	1.22(1.0-2.84)	Z=3.40 (P=0.001†)

Footnote: Median* estimates are presented as minimum to maximum values; †, statistically significant (p<0.05); z, Wilcoxon signed rank test; p, probability.

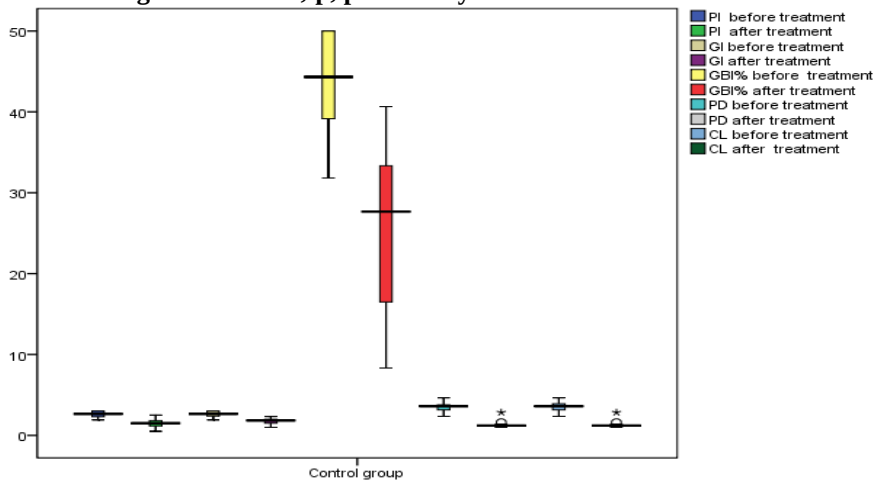

Figure (3): The median of clinical indices before and after treatment among control group.

The level of IL-β1 was determined in patents of both groups and was compared on between before and after therapy. Table (6). There is no statistically significant difference between both groups before treatment while there is significantly higher mean-values after treatment for control group (18.15 & 13.02, respectively).

Table (6): Level of IL-β1 of study & control groups (before Vs. after treatment)

IL-β1	Before treatment		Test Sig.	After treatment		Test Sig.
	Study Group	Control Group		Study Group	Control Group	
Mean±SD	34.2±5.40	31.81±5.72	t=1.18 p=0.25	13.02±3.54	18.15±3.05	t=4.26 p<0.001†

Footnote: t, Student t test; SD, Standard deviation; p, probability; †statistically significant (p<0.05)

The change-level of IL-β1 was determined in patents of both groups and compared before and after therapy and was found significant decreases after treatment among both groups with more significant decrease among the study group (61.9%) comparing to control group (42.9%) Table (7).

Table (7): The level of IL-β1 change between before and after treatment among study & control groups

IL-β1	Study Group		Test Sig.	Control Group		Test Sig.
	Before treatment	After treatment		Before treatment	After treatment	
Mean ±SD	34.2±5.40	13.02±3.54	t=23.07 p<0.001†	31.81±5.72	18.15±3.05	t=12.23 p<0.001†

Footnote: t, paired t test; SD, Standard deviation; p, probability; †statistically significant (p<0.05)

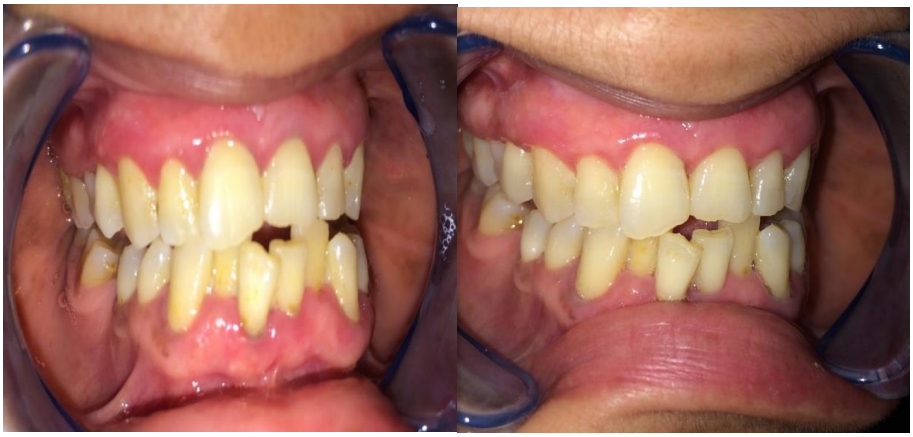

Image : Comparison between study groups (left; pre-treatment, Right; post- treatment study group (after scalling, root planning and local delivery of diacerein)

