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Original Article

Effect of Bioabsorbable Poly (DL-Lactide ε-Caprolactone) on Healing of Experimentally Injured Acute Traumatic Middle Ear Mucosa Damage

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BACKGROUND: Postoperative adhesion is an important complication after middle-ear surgeries. Although many materials have been tried to prevent this complication, the use of Poly (DL-lactide ε-caprolactone) as an anti-adhesive material after middle-ear surgery has not yet been reported. The aim of this study was to evaluate the anti-adhesive effect of poly (DL-lactide ε-caprolactone) on the ears of rats with middle-ear mucosa damage.

METHODS: In our study, 14 Wistar albino rats and 28 ears in total were used. The rats were randomly divided into 4 groups. Middle ear mucosa damage was performed in all groups with a transcanal approach under otomicroscopy in sterile conditions. The effects of poly (DL-lactide ε-caprolactone), silicone sheet, and absorbable gelatin sponge were compared histologically with the secondary healing group. In addition, hearing evaluation was performed before the procedure and on the 28th postoperative day.

RESULTS: No significant difference was observed in transient otoacoustic emission and distortion product otoacoustic emissions tests performed before and after the surgical procedure when the groups were compared. While adhesion was observed in the tympanic membrane in the absorbable gelatin sponge group, no adhesion was observed in the other groups. In the absorbable gelatin sponge group, increased fibroblastic activity, inflammation, and neovascularization were observed in the middle-ear mucosa. No significant difference was observed in silicone sheet, poly (DL-lactide ε-caprolactone), and control groups in terms of fibroblastic activity, inflammation, and neovascularization.

CONCLUSION: It can be concluded that absorbable poly (DL-lactide ε-caprolactone) is nonototoxic and biocompatible with the rat's middle ear cavity by short-term evaluation.

KEYWORDS: Adhesion, healing, histology, inflammation, middle ear

INTRODUCTION

Many factors including preoperative otorrhea, size of perforation, condition of the ossicles and middle ear mucosa, function of the eustachian tube, surgeon's experience, and graft material can affect the prognosis of hearing after middle-ear surgeries. Among them, the condition of the middle-ear mucosa and the presence or absence of stapes suprastructure are believed to be the most important factors for successful postoperative hearing restoration.[1] Presence of normal middle ear mucosa indicates proper middle ear ventilation. The healthy middle ear mucosa optimizes the mobility of the tympanic membrane after surgery and maintains the normal amplification mechanism of the middle ear and hearing.[2]

The aim of middle ear surgeries is to obtain a healthy middle ear cavity and protect the hearing mechanism. But one of the major problems after middle ear surgeries is adhesions between the mucosal part of the eardrum and the promontorium. These adhesions may also cause cholesteatoma by forming retraction pockets.[3]

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There have been various materials such as nonabsorbable silicone sheet (Sl) (Figure 1A), absorbable gelatin sponge (AGS) (Figure 1B), gelatin film, and polytetrafluoroethylene used to prevent retraction and adhesion of the graft membrane in chronic adhesive otitis cases where middle ear ventilation is insufficient.[4-7] Poly (DL-lactide ε-caprolactone) (PDLLCL) (Figure 1C) is made of 100% synthetic, absorbable, nontoxic copolymer material.[8] It can be used in a variety of soft tissue surgery applications. Recently, it has begun to be used in tissue regeneration studies. To date, there is no animal model study in the literature examining the anti-adhesive effect of absorbable PDLLCL on damaged middle ear mucosa. In this study, we aimed to compare the fibroblastic activity, inflammation, and neovascularization effects of AGS and Sl and PDLLCL on damaged middle ear mucosa and investigate the ototoxic effect of PDLLCL.

METHODS

The research protocol was submitted to and approved by the Sakarya University Ethics Committee for Animal Experiments (Decree no: 12). Fourteen female Wistar albino rats weighing from 200 to 240 g were included in the study. The ears of the rats were evaluated by otoscopic examination and subjects without any problems in the external auditory canal and middle ear structures were included in the study.

The rats were divided into 4 groups consisting of 7 ears, namely the control group in which secondary healing was followed after middle ear mucosal injury, and groups to which Poly (DL-lactide ε-caprolactone) (Vivosorb®, Polyganics, Groningen, Netherlands), silicone sheet (Invotec®, Jacksonville, USA), or absorbable gelatin sponge (Galenaspon®, Istanbul, Turkey) materials were applied.

