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Evaluation for Biocompatibility of Gentamicin-collagen Sponge on the Experimental Animal Wound Model

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Abstract : The objective of this study was to compare the biocompatibility for local irritation and bioavailability of Gentacol™ and Collatamp™, after single intramuscular loading in rats. Sixty-six male Sprague-Dawley rats were divided into 4 groups; (1) any test materials were not applied into the quadriceps muscles (control group, N = 6), (2) Gentamicin was injected into the quadriceps muscles (Gentamicin group, N = 6), (3) Collatamp was applied into the quadriceps muscles (Collatamp group, N = 27), and (4) Gentacol was applied into the quadriceps muscles (Gentacol group, N = 27). The concentration of gentamicin in muscles was gradually decreased with time after loaded in the both Gentacol™ and Collatamp™ loaded regions. No detectable gentamicin was observed in the plasma of Gentacol™ and Collatamp™ loaded rats. Histologically, moderate to severe inflammatory cell infiltrations including PMN, lymphoid cells and macrophages were observed with slight to moderate edematous changes of muscle fibers after intramuscular injection of gentamicin. However, these histopathological changes of gentamicin injection induced local irritations were dramatically decreases after intramuscular loading of Collatamp™ and Gentacol™. These results suggest Gentacol™ may show favorable local bioavailability and induce only slight local irritations as comparable as Collatamp™ without systemic exposures in the condition of this experiment.

Key words **:** Biocompatibility, gentamicin, collagen sponge.

Introduction

Gentamicin is an aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms, through irreversible binding the 30S subunit of the bacterial ribosome, interrupting protein synthesis (10). However, gentamicin is not used for *Neisseria gonorrhoeae*, *Neisseria meningitidis* or *Legionella pneumophila,* and gentamicin is also ototoxic and nephrotoxic, with this toxicity remaining a major problem in clinical use (9,16). In addition, many of its applications are restricted to low dose administrations, mainly because of the appearance of residues in the kidney and the high cost of the treatment (2). It is administrated in the form of injection, cream, ointment and suspension (8), and formulations have been attempted to reduce the systemic toxicity of gentamicin (4,7). In addition, gentamicin also showed severe local irritations after injection or loading after formulations, therefore, newly develop gentamicin formulations should show not only low systemic exposures but also low local irritations (1,11).

Antibiotic-loaded collagen sponge has been shown to be effective in treating soft tissue and bone infections and has the advantage of minimizing the risk of systemic toxicity such as nephrotoxicity (15). Although the primary function of gentamicin-containing collagen implants is to provide haemostasis, a number of studies have shown significant reductions in the incidence of surgical site infection associated with their use (3,12). Collatamp™ is a proprietary gentamicin impregnated sponge used routinely to prevent the bacterial infections after surgery with minimising the risk of systemic toxicity of gentamicin (7,13,14).

The objective of this study was to examine the biocompatibility for local irritation and bioavailability of newly developed gentamicin impregnated sponge formulation, Gentacol™ compared with commercial gentamicin impregnated sponge formulation, Collatamp™, after single intramuscular loading in rats.

Materials and Methods

Experimental animals

Sixty-six male Sprague-Dawley rats (6-week-old, Daehan bio link, Eumseong, Korea) were used after acclimation for 7 days. Animals were housed three per polycarbonate cage in a temperature (20-25ºC) and humidity (50-55%) controlled room. Light : dark cycle was 12 hr : 12 hr, and standard rodent chow

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(Samyang, Seoul, Korea) and water were supplied free to access. All laboratory animals were treated according to the national regulations of the usage and welfare of laboratory animals, and approved by the Kyungpook National University Experimental Animal Ethical Committee.

Animals were divided into 4 groups; (1) any test materials were not applied into the quadriceps muscles (control group, N = 6), (2) Gentamicin was injected into the quadriceps muscles (Gentamicin group, N = 6), (3) Collatamp was applied into the quadriceps muscles (Collatamp group, N = 27), and (4) Gentacol was applied into the quadriceps muscles (Gentacol group, N = 27).