Discussion

In our study, no significant difference was found between both groups regarding age (Table 1 , figure 1) however, recent studies have shown an association between age and the severity of chronic periodontitis.

Such increase is linked to the accumulative effect by the years and to the prolonged exposure to such risks including microbial challenge but not entirely due to ageing itself.(13) In addition, another study has revealed that that keeping a healthy oral and periodontal status may prevent the development and progression of periodontal disease.(14)

In our study, female gender was largely involved and were higher among the study group followed by the control group; 93.3% and 80% respectively. (Figure2) However, no significant difference was found in regarding gender between the two groups (Table 1 and Figure2). This might be attributed to the low number of participants in this study. In fact, a recent study that involved 1000 female patients have revealed that half of these have periodontal disease and that factors such as age and education are significant risk determinants for chronic periodontitis.(15)

The evaluation of clinical parameters (i.e. CAL, PI, GI, GBI and PPD) in this study revealed no significant difference ($p>0.05$) of clinical indices before treatment between both groups. (Table 3 and figure 3) However, a significant difference was found after treatment among both group (Table 4 and figure 4). In fact, a significant decrease of clinic indices was found after treatment compared to pre-treatment results among both groups (Table 5 and figure 5) . These findings support the ongoing understanding that the non-surgical SRP options is an important route in the management of chronic periodontitis.(16)

Local drug delivery system into periodontal pocket is an effective, desirable and non-invasive application.(6) In fact, the combination of various agents (e.g. antimicrobial and anti-inflammatory (NSAIDs)) have been proposed with encouraging results.(15) Such approaches (i.e. local delivery) can be used as an extension treatment to SRP in the management of chronic periodontitis. Also, the use of diacerein can cause uncomfortable GI irritation.(10) however no GI undesirable effects was documented in all participants within the study group.

Interleukin-1 beta (IL-1β) IFNγ, and tumour necrosis factor-alpha (TNF-α) are major biomarkers associated with the induction and severity of chronic periodontitis.(17) Recent studies have documented the association between clinical measures of periodontal diseases and salivary levels of IL-1β.(18) In the current study, the level of IL-β1 between both groups was found to be insignificantly different before treatment however a significant change was found after treatment between both groups with more significant decrease among the study group comparing to control group (Table 8). This is an important finding that potentially indicate the significant effect of diacerein among the study group in diminishing the level of IL-β1 resulting in a better resolution of inflammation comparing to the control group. Our results support previous report that also documented a significant decrease of IL-1ß among the lab-animals after administering diacerein suggesting the potential therapeutic role of diacerein in managing induced periodontitis.(19)

Conclusion

Our study reveals the effective use of diacerein along the non-surgical procedure as a potential drug for the management of chronic periodontitis. To our knowledge no previous report have described the therapeutic use of diacerein in the treatment of chronic periodontitis. Further investigations are needed to investigate the potential effect of diacerein on the level of other cytokines and other periodontal conditions.

