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RESEARCH ARTICLE

Catgut enriched with $CuSO_4$ nanoparticles as a surgical suture: Morphology, Antibacterial activity, Cytotoxicity and Tissue reaction

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ABSTRACT

Catgut was enriched with copper sulfate nanoparticles (CSNPs@Catgut), in order to develop a new composited suture with antibacterial and healing properties. Introducing copper sulfate nanoparticles to catgut was performed using a reverse micro-emulsion technique. It is an interesting method because of easy handling and relatively low costs. In the revers micro-emulsion medium, nano-spherical structures containing the salt solution are created. The nano-spheres penetrate into catgut fibers and precipitate after drying to form the salt nanoparticles. The prepared CSNPs@Catgut was characterized using scanning electron microscopy, X-ray diffraction (XDR) technique, tensile strength, antibacterial activity, and cytotoxicity tests. XRD and SEM confirmed the $CuSO_4$ nanoparticles formation and grafting on catgut surface. Antibacterial properties were illustrated by E. coli inhibition zone and CSNPs@Catgut showed a significant antibacterial activity compare with catgut. Results of cytotoxicity tests showed no difference between CSNPs@Catgut and catgut. The mechanical strength was improved and increased from 4.16 mm to 10.00 mm. Tissue reaction showed that necrosis and inflammatory cells were reduced from acute to subacute on day 14. Therefore, CSNPs@Catgut can be introduced as a reliable candidate for wound management.

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INTRODUCTION

Wounds are affected by bacteria and it can delay wound healing through a complex process. External materials such as surgical suture and *ex vivo* pathogen can cause complications, such as infection in surgical site [1-5]. Surgical sutures are sterile filament to support the healing process. They classified according to their degradation, composition and suture, including absorbable, non-absorbable, monofilament and multifilament [6-8]. Absorbable suture are divided to natural and synthetics, digested by enzymes and hydroxylation during the wound closure process, respectively. Gut and chromic gut are absorbable sutures that remain in the cutaneous and other tissue for 21-28 days after embedding. Poor knot security and high level of proteolytic enzyme in inflammatory cells are among the limitations of these stitches[9, 10].

The presence of sutures at surgical site have some adverse effects, such as surgical infection, clinical problems, prolong hospitalization and rising of health care cost [11-13]. Chromic catgut, the catgut sutures with chromic salts to crosslink the collagen molecules, have been widely used. At the first, carbolic acid was developed in 1881, after then ethylene oxide has been replaced for suture sterilization [14]. In recent years, suture coated with

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antibiotics and commercial antimicrobial suture, such as Vicryl-plus and Monocryl-plus have been used exclusively. Furthermore, polymer coating, such as carboxylic with an attaching antibiotic agent and natural polymer like chitosan and alginate, are well prospected for wound treatment [15-18].

Coating suture with nanoparticles, which can improve wound healing, surgical site infection (SSI) prevention and mechanical properties. Recently, suture has been enriched with silver nanoparticles using coating method [19, 20]. Copper nanoparticles is another type of nanostructure that its antibacterial properties has been demonstrated. The preferences of Cu nanoparticles that make it a suture investigation aspect are low production cost, wide range of antimicrobial potency, catalytic activity In addition, copper oxide and copper sulfate are well known compounds that have antibacterial properties comparable with copper metallic [21-23].

There are various methods such as chemical and physical vapor deposition, nanoimprint lithography and solid-state techniques for synthesis of the nanostructures used in the tissue engineering. The application of nanofibers was widely investigated in this research area. It has been demonstrated that the electrospun gelatin nanofibers was a good candidate for tissue scaffold. It has been reported that this scaffold exhibited desired biocompatibility and no toxicity after 24 and 48 hours in human foreskin fibroblast cells [24, 25]. The reverse micro-emulsion is another interesting technique due to its easy protocol and inexpensive requirements. In the micro-emulsion medium, some micro and nano-spherical structures are created that called micelles. Micelles are nano- capsules contain aqueous solutions. The main advantage of micro-emulsion method is the ability of the final particle sizes controlling [26].