Test materials implantation and sampling

Under general anesthesia of Zoletile mixture (25 mg/kg, IM, Virbac Lab., Paris, France), the sterile skin of left lateral femoral region was surgically incised, and the exposed lateral quadriceps muscles were injured by 2 cm sharp incision. Then, control animals were not treated, and gentamicin solution was injected into lateral quardriceps muscles in the gentamicin group (gentamicin 1 mg, IM). Each 0.5×1 cm^2 of gentamicin impregnated sponges (gentamicin 1 mg), Collatamp^{TM} and Gentacol^{TM} were applied on the injured lateral quadriceps muscle in Collatamp and Gentacol groups, respectively. The skin was sutured with 3-0 nylon (Braun, Waiblingen, Germany). Muscle samples for histological examination (6 samples per group) were collected at 7 days after surgery in all experimental groups. To compare the gentamicin concentration in tissue and blood after Collatamp and Gentacol implantation, muscles and blood samples of 3 rats per day were collected at 1, 2, 3, 4, 5, 6 and 7 days for LC-MS/MS analysis in the Collatamp and Gentacol groups. Treatments and sampling were performed by a veterinarian blinded to treatment groups.

Muscles sample preparation for LC-MS/MS analysis

Frozen muscle samples from each group (Collatamp^{TM} or Gentacol^{TM} loaded muscle) (0.4 g) were taken 50 mL in centrifuge tube, and homogenized with 0.4 mM EDTA and phosphate buffer which is included 2% trichloroacetic acid (TCA, Sigma-Aldrich, St Louise, MO, USA). After shaking it for 10minutes in the shaker, centrifuge for 10 minutes at 4,500 rpm. Filter supernatant with filter paper (No.1, Whatman, Kent, UK) and transfer it to a clean 50 ml centrifuge tube. Add 15 mL TCA phosphate buffer on the solid residue tube repeatedly and add separated supernatant in centrifuge tube. In addition, add about 30% of sodium hydroxide solution 0.2 ml and give 1 N hydrochloric acid or 1 N sodium hydroxide solution until pH 7.5. In the Vacuum manifold, equip HLB (200 mg, 6 ml) and WCX (150 mg, 6 cc) and connect HLB cartridge and WCX cartridge (Waters Corp., Milford, MA, USA) after activated it with 5 mL of methanol and 5 mL of distilled water. Add extract in the cartridge and pass it through cartridge at a speed of 1-3 mL/min, and wash it with 5 mL of distilled water. Remove water in the cartridge with vacuuming. Elute it with 1.6% TCA at the speed of 1-3 ml/min, and adjust elute at 6 mL filter it through a 0.45 μm PTFE filter to make test solution (Fig 1). Stock solution was prepared by dissolving gentamicin in 90% MeOH and Standard solutions were prepared by diluting serially with 90% MeOH ranging from 0.5 to 100 g/ml.

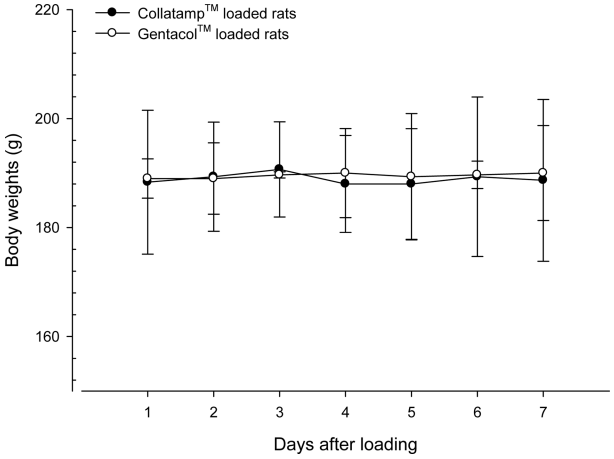

Fig 1. Body weight changes after single Gentacol^{TM} and Collatamp^{TM} loading. No significant or meaningful changes on the body weight were detected in Gentacol^{TM} loaded rats as compared with Collatamp^{TM} loaded rats at each point measured in this study. Values are expressed mean ± SD of three rats.

Plasma sample preparation for LC-MS/MS analysis

Thawed plasma samples from each group (Collatamp^{TM} or Gentacol^{TM}) were vortexed, and 500 μL were transferred to Eppendorf tubes. Plasma injection standards were prepared by adding 100 μL of the diluted gentamicin standards to control plasma to provide concentrations ranging from 0.02 to 20 μg/mL. Blanks were prepared from 0.5 mL control plasma. Tubes were briefly vortex-mixed and 100 μL of the precipitation solution (30% TCA) were added. Tubes were vortex-mixed for 30 s to thoroughly break up any clumping precipitate. Samples were centrifuged in the microfuge for 5 min at 14,000 rpm (20,000 RCF), resulting in a clear layer above a solid white precipitate. 300 μL of supernatant solution were transferred to conical polypropylene vials. For all samples, 5 μL were injected.