Otoacoustic emission (OAE) tests were performed to investigate the possible ototoxic effect PDLLCL. At the beginning of the experiment, all of the animals were assessed with distortion product otoacoustic emissions (DPOAE) and transient otoacoustic emission (TOAE) tests (Madsen Capella, Taastrup, Denmark). After the subjects were administered intramuscular ketamine hydrochloride 45 mg/kg and xylazine 5 mg/kg, the TOAE test was performed with signal frequencies between 750-1250, 1250-1750, 1750-2500, 2500-3500, 3500-4000, and 4000 Hz and above frequencies using a 75 dB sound source for acoustic stimulation. Distortion product otoacoustic emissions was determined as f2/f1 = 1.22 at 2 different frequencies (f1 and f2) and at 2f1-f2 where the best measurement would be obtained. Distortion product otoacoustic emissions measurements were performed in general diagnostic mode at frequencies of 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz. Basal values were recorded.

A 2 mm perforation in the posteroinferior quadrant of tympanic membranes of each subject was made under a surgical microscope (Leica Wild M655, Medical-Elektro, Mragowo, Poland) to explore and perform surgical procedures to the middle ear mucosa. By preserving the ossicular chain, injury was created in the middle ear mucosa with the help of a surgical pick. Then, 3 × 3 × 0.02 mm PDLLCL patches were placed on the damaged middle ear mucosa of the left ears of the subjects to create the PDLLCL group. In the right ear of the same animals, the damaged middle ear mucosa was left for spontaneous secondary healing to create the control group. The AGS group was formed by placing the material of AGS on the damaged middle ear mucosa in the left ear of the other 7 subjects, and the Sl group was formed by placing a 3 × 3 × 0.02 mm Sl on the damaged middle ear mucosa in the right ear of these animals. Later, an otomicroscopic examination was performed for all of the animals on the postoperative 28th day. The DPOAE and TOAE were repeated with the same methods and the animals were sacrificed.

Histological Examination

The tympanic bullas were removed, and the external auditory canal and tympanic membrane were examined under a surgical microscope after sacrifice. Bilateral bullaes of each animal were dissected, placed in 10% formalin solution, and fixed for 48 hours. Tissue samples were removed from formalin solution after fixation and were left for decalcification in nitric acid solution. Decalcification control was performed daily. Bullas that were soft enough to be sectioned were removed and routine histological tissue follow-up was performed in the form of dehydration with alcohol, transparentization with xylol, and embedding in paraffin. These histological procedures were performed using a tissue-tracking device (SLEE Medical, Mainz, Germany).

A total of 5 μm thick tissue sections were cut from tissue blocks embedded in paraffin using a Thermo Scientific HM 355S brand microtome (Thermo Fisher Scientific, Waltham, Mass, USA). Tissue sections placed on the slide were stained with Hematoxylin and Eosin (H&E) and Masson's Trichrome staining kit. They were examined under a light microscope (Nikon Eclipse Ni, Nikon, Tokyo, Japan) with a color digital camera (Nikon DS-Fi2, Nikon, Tokyo, Japan) attachment. Histopathological evaluation was performed by determining the tympanic bulla, ossicular chain, cochlea, and tympanic

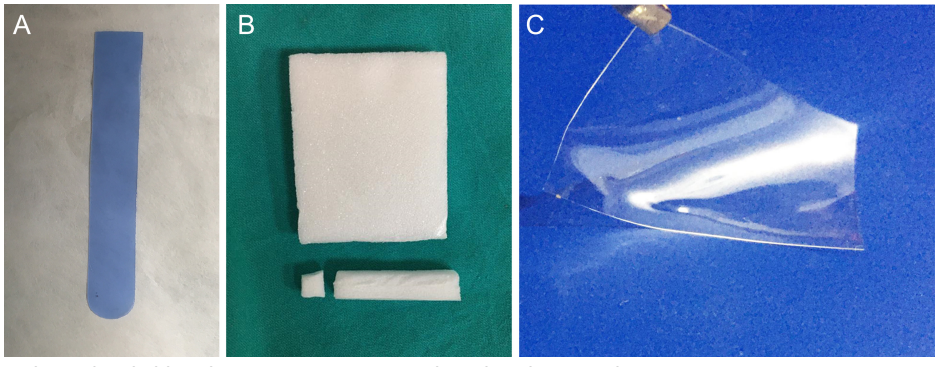

Figure 1. (A) Silicone sheet (Sl); (B) absorbable gelatin sponge (AGS); (C) poly (DL-lactide ε-caprolactone) (PDLLCL).

membrane regions on histological preparations and photographs were taken.

