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EFFECT OF LOW-LEVEL LASER THERAPY ON CISPLATIN INDUCED CYTOTOXICITY IN PAROTID GLAND OF RATS

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ABSTRACT

Objective: the current study was designed to evaluate the therapeutic efficacy of low-level laser therapy (LLLT) on parotid glands following cytotoxicity produced by cisplatin in rats. **Subject and Methods:** The study employed a sample of 36 adult males Sprague-Dawley rats were divided into three groups, each consisting of 12 rats. Group I: control group received phosphate-buffered saline. Group II: referred to as the cisplatin group, was administered a solitary intraperitoneal injection of the cisplatin medication at a dosage of 10mg/kg. Group III:received the dose of cisplatin used in group II, then exposed to a single session of LLLT on day 3 after cisplatin administration. After cisplatin injection and low-level laser irradiation, animals were sacrificed at 7 and 14 days. The sacrifice was examined histologically and ultra structurally. **Results:** The experimental LLL-treated group showed some improvement in the gland but could not regenerate to normal architecture. **Conclusion**: This study proved that LLL cannot improve cytotoxicity induced by cisplatin in parotid glands.

KEY WARDS: Parotid glands, cisplatin, low level laser.

INTRODUCTION

Cisplatin, also known as cis-diamminedichloro-platinum II (CP), is a highly efficacious and extensively utilized chemotherapeutic drug for the treatment of various malignancies located in the head and neck as well as the ovaries [(1)]. The mode of action of CP is ascribed to its capacity to generate adducts by crosslinking with the purine bases on DNA. This process hampers DNA repair systems and induces DNA damage. Additionally, CP induces cell cycle arrest in the G2 phase, ultimately resulting in apoptosis in cancer cells. Additional ways by which cisplatin has lethal effects on tumor cells encompass mitochondrial damage, diminished ATPase activity, and modified cellular transport processes. In addition to causing DNA damage, cisplatin also elicits the generation of reactive oxygen species, which subsequently initiate cell death [(2)].

Despite the potent chemotherapeutic effects of CP, it is accompanied by many unfavourable downsides due to its cytotoxic nature and lack of specificity towards cancer cells, hence affecting normal tissues as well [(1)]. It has general cytotoxic as well as many oral side effects like xerostomia, mucositis, bleeding tendency and dental infections[(3)]. Cisplatin was also shown to affect submandibular as well as parotid salivary glands [(4-5)].

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Low-level laser therapy (LLLT) refers to the utilization of light in a biological system with the aim of stimulating tissue regeneration, mitigating inflammation, and alleviating pain [6]. In contrast to other medical laser techniques, LLLT does not operate through an ablative or thermal mechanism. Instead, it exerts a photochemical impact, wherein the light is absorbed and induces a chemical change, the technique is referred to as "low level" because of its delivery of energy density at relatively low levels, which distinguishes it from other laser therapies commonly employed for ablation, cutting, and thermal tissue coagulation [7].

The utilization of LLLT has been employed considering its capacity to stimulate various metabolic and biochemical mechanisms, hence facilitating analgesia, tissue biomodulation, and modulation of the inflammatory process [8]. It possesses the ability to regulate the process of nucleic acid and protein synthesis, as well as growth factors, modulate the concentrations of cytokines, and inflammatory mediators. Additionally, it can induce cell proliferation and differentiation [9].

SUBJECT AND METHODS

Animals and experimental design

The animal handling and the application of the procedure were carried out at the house animals of Cairo University and approved by the local ethical committee Ref. No.592/1786. The animals were individually confined within cages, with unrestricted availability of water and food. The present study was carried out on adult male Sprague Dawley rats with an average age of around 2 months old, and their weight measured 200-250gm.

Animal grouping

The animals will be divided randomly into three main groups, 12 rats in each group as the following:

Group I: (control group) will receive 0.5 ml phosphate-buffered saline.

Group II: (cisplatin group) will receive a single intraperitoneal injection of cisplatin drug (10mg/kg)[10]. Cisplatin was obtained from ADWIA CO., Cairo, Egypt.

Group III: (Laser group) will receive the dose of cisplatin used in group II and then be exposed to single session of LLLT on day 3 after cisplatin administration to make sure that cisplatin induced cytotoxicity has already been established.