LC-MS/MS conditions

Concentrations of gentamicin in the rat plasma and muscle samples were determined LC-MS/MS method. Chromatographic analysis was performed using an Agilent 1100 Series HPLC (Agilent Technologies, Palo Alto, CA, USA) equipped with on-line degasser, binary pump, autosampler and column compartment. Separation of the analyte from potentially interfering material was achieved at ambient temperature using VDSpher PUR100 C18-E columns (2.0×75 mm, 3.5 μm) (VDS Optilab Chromatographietechnik GmbH, Berlin, Germany) at column oven 40ºC. The mobile phase used for the chromatographic separation was composed of 5% acetonitrile/95% distilled water (20 mM heptafluorobutyric acid (HFBA)) to 50% acetonitrile/50% distilled water (20 mM HFBA), and was delivered gradiently at a flow rate of 0.4 ml/min. The column effluent was monitored using an API 2000 triple-quadruple massspectometric detector (Applied Biosystems, Palo Alto, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode, and controlled by

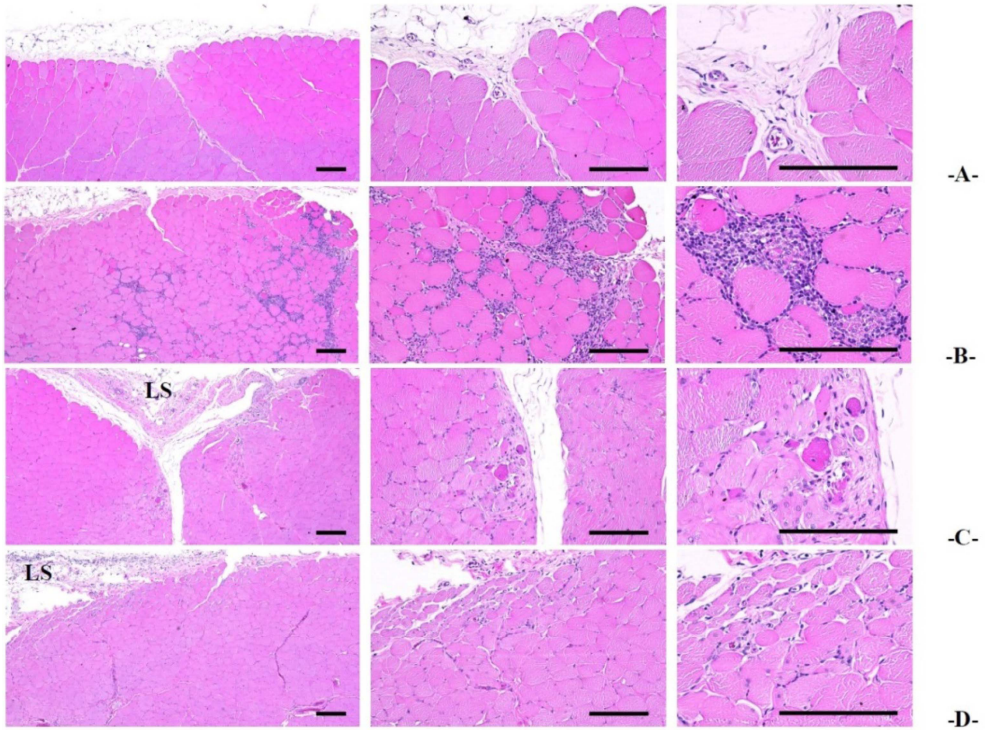

Fig 2. The representative histopathological profiles of muscles, taken from intact, gentamicin injected or Collatamp™ and Gentacol™ loaded rats. Note that moderate to severe inflammatory cell infiltrations including PMNs, lymphoid cells and macrophages were observed with slight to moderate edematous changes of muscle fibers at histopathological observations after intramuscular injection of gentamicin. However, these histopathological changes of gentamicin treatment related local irritations were dramatically decreases after intramuscular loading of two different sponge formulations, Collatamp™ and Gentacol™, respectively. No significant or meaningful changes were demonstrated between Collatamp™ and Gentacol™ loaded muscles in this study.
A: Intact control muscle B: Gentamicin injected muscle
C: Collatamp™ loaded muscle D: Gentacol™ loaded muscle
PMNs = polymorphonuclear cells, LS = loading site, All Hematoxylin-Eosin stain, Scale bars = 160 μm