In this study, copper sulfate nanoparticles (CSNPs) were formed in catgut absorbent mass. An effective method was developed for preparation of CSNPs@Catgut (the CSNPs penetrated in and coated on catgut fibers) as a suture with positively different properties from plain and chromic catgut. Catgut was immersed in a micro-emulsion solution containing $CuSO_4$ and conditions (concentration and immersing time) were changed to find the maximum salt loading. Mechanical strength and surface morphology of enriched suture were analyzed. Cytotoxicity, antimicrobial activity and anti-inflammatory of CSNPs@Catgut were also evaluated.

EXPERIMENTAL

Materials

Absorbable catgut plain suture as well as nylon, silk and vicryl sutures were purchased from local veterinary pharmacies (Isfahan, Iran). Copper sulfate pentahydrate ($CuSO_4.5H_2O$), Triton X-100, *n*-hexane, *n*-butanol and ethanol all were purchased from Merck.

Methods

The catgut enrichment

The catgut was enriched by CSNPs via immersing it in a reverse micro-emulsion mixture, using Triton X-100 (surfactant) and *n*-hexane as organic phase and *n*-butanol as co-surfactant. The aqueous solutions containing $CuSO_4.5H_2O$ with different concentrations were prepared and added dropwise to the surfactant mixture. It was stirred for one hour vigorously until obtaining a homogenous and clear mixture. Catgut samples were immersed in solutions with different concentrations of $CuSO_4$ (0.01-1 mole.L^{-1}) for different times (10-1440 min) to find the optimum time for loading. Copper sulfate was loaded on catgut by micelles uptake to catgut. The swollen catguts were brought out of mixture and dried in an oven at 90°C for 48 hours. After complete drying, samples were immersed in absolute ethanol for 12 hours to dissolve micelles remnants and better participating of $CuSO_4$ salt on catgut. They were dried again in oven at 75°C for 12 hours, so the CSNPs@Catgut were ready to use.

CSNPs@Catgut characterization

The surface morphology of prepared suture was characterized using scanning electron microscopy (SEM). The SEM micrographs were token using Hitachi-54160, Chiyoda-ku, Japan operated at 15 kV. The samples were placed in a vacuum chamber and coated with a thin god layer to improve their surface conductivity and subsequently obtain clear micrographs [27]. They were presented on different magnifying and resolutions to see if copper sulfate particles grafted on catgut surface and penetrated in its bulk. The technique also was carried out to evaluate the successfulness of nano size preparation with micro-emulsion synthesis method. The X-ray diffraction (XRD) technique (X'Pert Philips 3040/60, Cu/Kα) was also used with to confirm the existence of $CuSO_4$ phase deposited on catgut. As another characteristic test, the effect of copper grafting on tensile strength, catgut and CSNPs@Catgut were analyzed using Santam machine

Table 1: The table of experimental design for finding maximum $CuSO_4$ loading in micro-emulsion mixture.

Run	Time (min)	Micro-emulsion concentration (M)	Loaded $CuSO_4$ (g)
1	1440	0.1	0.006
2	1440	0.01	0.06
3	725	0.055	0.009
4	10	0.1	0.004
5	10	0.01	0.002
6	1440	0.055	0.005
7	725	0.1	0.06

controller. The force required for rupture starting of each sample was measured and recorded in Newton.

Antibacterial and cytotoxicity tests

The antibacterial activity of CSNPs@Catgut suture was assessed by the zone of bacterial inhibition. It was evaluated and compared with antibacterial disk, and then the zones of bacterial inhibition in treated and untreated sutures were determined. Pieces of sutures were inoculated with approximately 1×10^8 to 2×10^8 $CFU.mL^{-1}$ *E. coli* (ATCC25922) per plate, and incubated for 24 h at 37°C.

Viability and proliferation assays were investigated by counting live, dead (by 0.4% trypan blue solution), suspended cells in the medium, and attached cells to a petri dish, after trypsinization with hemocytometer chamber, separately. Human menstrual blood stem cells (hMBSC) were cultured and the toxicity of suture was determined by cell counts. For this purpose, the culture medium was removed from petri dish and then the petri dish was washed with PBS. The harvesting of the cells was performed by adding Trypsin/EDTA (4%) with concentration of 50 $\mu L.cm^{-2}$ and then incubation at 38.5 °C. After neutralizing trypsin with serum-containing culture medium, the cells washing and dilution was performed. Eventually, hemocytometer was filled and the cells were observed under an inverted microscope. The number of dead and live cells was counted in different days (5-10-15).