After 7 and 14 days from cisplatin administration and laser irradiation, the rats will be anesthetized, sacrificed and the parotid gland will be dissected out and prepared for:

- Haematoxylin and Eosin staining as a routine stain.
- Transmission electron microscope: Examination was carried out using the T.E.M. (JEOL1000) in faculty of science, Al-Azhar University.

Low-level-laser therapy:

In the present study, we use siro laser xtend diode laser sirona from dent supply (Siro laser blue, Germany).

The laser-treated group received LLLT 72 hours after cisplatin. Continuous-wave laser irradiation was used in the experiment. The study parameters were: The system under discussion runs at 830 nm, an infrared wavelength. Its 100-mW output power indicates its power capacity. This system has a power density of 3.57 W/cm2. The dosage was 135J/cm^2, energy 4 J, and application time 40 seconds. The mouse's parotid glands were targeted by placing the spot point directly on its dermis. One point was inserted into each parotid gland. Refraction was minimized by incidenting the light beam on tissue as close to perpendicular as possible. Maintaining 0.5 cm between the probe and the targeted area [11].

Image analysis:

The process involved the digitization of slides using an Olympus® digital camera that was put

on an Olympus® microscope equipped with a 1/2 X picture adaptor. The slides were captured with a 400 X objective. The result photos were analyzed using Video Test Morphology® software (Russia) on a computer equipped with an Intel® Core I7® processor. The software had a dedicated routine for area measuring. A total of 2 slides from each rat were selected for analysis, and 5 random fields from each slide were examined to obtain intracytoplasmic vacuolation.

Step 1: Life Images were transferred from the camera to the computer using a u-tech® frame grabber. The required images were captured as a snapshot and saved as 1024 X 768 dpi TIFF format.

Step 2: Automatic image adjustment (including automatic color balance and contrast) was done to obtain a high contrasted image and a well-defined hue range of the target stain. That also reduces the background interference with the target stain which may affect the result.

Step 3: The enhanced image with high image details was then subjected to automatic thresholding using the target-stained area to adjust the threshold level to select intracytoplasmic empty areas. That converts the target area to a binary mask that overlay the original image. This area is defined as (ROI) region of interest. The system uses this mask in calculations.

Step 4: % area of ROI was calculated and tabulated.

N.B. in some images, artifacts due to histological processing technique were manually eliminated to prevent interference with the results.

Statistical analysis:

The data were tabulated, coded, and then analyzed. One way analysis of variance (ANOVA) test will be used for comparison between the groups.

RESULTS

Group I: (control group)

Histologic features: The parotid salivary gland appeared to be composed of secretory end pieces and duct system arranged into lobes and lobules separated by connective tissue septa. The secretory end piece or the acini were found to be composed of pyramidal-shaped serous cells. The identification of intercalated ducts poses challenges due to their compression between secretory units, while the striated duct cells were tall columnar with centrally placed open-faced nuclei with basal striation and surrounded by blood capillaries. Blood vessels are present in the connective tissue that supply the parenchymal elements. (Fig.1).

Group II: (cisplatin group)

Histologic features at 7 days: The specimen showed completely atrophied, shrunk acini with large spaces in between lobules, some lobules demonstrated liquefaction necrosis in between the remnant of atrophied acini, while others showed atrophy and vacuolization. The intercalated duct couldn't be identified, while striated ducts showed loss of their cellular boundaries with vacuolization and degeneration. (Fig.2).

Histologic features at 14 days: The specimen showed different histological patterns ranging from completely atrophied degenerated shrunk acini with loss of normal architecture of acinar cells, other acini completely disappeared, areas of liquefaction necrosis, and areas of hyalinization were seen between lobules. The acinar cells exhibited loss of boundaries, their cytoplasm showed signs of vacuolation, and the nucleus showed different degrees of necrosis, also dilated striated and excretory duct with stagnation of secretion were seen. (Fig.3).

Group III: (low-level laser group)

Histologic features at 7 days: The specimen revealed variable histological alteration in the gland that was evidenced by loss of the typical appearance of the serous acini that tend to be atrophied and

vacuolated. Most of the acini were distended with ill distinct cell boundaries and vacuolated cytoplasm. Striated ducts appeared with indistinct boundaries, and vacuolated cytoplasm also showed a normal appearance of the nucleus and wide lumen. (Fig.4).