References

1. ***Sima C, Van Dyke TE.*** *Therapeutic Targets for Management of Periodontitis and Diabetes. Current Pharmaceutical Design. 2016;22(15):2216-37.*

2. ***Pihlstrom BL, Michalowicz BS, Johnson NW.*** *Periodontal diseases. Lancet 2005;19(9499):1809-20.*

3. ***Kaur M, Malik B, Garg T, Rath G, Goyal AK.*** *Development and characterization of guar gum nanoparticles for oral immunization against tuberculosis. Drug Delivery. 2015;22(3):328-34.*

4. ***Bartold PM, Cantley MD, Haynes DR.*** *Mechanisms and control of pathologic bone loss in periodontitis. Periodontology 2000. 2010;53:55-69.*

5. ***American Academy of Periodontology*** *Task Force Report on the Update to the 1999 Classification of Periodontal Diseases and Conditions. Journal of Periodontology. 2015;86(7):835-8.*

6. ***Anonymous****. Treatment of Plaque-induced Gingivitis, Chronic Periodontitis, and Other Clinical Conditions. Pediatric Dentistry. 2017;39(6):445-454.*

7. ***Nair SC, Anoop KR****. Intraperiodontal pocket: An ideal route for local antimicrobial drug delivery. Journal of Advanced Pharmaceutical Technology and Research. 2012;3(1):9-15.*

8. ***Agossa K, Morand DN, Tenenbaum H, Davideau JL, Huck O.*** *Systemic Application of Anti-inflammatory Agents in Periodontal Treatment. Clinical Anti-Inflammatory and Anti-Allergy Drugs. 2015;2(1):3-13.*

9. ***Huang RY, Lu SH, Su KW, Chen JK, Fang WH, Liao WN, et al.*** *Diacerein: a potential therapeutic drug for periodontal disease. Medical Hypotheses. 2012;79(2):165-7.*

10. ***Panova E, Jones G****. Benefit-risk assessment of diacerein in the treatment of osteoarthritis. Drug Safety. 2015;38(3):245-52.*

11. ***Wiebe CB, Putnins EE****. The periodontal disease classification system of the American Academy of Periodontology--an update. Journal (Canadian Dental Association). 2000;66(11):594-7.*

12. ***Ahmad N, Lonardo EC, Patel KJ, Lin SY, Wearley LL, Matheson JN, Wiita B.*** *Novel methods of treating local and bacterial infections. US Patents 200301302251A, 2003*

13. ***Jo~ao Botelhoa, Vanessa Machadoa, Antonio Amarala, Ricardo Alvesa, Luıs Proenc¸ab, Jose Jo~ao Mendesb, et al.*** *Association between age and chronic periodontitis in a Portuguese population. 2nd International Congress of CiiEM - Translational Research and Innovation in Human and Health Sciences. At: Almada, Portugal. Volume: Annals of Medicine. 2018;50(sup 1):S70-S71.*

14. ***Schatzle M, Loe H, Lang NP, Heitz-Mayfield LJ, Burgin W, Anerud A et al.*** *Clinical course of chronic periodontitis. III. Patterns, variations and risks of attachment loss. Journal of Clinical Periodontology. 2003;30(10):909-18.*

15. ***Al Qahtani NA, Joseph B, Deepthi A, Vijayakumari BK.*** *Prevalence of chronic periodontitis and its risk determinants among female patients in the Aseer Region of KSA. Journal of Taibah University Medical Sciences. 2017;12(3):241-48.*

16. ***Sanz I, Alonso B, Carasol M, Herrera D, Sanz M****. Nonsurgical treatment of periodontitis. Journal of Evidence-Based Dental Practice. 2012;12(3 Suppl):76-86.*

17. ***Gomes FI, Aragão MG, Barbosa FC, Bezerra MM, de Paulo Teixeira Pinto V, Chaves HV****. Inflammatory Cytokines Interleukin-1β and Tumour Necrosis Factor-α - Novel Biomarkers for the Detection of Periodontal Diseases: a Literature Review. Journal of Oral and Maxillofacial Research. 2016;7(2):e2.*

18. ***Ng PY, Donley M, Hausmann E, Hutson AD, Rossomando EF, Scannapieco FA****. Candidate salivary biomarkers associated with alveolar bone loss: cross-sectional and in vitro studies. FEMS Immunology and Medical Microbiology. 2007;49(2):252-60.*

19. ***Zaki BM, Mahmoud EA, Aly AA****. Diacerein: A potential therapeutic drug for the management of experimental periodontitis in rats. Electronic Physician. 2015;7(5):1290-5.*