Animal and histological experiments

Eighteen adult female mice, weighting (25-30 g) were purchased from the pharmacy research institute (Isfahan, Iran). They were kept in standard condition and divided into control and treated groups. For this purpose, CSNPs@Catgut and simple catgut sutures were imbedded in the muscles of femur. At the end of the study, the mice (from each group) were scarified on the days 3, 7, 14, foot of mice were separated, and fixed by 85 percent paraformaldehyde. The staining of the section of muscle, including suture embedding, was performed with Hematoxylin and Eosin (H&E). The data were expressed as mean ± standard deviation for three experiments (n=3). Two-way multivariate analysis of variance was used for the results statistical evaluation.

RESULTS

Copper sulfate optimum loading

An experimental design was carried out to find the optimum $CuSO_4$ micro-emulsion concentration and immersing time. A table of experimental design was created by SAS-JMP software for changing these two factors with three levels (Table 1). Salt uptake was performed and the table was completed. Data was analyzed, variations were plotted versus loading and the optimum points for each factors were derived. As shown in Fig. 1 the maximum $CuSO_4$ was loaded during 880 min and in 0.06 M solution.

A maximum loaded amount of $CuSO_4$ on catgut during time was observed because the suture has a limit capacity of absorbance. It seems that the suture is not saturated in time durations less than 880 min and more than that has no capacity for $CuSO_4$ absorption. A maximum point was observed on loaded $CuSO_4$ vs micro-emulsion concentration. It can be related to bigger sizes of micelles in concentrated solutions because of Cu^{2+} cations and SO_4^{-2} anions are closer in concentrated solutions. The phenomenon can limit the diffusion of micelles into the catgut and subsequently limit the $CuSO_4$ loading.

Morphological analysis of CSNPs@Catgut

The distribution and size evaluation of copper sulfate particles on catgut suture were investigated using SEM. Fig. 2 shows SEM micrographs

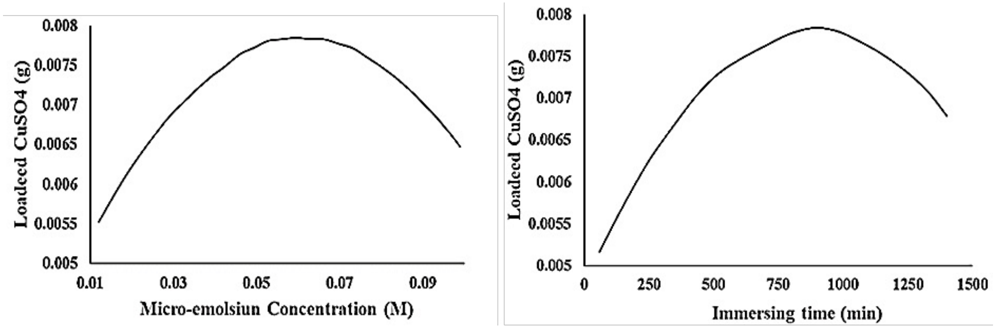

Fig.1: Graphs derived from experimental design analysis for immersing time and micro-emulsion concentration