Histologic features at 14 days:

The specimen showed that the acini appeared with a different shape ranging from distention to completely atrophied acini with well-developed acinar membrane and narrow lumen, most acinar nuclei appeared open-faced vesicular nucleus, while others showed atrophy and degeneration with cytoplasmic vacuolation. Patent blood vessels were seen between acini.

Striated ducts appeared with ill-defined boundaries and wide lumen containing vesicular nucleus and cytoplasmic vacuoles. (Fig.5).

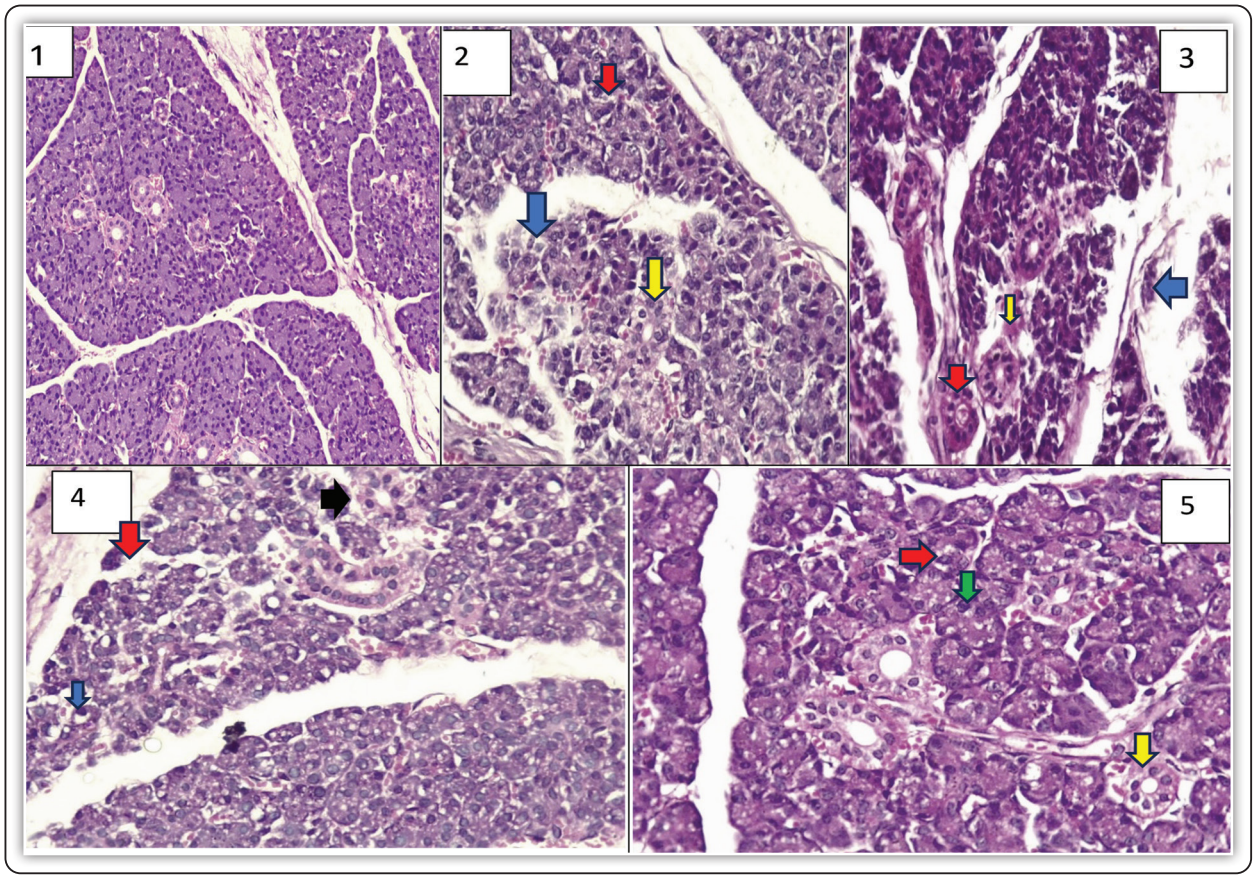

FIG (1) Parotid salivary gland of a rat of the control group showing a normal serous acinus with fibrous tissue between lobules while some collecting ducts lie among serous acini (H&E, X200).