the Analyst version 1.4.1 software (Applied Biosystems, Palo Alto, CA, USA). Samples were introduced to the interface through a Turbo IonSpray with the temperature set at 400°C. A high positive voltage of 4.0 kV was applied to the ion spray. Nitrogen was used as the nebulizer gas, curtain gas, and collision gas with the settings of 7.5, 10, and 4, respectively. The multiple reaction monitoring (MRM) detection method was employed for the detection of gentamicin; m/z 478 > 322 (Retention time: 7.5min), 464 > 322 (Retention time: 7.4min), 450 > 322 (Retention time: 7.3min) (Fig 2). Calibration curves of gentamicin were linear over the ranges studied with r2£æ0.999. The lower limit of quantification (LLOQ) of the gentamicin was 20 ng/ml. Most of reagents used in analysis were obtained from Sigma-Aldrich, St. Louise, MO, USA, whenever special comments are not indicated.

Histopathological observations

Muscles just immediately under loading sites were sampled, and all individual muscle samples were crossly trimmed as loading sites were situated as upper surface, if possible (6). All trimmed muscles were re-fixed in 10% neutral buffered formalin. After paraffin embedding, 3 μm-thick sections were prepared and representative sections were stained with Hematoxylin and eosin (H&E) for light microscopically examination, and the histological profiles of individual muscle was observed under a light microscope (Nikkon; E400, Japan). To observe more detail histopathological changes, the semiquantative histological damage and edema scoring systems as indication of possible local irritation were applied based on the four degrees of scoring systems; 3+: Severe, 2+: Moderate, 1+: Slight, 0: not detected-normal appearances (Max = 3). In addition, the numbers of inflammatory cells, polymorphonuclear cells (PMNs), lymphoid and macrophages, were also counted in a restricted view fields (mm^2) around loading surfaces using automated image analyzer (*i*Solution FL ver 9.1, IMT *i*-solution Inc., Quebec, Canada), according to the previous local irritation tests and some modifications (5,6). The histopathologist was blinds to group distribution when this analysis was made.

Statistical analysis

A multiple comparison tests for different dose groups were conducted. Variance homogeneity was examined using the Levene test. If the Levene test indicated no significant deviations from variance homogeneity, the obtain data were analyzed by one way ANOVA test followed by Scheffe test to determine which pairs of group comparison were significantly different. When a significant difference is observed in the Kruskal-Wallis H test, the Mann-Whitney U (MW) test was conducted to determine the specific pairs of group com-

Table 1. The local muscular concentration (μg/ml) of gentamicin after single Gentacol™ and Collatamp™ loading by LC-MS/MS system

Loaded materials	Days after loading						
	1	2	3	4	5	6	7
Collatamp™	29.01 ± 7.31	12.06 ± 6.96	15.15 ± 2.08	8.26 ± 1.62	6.84 ± 2.45	4.62 ± 1.74	3.10 ± 1.16
Genta Q™	21.62 ± 4.84	16.36 ± 13.02	14.14 ± 1.92	7.88 ± 2.48	4.06 ± 1.03	4.29 ± 1.55	3.77 ± 1.35

Table 2. Histomorphometrical changes detected in muscle at 7 days after test materials loading

Groups Index	Intact control muscle	Gentamicin-injected muscle	Test material loaded muscles	
			Collatamp™	Gentacol™
Semiquantative scores (Max = 3)				
Histological damage	0.33 ± 0.52	2.50 ± 0.55[a]	1.33 ± 0.52[ab]	1.33 ± 0.52[ab]
Edema	0.17 ± 0.41	1.50 ± 0.55[a]	0.67 ± 0.82[c]	0.50 ± 0.55[c]
Inflammation	0.33 ± 0.52	2.50 ± 0.55[a]	0.50 ± 0.55[b]	0.67 ± 0.52[b]
Inflammatory cell numbers				
PMNs	2.33 ± 0.82	7.67 ± 1.51[a]	1.83 ± 0.75[b]	1.67 ± 0.52[b]
Lymphoid cells	2.67 ± 0.82	91.33 ± 21.59[d]	6.17 ± 2.48[de]	6.00 ± 0.89[de]
Macrophages	2.00 ± 0.89	36.50 ± 7.66[d]	3.17 ± 1.17[de]	3.00 ± 2.61[e]