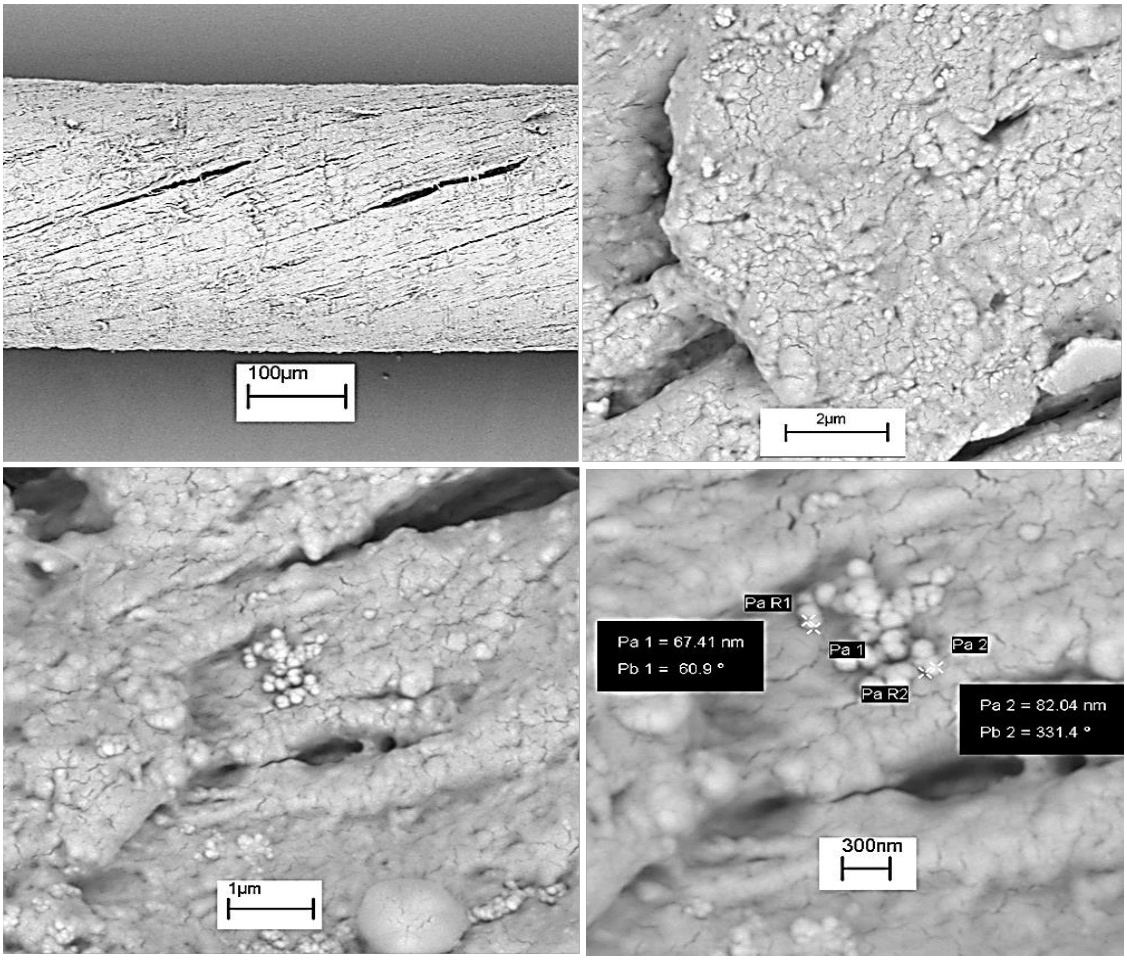

Fig. 2: Scanning electron microscopy micrographs of CSNPs@Catgut with different magnifying.

of CSNPs@Catgut with different magnifying. Moreover, the presence of particles was also visible, among the filaments of the suture. The nanoparticles clearly covered the suture surface by filling the pore between fibers of the yarn. The SEM analysis showed copper sulfate particles distribution on catgut surface relatively good. The micrographs also show $CuSO_4$ particles sizes between 50 and 100nm. It was the main idea of this research that particles attached on surface or penetrated in bulk of catgut can release

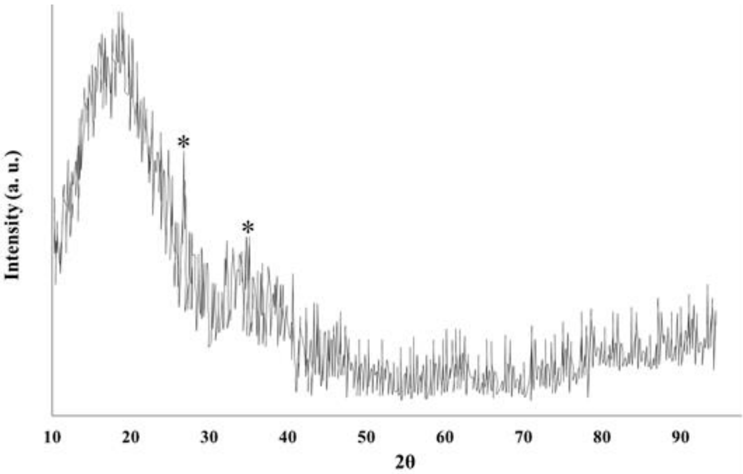

Fig. 3: The XRD pattern of CSNPs@Catgut; Marked peaks with (*) can be related to characteristic peaks of $CuSO_4$.