FIG (2) Cisplatin group at 7 days showing a- necrosis between atrophied acini(blue) b-atrophied striated duct with degenerated cytoplasm(yellow) c- acinar vacuoles(red) (H&E, X 400).

FIG (3) Cisplatin group at 14 days showing a- atrophied acini with degenerated cytoplasm(blue) b- striated duct with stagnation of secretion(red) d-eosinophilic coagulum (yellow) (H&E, X 400).

FIG (4) Laser group at 7 days showing a- acinar vacuoles (blue) b- striated duct with ill-defined border and vacuolated cytoplasm(black) c- liquefaction necrosis(red) (H&E, x400).

FIG (5) Laser group at 14 days showing a- -vacuolated acini (red) b- striated duct with some vacuoles(yellow) c- open-faced nucleus(green)(H&Ex400).

Electron microscopic investigations

Group I: (control group) The secretory acinar cells appeared as pyramidal shape structures. They connected with each other by cell-to-cell junctions in the form of tight junctions, gap junctions. The secretory units exhibited basally located nuclei and a relatively homogenous secretory granules embedded with the cytoplasm, they have ahigh developed regularly arranged RER and elongated mitochondria. (Fig.6).

Group II: - (cisplatin group)

Electron microscopic investigations at 7 days: Showing sever alterations, also the cell junctions become ill defined. The nucleus appeared rounded in some cases and located basally, the cytoplasm appeared loden with dense electron secretory granules which have different size and density. RER decreased in number with abnormal shape and arrangement, also rounded and sometimes flat shaped mitochondria was seen in the cytoplasm with decreased in their number. Fig. (7).

Electron microscopic investigations at 14 days: Sever changes as the acini totally collapsed with narrowing of the lumen and lose of cellular boundaries, The nucleus was degenerated, and some become fragmented while the other have different size and shape with irregular nuclear membrane, the RER were decreased in number and some of them become fragmented, the secretory electron dense granules decreased in number and have different size and densities.

The mitochondria also decreased in number and their cisterna invisible some of them become elongated and degenerated, Lysosomal bounded membrane bodies were seen in relation to the degenerated and vacuolated cytoplasmic organelles. Fig. (8).

Group III: - (LLL group)

Electron microscopic investigations at 7 days: Electron microscopic examination of this group revealed that the acinar cells showing that the shape and boundaries of the cells is irregular with vacuolated cytoplasm, the nucleus appeared rounded with distinct nuclear membrane and euchromatin. The cells contained different size and density of electron dense secretory granules, RER appeared as highly developed and parallelly arranged while some other showing degeneration and fragmentation, the mitochondria appeared rounded and distributed throughout the cytoplasm. Fig. (9).

Electron microscopic investigations at 14 days Revealed that some acinar cells still preserve their shape, size, and architecture with minimal or sever structural changes. The cytoplasm appeared filled with cell organelles, the electron dense secretory granules appeared with different size and density, some of them were fused with one another, Some acini showing vacuolated cytoplasm.

The RER appeared well developed and parallel to each other forming a network and located all over the cytoplasm with some areas of fragmentation and degeneration were seen. Mitochondria were seen in between the RER and secretory granules. Fig. (10).