Values are expressed as Mean ± SD of six rat muscles (around injected or loaded sites).
Semiquantative scores = 3+: Severe, 2+: Moderate, 1+: Slight, 0: not detected-normal appearances (Max = 3)
* PMNs = polymorphonuclear cells
[a] $p < 0.01$ as compared with intact control muscle by LSD test
[b] $p < 0.01$ and [c] $p < 0.05$ as compared with gentamicin injected muscle by LSD test
[d] $p < 0.01$ as compared with intact control muscle by MW test
[e] $p < 0.01$ as compared with gentamicin injected muscle by MW test

parison, which are significantly different. Statistical analyses were conducted using SPSS for Windows (Release 14.0K, SPSS Inc., Chicago, IL, USA). Differences were considered significant at $P < 0.05$. In addition, the changes between groups were calculated to help the understanding of results as follows.

Percentage Changes Compared with Intact Control (%)
= ((Data of gentamicin injected muscle – Data of intact control)/Data of intact control) × 100

Percentage Changes Compared with Gentamicin Injected Muscle (%)
= ((Data of test formulation loaded muscle – Data of gentamicin injected muscle)/Data of gentamicin injected muscle) × 100.

Percentage Changes between Collatamp™ and Gentacol™ Loaded rats (%)
= ((Data of Gentacol™ loaded rats – Data of Collatamp™ loaded rats)/Data of Collatamp™ loaded rats) × 100.

Results

Body weights

No significant or meaningful changes on the body weight were detected in Gentacol™ loaded rats as compared with Collatamp™ loaded rats at each point measured in this study (Fig 1). All rats used in this experiment, showed normal body weight increases, ranged in normal age-matched rats regardless of treatment.

Measurement of gentamicin concentration in the tissue

Gentamicin was detected in the muscles around Gentacol™ and Collatamp™ loaded regions at all seven time points sampled, and no significant changes on the muscular gentamicin concentrations were demonstrated in Collatamp™ loaded rats as compared with Collatamp™ loaded rats throughout 7 days of loading periods; They were gradually decreased with time after loaded in the both Gentacol™ and Collatamp™ loaded regions (Table 1).

Measurement of gentamicin concentration in blood

No detectable gentamicin was observed in the plasma, collected from vena cava of Gentacol™ and Collatamp™ loaded rats, whenever measuring points, 1, 2, 3, 4, 5, 6, and 7 days after loading; They were outranged in lower limit of quantification (LLOQ; 20 ng/ml) of the LC-MS/MS condition of this experiment (data not shown). These mean that Gentacol™ did not induce systemic exposures of gentamicin, as comparable as Collatamp™ in this study.

Evaluation of histopathology

After intramuscular injection of gentamicin, moderate to severe inflammatory cell infiltrations including PMN, lymphoid cells and macrophages were observed with slight to moderate edematous changes of muscle fibers at histopathological observations (Fig 1). However, these histopathological changes of gentamicin injection induced local irritations were dramatically decreased after intramuscular loading of two different sponge formulations, Collatamp™ and Gentacol™ (Fig 1).

Consequently, the scores of edema and inflammation significantly ($p < 0.01$) increased in gentamicin injected muscles as compared with intact control muscles, and infiltrated PMNs, lymphoid cells and macrophages between muscle fibers also significantly ($p < 0.01$) increased in this experiment. The semiquantative histological scores and the numbers of inflammatory cells infiltrated significantly ($p < 0.01$ or $p < 0.05$) decreased in the both Collatamp^{TM} and Gentacol^{TM} loaded muscles as compared with gentamicin injected muscles (Table 2). No significant or meaningful changes were demonstrated between Collatamp^{TM} and Gentacol^{TM} loaded muscles in this study (Table 2).

Discussion

In general, it has been well known that care should be taken when it needs to use gentamicin systemically due to its toxicity such as ototoxic and nephrotoxic (16). There are also some limitation of gentamicin like low dose administration, high cost, and local irritation. Based upon these backgrounds, gentamicin impregnated collagen sponge (Collatamp) was developed for the purpose of preventing of local tissue or bone infection as well as providing hemostasis after surgery.