The "NIS-Elements Imaging Software" computer program (Nikon, Tokyo, Japan) integrated with a light microscope was used for grading fibroblastic activity, inflammation, and neovascularization in the middle ear mucosa.

In order to evaluate inflammation and fibroblastic activity under the light microscope, sections were taken from the same region in each ear, and at least 75 different thickness measurements were made to measure the average value. For the evaluation of neovascularization, the number of vessels was calculated on the tissue sections divided into grids using the NIS-Elements Imaging software program under 20× objective magnification in the sections of each ear sample.

Histopathological scoring was done in PDLLCL, AGS, SI, and control groups. Subjective scoring was carried out according to the fibroblastic reaction and neovascularization degree between 0 and 3 (score 0: no fibroblastic activity and inflammation, and no neovascularization; score 1: mild fibroblastic activity, inflammation, and neovascularization; score 2: moderate fibroblastic activity, inflammation, and neovascularization; score 3: severe fibroblastic activity, inflammation, and neovascularization). Histopathological examination was done blindly by histopathologists, and results were compared.

Statistical Analysis

Statistical analyses were performed using commercial software Statistical Package of Social Sciences Version 20.0. (IBM SPSS Corp.; Armonk, NY, USA). Accordingly, Wilcoxon's signed ranks test was used for the analysis evaluating within groups, before and after the operation. Kruskal–Wallis test was used to analyze DPOAE and TOAE values between groups of adult rats and to evaluate histological data. $P < .05$ was considered statistically significant.

RESULTS

In PDLLCL, AGS, SI, and control groups, there was no significant decrease in TOAE values before and after the operation. However, a significant decrease was observed between the preoperative and postoperative DPOAE values of each group (Table 1). Since the 4 groups were compared before surgery, there was no significant difference between TOAE and DPOAE values ($P = .208$ for TOAE; $P = .376$ for DPOAE). Likewise, no significant difference was observed when the groups were compared with each other after surgery ($P = .390$ for TOAE; $P = .059$ for DPOAE).

Table 1. Comparison of TOAE and DPOAE Values Before and After the Operation (Wilcoxon Signed Ranks Test)

		Before the Operation	28 days After the Operation	*P*
TOAE	PDLLCL (n = 7)	−1.1333 ± 1.75	−1.4786 ± 3.44	.612
	Control (n = 7)	0.2310 ± 2.51	−2.0095 ± 1.74	.128
	AGS (n = 7)	2.7214 ± 5.67	−0.7786 ± 2.56	.310
	SI (n = 7)	3.2452 ± 5.17	−0.7500 ± 1.00	.128
DPOAE	PDLLCL (n = 7)	11.6482 ± 6.8	2.7982 ± 2.96	**.028**
	Control (n = 7)	15.8911 ± 5.77	6.1518 ± 4.31	**.018**
	AGS (n = 7)	10.8946 ± 3.95	−3.8857 ± 9.24	**.018**
	SI (n = 7)	9.8946 ± 6.48	−1.2304 ± 8.1	**.028**

AGS, absorbable gelatin sponge; DPOAE, distortion product otoacoustic emissions; PDLLCL, Poly (DL-lactide ε-caprolactone); TOAE, transient otoacoustic emission; SI, silicone sheet.

When the preparations belonging to the experimental groups (PDLLCL, SI, AGS, and control groups) were compared with the light microscope, severe inflammation was found in the middle ear in the AGS group. In addition, in the AGS group, it was observed that there was an increased level of inflammatory bridge and prominent retraction in the eardrum between the promontory and the tympanic membrane compared to the other experimental groups. In the middle ear cavity, a severe inflammatory response was observed around the AGS remnant (Figure 2). In the PDLLCL group, an inflammatory response was observed in the promontorium and middle ear mucosa. No severe inflammation was observed in the damaged middle ear mucosa in the control group. In the SI group, an inflammatory response was observed around the middle ear and ossicle (Figure 3).