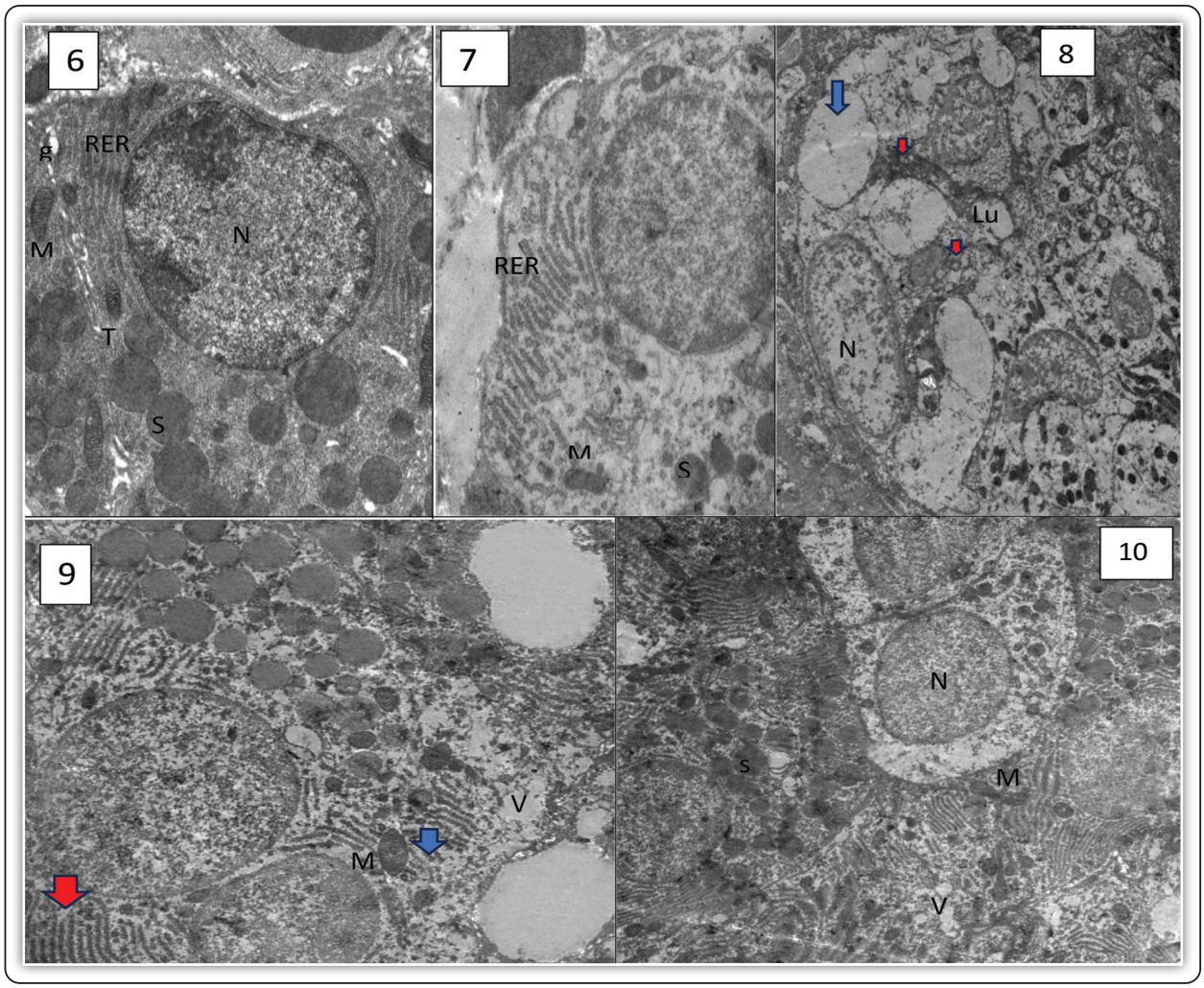

FIG (6) Electron micrographs of parotid glands of control group showing the nucleus (N), RER, mitochondria(M), tight junction (T) and electron dense decretory granules (S) (X15000).

FIG (7) Electron micrographs of parotid glands of cisplatin group at 7 days showing a- dilated and fragmented RER b- few secretory granules (s) c- flat shaped mitochondria(M) (X15000).

FIG (8) Electron micrographs of parotid glands of cisplatin group at 14 days showing acini bordering narrow lumen (Lu) contain a-nucleus with different size and shape (N) b- degenerated nucleus(blue) c-few secretory granules d- loss of cell junctions e- lysosomes(red). (X6000).

FIG (9) Electron micrographs of parotid glands of laser group at 7 days showing a- nucleus with euchromatin b-parallel RER (red), degenerated RER (blue) c- mitochondria e- vacuoles (X10000).

FIG (10) Electron micrographs of parotid glands of laser group at 14 days showing a- nucleus b- RER c- mitochondria d- vacuoles e- fused secretory granules. (X6000).

Statistical investigations

Table (1) Comparison between cisplatin, laser, and control group regarding the percentage of the area of intracytoplasmic vacuolations due to glands atrophy on day 7 and day 14.