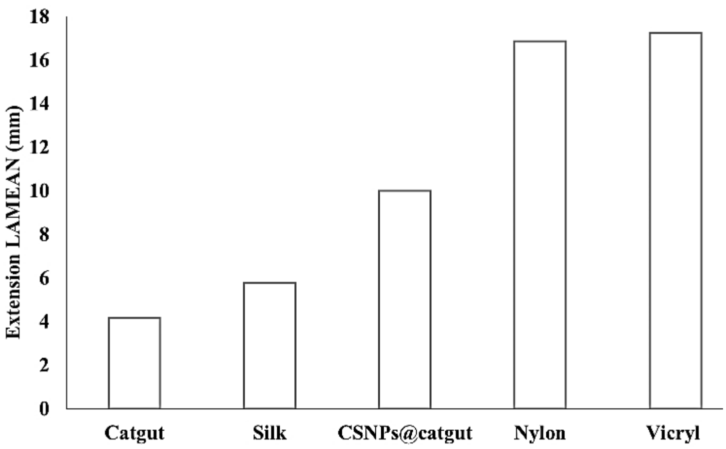

Fig. 4: Tensile strength tests for catgut, CSNPs@Catgut, nylon, silk and vicryl sutures.

slowly around the wound with absorbing the yarn. It is a fact that smaller particles have higher surface area and better performance of activation.

XRD pattern

XRD technique was performed to confirm the deposition of $CuSO_4$ on catgut suture. Fig. 3 shows The XRD pattern of CSNPs@Catgut. Peaks at 2θ= 19.3, 31.7 and 46.8 can be related to $CuSO_4$ crystalline phase. The patterns also shows no crystallinity for catgut because it is relatively an amorphous phase.

Tensile strength test

The tensile strength test was performed, in order to compare the tensile strength of catgut, CSNPs@Catgut, nylon, silk and vicryl sutures. The test showed changing in tensile strength of catgut with adding $CuSO_4$ nanoparticles. Fig. 4 shows that $CuSO_4$ can improve the mechanical properties of yarn so that CSNPs@Catgut tensile strength be relatively comparable with nylon. The mean maximum tensile strengths at the breakdown point for CSNPs@Catgut and catgut samples were (10.0075± 0.35 N) and (4.16± 1.02 N), respectively. Therefore, catgut enrichment with $CuSO_4$ significantly improved the strength of suture stretching. It seems that salt penetration to catgut bulk has occurred uniformly so that made the suture a semi nanocomposite structure.

Antibacterial activity and Cytotoxicity

The microbiological characterizations were performed on CSNPs@Catgut and plain catguts

Table 2: Dead and live cells were expressed as mean ± standard deviation (n=3) for CSNPs@Catgut and catgut in different days.

	CSNPs@Catgut		Catgut	
Day	Live	Dead	Live	Dead
5	48000 ± 500^a	26400 ± 100^a	358800±10000	18200±100
10	643066±15275	24200±100	643200±100	24233±208
15	728100±100	31100±100	728300±100	30900±100

a; Significant difference between groups in row (P < 0.05).

Fig. 5: The antibacterial activity of CSNPs@Catgut and plain catgut sutures.

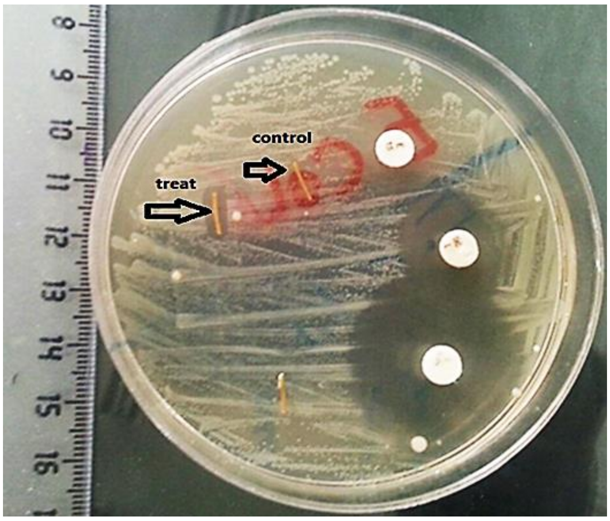

Table 3: Evaluation of necrosis and severity in control and treatment groups on 3, 7 and 14 days.