When the light microscopic sections of the experimental groups were compared in terms of increased fibroblastic activity and inflammatory changes, significantly increased fibroblastic activity and inflammation were observed in the AGS group compared to the control ($P < .001$). When the other groups were compared in terms of these parameters, no statistically significant difference was found (Table 2).

In terms of neovascularization, a significantly increased neovascularization was observed in the AGS group compared to the control ($P < .001$). There was no statistically significant difference between the other groups (Table 3).

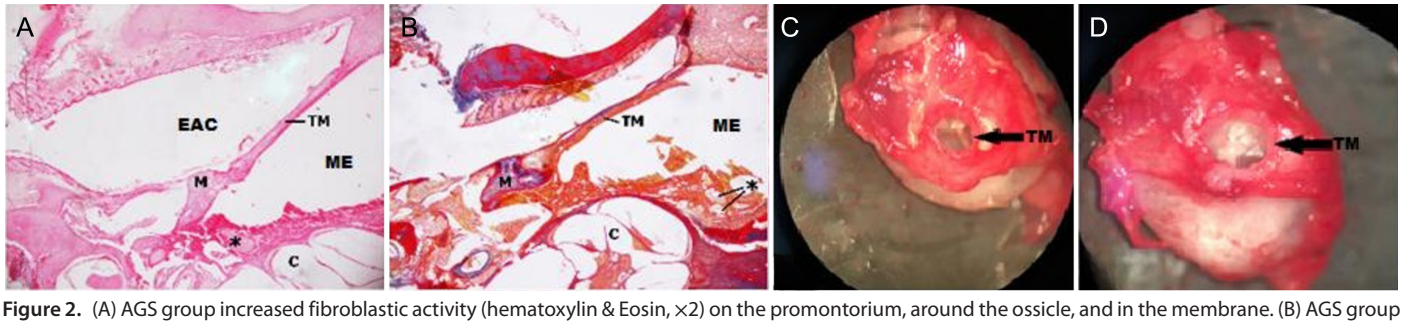

Figure 2. (A) AGS group increased fibroblastic activity (hematoxylin & Eosin, ×2) on the promontorium, around the ossicle, and in the membrane. (B) AGS group increased fibroblastic activity on the promontorium, around the ossicle, and in the membrane (Masson trichrome, ×2). (C) View of the dissected tympanic bulla and tympanic membrane in control group under a surgical microscope. (D) Tympanic bulla with retraction of the tympanic membrane in AGS group. AGS, absorbable gelatin sponge; EAC, external auditory canal; c, cochlea; M, malleolus; ME, middle ear; TM, tympanic membrane; star, AGS remnant.