% area of intracytoplasmic vacuolations due to glands atrophy		Cisplatin group No. = 120	Laser group No. = 120	Control group No. = 120	Test value	P-value	Sig.
Day 7	Mean ± SD	22.68 ± 1.93	16.1 ± 1.32	4.47 ± 0.64	5199.104	**<0.001**	HS
	Range	17 – 28.5	13.2 – 20.2	2.6 – 6.4			
Day 14	Mean ± SD	28.05 ± 3.04	17.31 ± 1.95	4.47 ± 0.64	3734.498	**<0.001**	HS
	Range	21.2 – 36	13.1 – 21.6	2.6 – 6.4			
Post Hoc analysis							
		P1	**P2**	**P3**			
Day 7		**<0.001**	**<0.001**	**<0.001**			
Day 14		**<0.001**	**<0.001**	**<0.001**			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•*: One Way ANOVA test*

P1*: Cisplatin Vs laser;* **P2***: Cisplatin Vs control;* **P3***: laser Vs control*

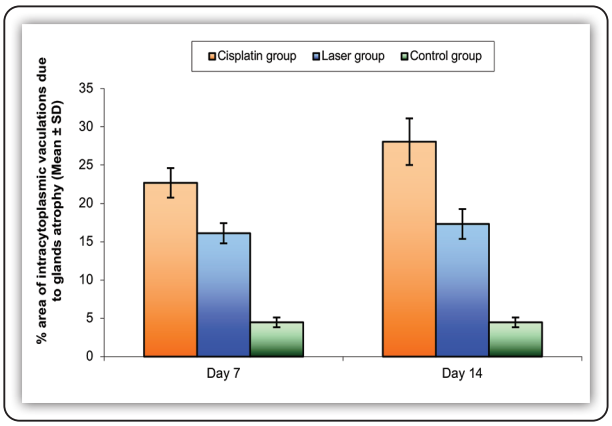

FIG (11) Comparison between cisplatin, laser, and control group regarding the percentage of the area of intracytoplasmic vacuolations due to glands atrophy on day 7 and day 14.

DISCUSSION

The parotid gland is classified as a serous gland, exclusively producing a watery secretion. This gland is responsible for around 25 to 35 percent of the total daily output of salivary secretions [12]. Chemotherapy plays a vital role in the systemic management of salivary gland tumors, with a particular emphasis on those impacting the parotid glands, which constitute approximately 80% of the total salivary gland tumor cases. Subsequently, the submandibular glands and sublingual glands are also affected by these tumors [13]. Cisplatin is a chemotherapeutic drug that is extensively utilized and recognized for its high efficacy in treating various malignancies located in the head, neck, and ovaries [14]. Despite the potent chemotherapeutic effects exhibited by cisplatin, it is accompanied by many unfavourable downsides stemming from its cytotoxic nature and lack of specificity towards cancer cells, hence impacting normal tissues as well [1]. The administration of cisplatin has been found to induce functional and morphological deterioration in salivary gland tissue, resulting in various adverse effects such as modified saliva production, impaired swallowing, speech and taste impairments, oropharyngeal discomfort, and oral infections [15]. So, this work is directed to counter act the harmful effects of cisplatin on normal cells.

Adult male Sprague-Dawley rats were used for this study due to their small size, cleanliness, docility, and housing ease. These animals grow quickly and are easy to handles [16].

Cisplatin is proven to cause deterioration on salivary glands after 72 hours of systemic administration[4], so we chose to start the LLL therapy on day 3 to make sure that cisplatin-induced tissue damage has already been established.

The histological results in the cisplatin group at 7 days revealed completely shrunk acini with large spaces between lobules. These results were coincidental with the study by Shaymaa M. et al., who found that cisplatin significantly reduced serous acini and glandular lobules, along with interstitial edema and multiple cytoplasmic vacuoles [17].

The current work revealed the presence of intracytoplasmic vacuoles ranging from small to large vacuoles; this work is coincidental with Conklin KA., who postulated that this vacuolation is caused by the released free radicals from cisplatin, which caused damage to the cellular components[18]. According to Terzi et al., cisplatin accelerates acinus cell apoptosis and degeneration, causing vacuoles[19].