	Necrosis		Severity	
Day	Control	Treat	Control	Treat
3	$2.3\pm0.57_a$	2_a	$2.3\pm0.57_a^A$	2_a^B
7	$1.3\pm0.57_b$	$1.3\pm0.57_b$	$2.3\pm0.57_b^A$	$1.3\pm0.57_b^B$
14	$1.6\pm0.57_c$	1_c	$1.6\pm0.57_c^A$	1_c^B
Total	1.7±0.66	1.4±0.52	2.1±0.60	1.4±0.52

a,b,c ; significance between days
A, B; significance between groups

as the control group. The zone of *E. coli* inhibition was compared with antibacterial disk, qualitatively (Fig. 5).

Tissue and wound healing effect

H&E staining section was compared between the control and treated group. In the treated group, inflammation was reduced and CSNPs@Catgut affected the wound healing factor. As shown in Table 3, there was a significant difference between the mean of necrosis and intensity of inflammation in all groups (control and treated) on days 3-7 and 14 ($p< 0.05$). The significant differences between the treated and control groups were observed on days 3-7 and 14 in terms of the intensity of inflammation. However, no significant differences were observed between the treated and control groups in the necrosis variable ($p>0.05$), but a significant difference was observed among 3rd, 7th and 14th days, in terms of the mean of necrosis variables.