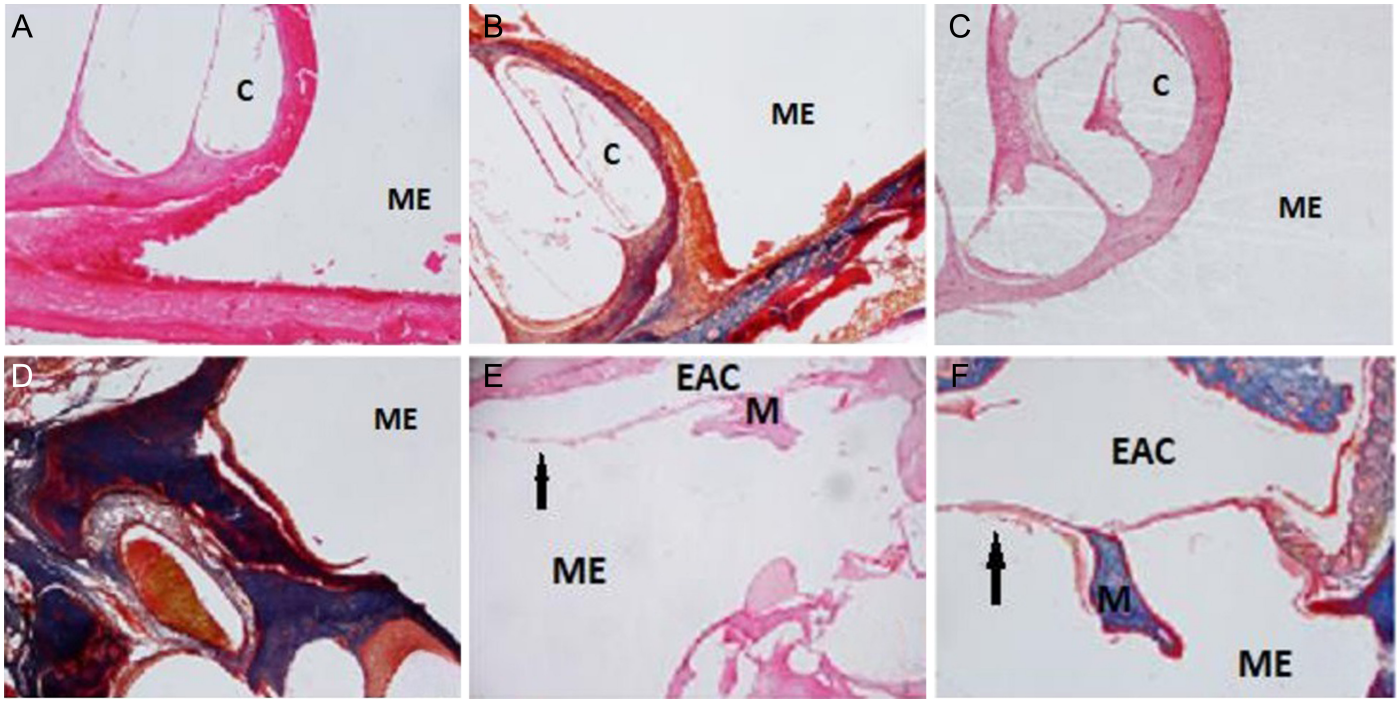

Figure 3. (A) Inflammation on and around the promontorium in PDLLCL group (H&E, 4×); (B) inflammation on and around promontorium in PDLLCL group (Masson Trichrome, 4×); (C) control group, promontorium, and mucosa (H&E, 4×); (D) control group, promontorium, and mucosa (Masson trichrome, 4×); (E): inflammation around the ossicle in Sl group (H&E, 2×); (F) inflammation around the ossicle in Sl group (Masson trichrome, 4×); c: cochlea; EAC, external auditory canal; M, malleolus; ME, middle ear cavity; PDLLCL, poly (DL-lactide ε-caprolactone); arrow, tympanic membrane.

Table 2. Statistical Comparison of Fibroblastic Activity and Inflammation Scoring Between Sections of Experimental Groups (Kruskal–Wallis Test)

Sample 1-Sample 2 (n = 7)-(n = 7)	Test Statistics	Std. Error	Std. Test Statistics	*P*	Adj. *P*
Control-Sl	−10.286	4.397	−2.339	.019	.116
Control-PDLLCL	11.286	4.397	2.567	.010	.062
Control-AGS	−17.571	4.397	−3.996	.000	**≤.001**
Sl-PDLLCL	1.000	4.397	.227	.820	1.000
Sl -AGS	7.286	4.397	1.657	.098	.585
PDLLCL-AGS	−6.286	4.397	−1.430	.153	.917

Adj. *P*, adjusted *P* value; AGS, absorbable gelatin sponge; PDLLCL, poly (DL-lactide ε-caprolactone); Sl, silicone sheet; Std, standard.

Table 3. Statistical Comparison of Neovascularization Scoring Between Groups of Experimental Groups (Kruskal–Wallis test)

Sample 1-Sample 2 (n = 7)-(n = 7)	Test Statistics	Std. Error	Std. Test Statistics	*P*	Adj. *P*
Control-Sl	10.429	4.397	2.372	.018	.106
Control-PDLLCL	−10.714	4.397	−2.437	.015	.089
Control-AGS	−20.857	4.397	0.065	.000	**≤.001**
Sl-PDLLCL	−0.286	4.397	−2.372	.948	1.000
Sl-AGS	−10.429	4.397	2.307	.018	.106
PDLLCL-AGS	10.143	4.397	−1.430	.021	.126

AGS, absorbable gelatin sponge; adj. *P*, adjusted *P* value; PDLLCL, poly (DL-lactide ε-caprolactone); Std: standard; Sl, silicone sheet.

DISCUSSION

The success of middle ear biomaterials depends on their mechanical and chemical properties and the biological responses that occur in the middle ear mucosa. One of the factors determining the success of the material is the inflammatory reaction.[9,10] In this study, we showed that PDLLCL did not cause more inflammation or fibrosis in the damaged middle ear mucosa compared to the control, Sl, and AGS groups.