The current study at 14 days unveiled the presence of degenerative indications in the majority of nuclei, potentially associated with the mechanism of cisplatin action. Upon cellular entry, cisplatin undergoes activation and displacement of chloride atoms by water molecules. Subsequent to hydrolysis, the resultant product can engage with nitrogen donor atoms present on nucleic acids, thereby resulting in detrimental effects such as DNA damage, impeded cellular division, and the initiation of non-discriminatory apoptosis. Consequently, both tumor cells and normal cells are affected by these processes [20], and this may clarify the changes in the nucleus that were noted in the results, including degenerated and fragmented nuclei, while the others have different sizes and shapes with irregular nuclear membrane.

The results revealed dilated striated and excretory ducts with the stagnation of secretion, and our results in accordance with Eman Hany et al., who revealed similar findings, suggesting that the observed outcomes may be attributed to the pathogenic impact of chemotherapy on myoepithelial cells. This, in turn, may result in a compromised ability to expel secretions into the mouth cavity, ultimately leading to failure in this process [20].

Presence of Lysosome was found that's engulf secretory granules, mitochondria, and other organelles in accordance with the study by Kitashima who found the same results and demonstrate that auto phagocytosis in acinar cells is the first step toward recovery through digestion of cellular contents that were damaged by CDDP [4]. Moreover, in the present study at cisplatin group the mitochondrial cisterna became invisible, some of them become elongated, swallowed, and degenerated, this changes in mitochondria agreed with Eman Hany et al., who found the same results[20].

The laser group at the end of the seven-day period demonstrated a higher degree of vacuolated cells in comparison to the control group, although this observation was less prominent than in the cisplatin group; as for acinar structure, the acini were further apart from each other with ill distinct cell boundaries. This result is coincidental with the study by Monique D. et al., who found vacuolated cells in the laser group at seven days with marked acinar disorganization[11].

The lase group at 14 days revealed some improvement in acinar cells with open-faced vesicular nucleus and new blood vessels, while others showed atrophy and degeneration with cytoplasmic vacuolation. The acute impact of cisplatin on the function of salivary glands has been attributed to the identification of atrophy and degeneration of acinar cells. Plavnik et al. conducted a study aimed at examining the effects of a helium-neon laser on the structural and ultrastructural features of the submandibular gland in adult guinea pigs observed

notable changes, including pronounced vasodilation accompanied by blood cell extravasations and acinar necrosis [21]. The efficacy of multiple laser irradiations on tissue surpasses that of single irradiation, making it a crucial element in tissue formation and cell proliferation. Rats subjected to multiple LLLT sessions exhibited a noteworthy decrease in TNF levels, indicating sustained reductions in these proinflammatory biomarkers over an extended period [22]. However, it could be emphasized that many variable factors affected the bio-stimulatory effect of LLLT. The wavelength, energy, pulse, duration, and tissue interaction may alter the bio-stimulatory effect of LLL irradiation. Additionally, it is imperative to perform further studies utilizing diverse LLLT regimens and examining the glandular response, both in the short and long term.

CONCLUSION

LLLT did not improve the gland in 7 days. Also, there were new blood vessels in 14 days around ducts and acinar cells so longer period and different laser protocol were needed to know more about healing.