The goal of this study was to compare newly developed gentamicin impregnated sponge formulation, Gentacol^{TM} with Collatamp^{TM} through bioavailability and biocompatibility test after single intramuscular loading in rats.

For comparison of the bioavailbility, we examined the local muscular concentration and blood concentration of gentamicin after Gentacol^{TM} and Collatamp implantation into lateral regions of quadriceps muscles by serial measurement by LC-MS/MS according to established methods.

There were no significant changes on the muscular gentamicin concentrations in Collatamp^{TM} loaded rats as compared with Collatamp^{TM} loaded rats during the experiment. Then, they were gradually decreased with time after loaded in the both Gentacol^{TM} and Collatamp^{TM} loaded regions. It was suggested that gentamicin was effectively well localized into loading sites by impregnated sponge formulations, and Gentacol^{TM} may show favorable local bioavailability as comparable as Collatamp^{TM}, at least, in the condition of this experiment.

In addition, when plasma concentration of gentamicin also was measured to observe systemic exposures after single loading of two gentamicin impregnated sponge formulations, Gentacol^{TM} and Collatamp^{TM}, the level of gentamicin was not observed in the plasma in Gentacol^{TM} and Collatamp^{TM} loaded rats during experimental period after loading. These mean that Gentacol^{TM} did not induce systemic exposures of gentamicin, as comparable as Collatamp^{TM} in this study.

In the present study, the local irritations were evaluated based on the semiquantative histological damage and edema scoring systems with the numbers of inflammatory cells, PMNs, lymphoid and macrophages (5,6).

Histopathologically, it was examined that muscular injection of gentamicin induced moderate to severe inflammatory cell infiltrations with slight to moderate edematous changes of muscle fibers. However, these histopathological changes of gentamicin injection induced local irritations were dramatically decreased after intramuscular loading of two different sponge formulations, Collatamp^{TM} and Gentacol^{TM}. Based on these results, it could be suggested that gentamicin injection related local irritations are reduced by gentamicin impregnated sponges formulations and that Gentacol^{TM} may induce only slight local irritations as comparable as Collatamp^{TM} in this our experiment.

Conclusion

The results in this study suggested that gentamicin is well localized into around loading tissue and gentamicin related local irritations are reduced by impregnated sponge formulations (Collatamp and Gentacol) and Gentacol^{TM} may show favorable local bioavailability and induce only slight local irritations as comparable as Collatamp^{TM} without disquieting systemic exposures in the condition of this experiment.

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실험동물 창상 모델에서 겐타마이신 함유 콜라겐 스폰지의 생체적합성 평가

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요 약 : 본 연구의 목적은 겐타마이신 함유 스폰지인 겐타콜과 콜라텝프를 랫드 근육내 이식 후 생체적합성을 비교하는 것이다. SD 랫드 66 마리를 네 그룹으로 나누었다; (1) 대퇴사두근에 무처치한 군 (대조군, 6 마리), (2) 대퇴사두근에 겐타마이신 액을 주사한 군 (겐타마이신 군, 6 마리), (3) 대퇴사두근에 콜라텝프를 이식한 군 (콜라텝프 군, 27 마리), (4) 대퇴사두근에 겐타콜을 이식한 군 (겐타콜 군, 27 마리). 겐타콜과 콜라텝프 이식 한근육 내 겐타마이신 농도는 시간이 지남에 따라 점차 감소하였다. 혈액 내에 겐타마이신 농도는 측정되지 않았다. 조직학적으로 겐타마이신 액을 주사 후 근육 내에 다형핵백혈구, 림프구, 대식세포를 포함하는 염증세포가 중등도에서 심하게 침윤되었고, 경도에서 중등도의 근육내 부종이 관찰되었다. 그러나, 이러한 국소 자극의 조직학적 변화는 콜라텝프와 겐타콜 군에서는 현저히 감소하였다. 이상의 결과, 겐타콜은 콜라텝프와 비교하였을 때에 전신적인 영향을 미치지 않으며 국소자극의 정도가 유사하였고, 생체이용성이 유사하여 좋은 생체적합성을 가지는 것으로 생각된다.

주요어 : 생체적합성, 겐타마이신, 콜라겐 스폰지