Increased inflammation and fibroblastic activity in the middle ear mucosa and increased vascularization and fibroblastic activity around AGS were observed in the histological examination in our study. In addition, it was seen both otomicroscopically and histologically that the increased inflammation and fibroblastic activity extended between the promontorium and the tympanic membrane, causing retraction in the membrane. These results are compatible with the literature.[11,12]

Among the nonabsorbable anti-adhesive materials, Sl is widely used as a physical barrier to prevent adhesion between the medial surface of the tympanic membrane and the promontorium in surgeries involving middle ear mucosa resection.[13,14] In a study examining the effect on hearing and histological healing with the use of Sl, it was shown that Sl prevents adhesion formation and recurrence, and positively affects hearing.[13] However, in another study by Ng et al.,[5] increased fibroblastic activity between the eardrum and promontorium and Sl were insufficient to prevent adhesion. In the same study, the duration of the Sl in the middle ear and the

fibroblastic activity were also studied, and it was observed that the fibrosis increased as time increased.[5] The major drawback of this material is that because of its nonabsorbable nature, it needs to be surgically removed.[15] Furthermore, the silicone component of SI may act as a potential nidus of infection, leading to subsequent graft loss and rejection.[16]

Polylactic acid film (PLA) is an absorbable material just like PDLLCL, and in experimental studies on guinea pigs, inflammation and fibroblastic activity in the middle ear mucosa were examined, and no significant difference was found when compared with control groups. Its use as an anti-adhesive material has been suggested.[15,17] In the present study, there was no statistically significant difference in terms of increased fibroblastic activity, inflammation, and neovascularization between PDLLCL group and SI group. However, since our study covered a short period of 28 days, long-term effects were not observed. It may be possible to obtain different results regarding fibroblastic activity in studies with longer follow-up periods.

Thanks to its hydrophilic structure, the PDLLCL membrane allows the passage of nutritional metabolites and water required for tissue healing. In an animal study investigating the healing of sciatic nerve damage in which PDLLCL was used as a tube formation, cells were observed only in the surrounding tissues in terms of foreign body reaction, and no local or general toxic effects were observed. Nerve healing was observed in the lumen.[18] In another study conducted with rabbits, it was shown that PDLLCL is biocompatible in the subconjunctival region and can be used safely.[19] In an animal study comparing the healing effect on the tympanic membrane with epifilm (hyaluronic acid), increased fibroblastic activity and neovascularization were observed in PDLLCL compared to epifilm.[20] This study is the first experimental study in the literature that examined the effect of PDLLCL on middle ear mucosa healing. In this study, no significant increase was observed in the PDLLCL group in terms of fibroblastic activity, and neovascularization. Poly (DL-lactide ε-caprolactone) can be used as an anti-adhesive material in the middle ear. Since it is a flexible sheet material like SI, it does not have the volume to support the graft. It maintains its mechanical effectiveness for up to 10 weeks after application, then decreases with hydrolysis.[21]

No significant difference was observed in SI, PDLLCL, and control groups in terms of fibroblastic activity, inflammation, and neovascularization. We think that this is because there was no contact between the healthy tympanic membrane and the damaged middle ear mucosa, and this was the main deficiency of this study.

CONCLUSION

Fibroblastic activity, inflammation, and neovascularization were statistically significantly less than the AGS group in the PDLLCL group and the SI group. However, PDLLCL has, of course, an advantage due to the lack of need for revision surgery. Clinical studies will also be required to establish the clinical usefulness and safety of PDLLCL as surgical anti-adhesive material in the middle ears of patients. We think that it would be beneficial to include groups formed by using PDLLCL and AGS together in new studies planned on this subject.

Ethics Committee Approval: The research protocol was submitted to and approved by the Sakarya University Ethics Committee for Animal Experiments (Decree no: 12, Date: May 8, 2019).

Informed Consent: N/A.

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Author Contributions: Concept – M.S.Y.; Design – M.S.Y.; Supervision – A.K., M.G.; Resources – N.İ.; Materials – N.İ., E.Ş., M.E; Data Collection and/or Processing – N.İ., A.K.; Analysis and/or Interpretation – N.İ., D.D.; Literature Search – N.İ., A.K.; Writing – N.İ., A.K; Critical Review – M.S.Y., D.D.

Declaration of Interests: The authors declare that they have no competing interest.

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