REFERENCES

1. Hitomi S, Ujihara I, Sago-Ito M, Nodai T, Shikayama T, Inenaga K, Ono K. Hyposalivation due to chemotherapy exacerbates oral ulcerative mucositis and delays its healing. Arch Oral Biol. 2019 Sep; 105:20-26.
2. Crul M, Schellens JHM, Beijnen JH, Maliepaard M. Cisplatin resistance and DNA repair. Cancer Treat Rev 1997; 23:341–366.
3. López BC, Esteve CG, Pérez GS. Dental treatment considerations in the chemotherapy patient. J Clin Exp Dent 2011;3: e31-e42.
4. Kitashima S. Morphological alterations of submandibular glands caused by cisplatin in the rat. Kurume Med J 2005; 52:29-38.
5. Hey J, Setz J, Gerlach R, Vordermark D, Gernhardt CR, Kuhnt T. Effect of Cisplatin on parotid gland function in concomitant radio chemotherapy. Int J Radiat Oncol Biol Phys 2009; 75:1475-1480.
6. Huang YY, Chenet AC, Carroll JD, Hamblin RM. Biphasic dose response in low level light therapy. Dose Response. 2009;7(4):358–83.
7. Hamblin MR. Hamblin MR Mechanisms of low-level light therapy. Of SPIE. 2009; 6140:614001–1.
8. T. Karu, "Primary and secondary mechanisms of action of visible to near-IR radiation on cells," J. Photochemical. Photo biol.1999; 49(1), 1–17.
9. J. B. Dawson et al., "A theoretical and experimental study of light absorption and scattering by in vivo skin," Phys. Med. Biol.1980; 25(4), 695–709.
10. Roldán-Fidalgo A, Martín Saldaña S, Trinidad A, Olmedilla-Alonso B, Rodríguez-Valiente A, García-Berrocal JR,Ramírez-Camacho R. In vitro and in vivo effects of lutein against cisplatin-induced ototoxicity. Exp Toxicol Pathol 2016; 68:197-204.
11. Monique Dossena Acauan,a Ana Paula Neutziling Gomes,b Aroldo Braga-Filho,c Maria Antonia Zancanaro de Figueiredo, a Karen Cherubini,a and Fernanda Gonçalves Saluma, Effect of low-level laser therapy on irradiated parotid glands—study in mice. Journal of Biomedical Optics 2015; vol. 20, Issue 10, 108002.
12. Amano, O. The salivary gland: anatomy for surgeons and researchers. Jpn. J. Oral Maxillofac. Surg.2011; 57;384–393.
13. Wang G, Reed E, Li QQ. Molecular basis of cellular response to cisplatin chemotherapy in non-small cell lung cancer (Review). Oncol Rep 2004; 12:955-965.
14. Ito FA, Ito K, Vargas PA, de Almeida OP, Lopes MA. Salivary gland tumors in a Brazilian population: a retrospective study of 496 cases. Int J Oral Maxillo fac Surg. 2005; 34:533–6.
15. Al-Refai AS, Khaleel AK, Ali S. The effect of green tea extract on submandibular salivary gland of methotrexate treated albino rats: immunohistochemical study. J Cytol Histol 2014; 5:212–220.
16. Souza, M. F., Couto-Pereira, N. S., Freese, L., Costa, P. A., Caletti, G., Bisognin, K. M., et al. Behavioral effects of endogenous or exogenous estradiol and progesterone on cocaine sensitization in female rats. Brazilian Journal of Medical and Biological Research, 2014; 47(6), 505–514.
17. Shaymaa Mamdouh Dessoukey; Ahmed Mahmoud Halawa; Iman Ahmed Fathy; Dina Mohammad Kashkoush: The Effect of Adipose Derived Stem Cells versus Platelet Rich Plasma in Ameliorating Cisplatin-Induced Injury on The Submandibular Salivary Gland." A Comparative Histological Study, Egyptian journal of histology. June 2021; Page 406-417.

18. Conklin KA: Chemotherapy-Associated Oxidative Stress: Impact on Chemotherapeutic Effectiveness. Integr Cancer Ther. 2004; 3(4): 294-300.
19. Terzi S, Özgür A, Mercantepe T, Çeliker M, Tümkaya L and Dursun E: The effect of astaxanthin on salivary gland damage caused by cisplatin in the rat. Int J Res Med Sci. 2017; 5(4): 1410-1414.
20. S. Dasari and P. B. Tchounwou, Cisplatin in cancer therapy: Molecular mechanisms of action, European Journal of Pharmacology, 2014; 740, 364-378.
21. Eman Hany, Mohammed A. Sobh, Mazen T. Abou ElKhier, Heba M. ElSabaa and Ahmed R. Zaher. The Effect of Different Routes of Injection of Bone Marrow Mesenchymal Stem Cells on Parotid Glands of Rats Receiving Cisplatin: A Comparative Study. International Journal of Stem Cells 2017; 10:169-178.
22. Plavnik LM, De Crosa ME, Malberti AI. Effect of low power radiation (helium/neon) upon submandibular glands. J Clin Laser Med Surg, 2003; 21:219–225.
23. Theodoro LH, Longo M, Ervolino E, Duque C, Ferro-Alves ML, Assem NZ, Louzada LM, Garcia VG. Effect of low-level laser therapy as an adjuvant in the treatment of periodontitis induced in rats subjected to 5-fluorouracil chemotherapy. J Periodont Res 2016; 51: 669–680.