Fig. 6 shows different characteristics between

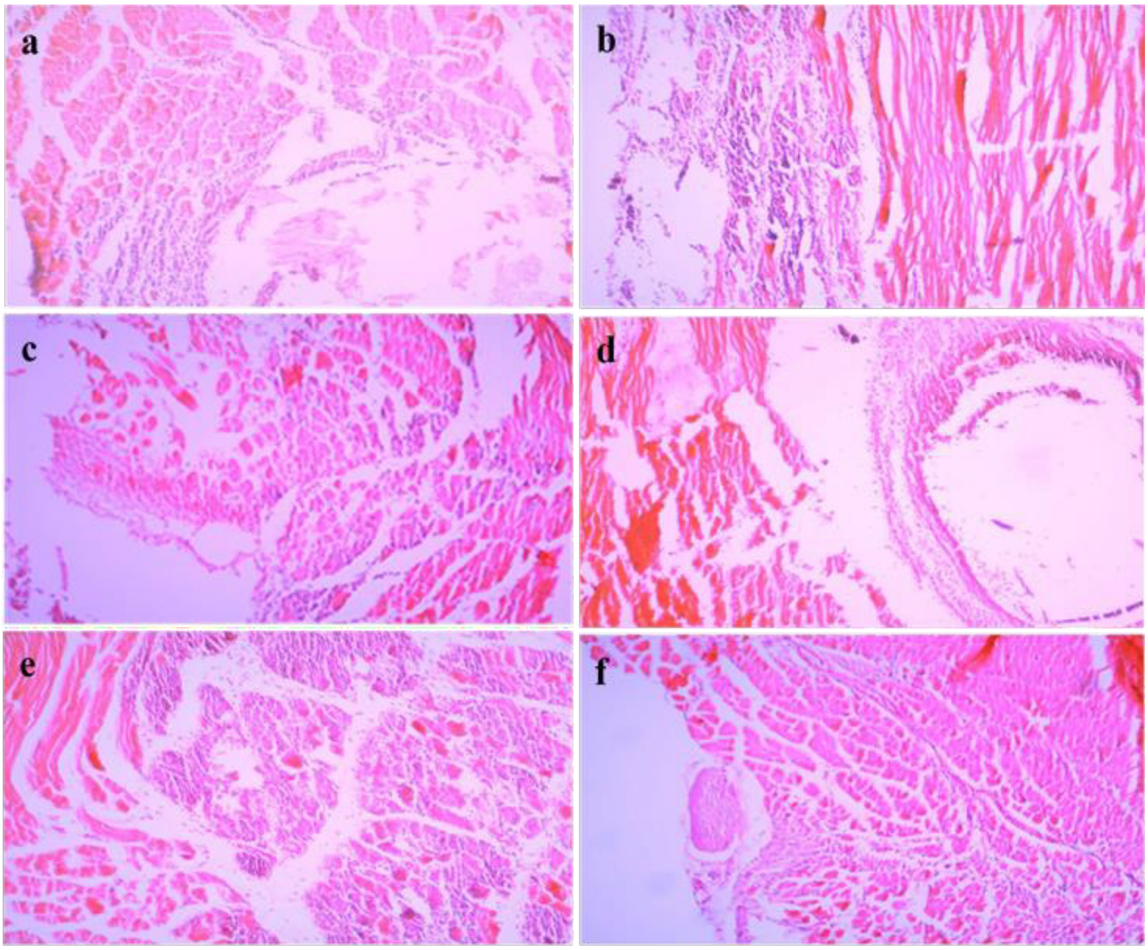

Fig. 6: Muscle necrosis in the site of suture with relatively mild accumulation of inflammatory cells (H & E, X10), in the treatment groups on the third day (a), control group on the third day (b), treatment group on the seventh day (c), control group on the seventh day (d), control group on the fourteenth day (e) and treatment group on the fourteenth day (f).

the control and treated group. So that on day 3, acute inflammation with necrosis and bleeding can be seen in the control and treatment group (Figs. 6a & 6b). This trend changed from day 7 in the treatment group with decreasing intensity of inflammation and bleeding, compared to the control group (Figs. 6c & 6d), so that the intensity of inflammation of the treatment group was less than control group (Figs. 6e & 6f).

DISCUSSION

Despite suture sterility, different approaches adapted for wound management may cause contamination, delay in wound healing and susceptibility to secondary infection. One of the approaches of wound management with a goal to improve the healing process is to prevent the bacterial adherence to the surgical suture and to fight against the formation of these contaminated points. Considering the degree of adherence of bacteria to the suture and its impact on infection and delay in wound healing, fighting against bacteria will be considered as a practical way to improve wound management. Antibiotic-resistant is another concern in the surgical site infection. Therefore, the role of metal and salt particles especially in the nano scales is inevitable for managing wound healing and infection [28, 29].

A novel copper sulfate nanoparticles/catgut (CSNPs@Catgut) with antimicrobial properties, reduced inflammation and increased wound healing was developed. The dispersion of nanoparticles on surface and in matrix of suture significantly improved its physical and chemical properties as a semi nanocomposite. The mechanical properties of the treated catgut sutures were evaluated because the reduction in the strength of the suture material can result in unexpected suture breakage, so inducing complications in healing tissues and tensile strength could reduce healing time with mechanical tissue effects. Although, types of sutures do not cause a significant difference in the process of wound healing, but it shows different tissue reaction in different conditions.

The prepared CSNPs@Catgut was characterized using SEM, XRD, tensile strength, antibacterial activity and cytotoxicity tests. SEM analysis showed the effectiveness of the dipping process, in providing a homogeneous distribution of $CuSO_4$ on the catgut suture. XRD showed characteristic peaks of $CuSO_4$ and confirmed the deposition its particles on catgut. The mechanical properties of the treated suture increased 2.5 times, compared to the control sample, which caused a significant difference in the strength of the material after treatment. The detail of investigation has indicated that the CSNPs@Catgut degrades in a slower rate after 7 days of the degradation process. Antibacterial activity tests demonstrated that CSNPs@Catgut can be utilized against bacterial colonization like *E. coli* without any cell toxicity. The histopathological study clearly demonstrated that grafting of copper sulfate nanoparticles on suture could decrease inflammation. Therefore, application of anti-inflammatory agent adapted as an effective approach to enhance healing pressure and regeneration. Suture strength, antibacterial properties and cytotoxicity positively affected the inflammatory stage of wound healing.

CONCLUSION

An effective nano-enriched suture was designed and prepared using $CuSO_4$ nanoparticles grafting on catgut. Nanoparticles were deposited on suture using revers micro-emulsion method. Experimental design revealed loading capacity of catgut by micro-emulsion solution concentration and immersing time duration. Results of characterizations showed a complete excellence of CSNPs@Catgut compared with simple catgut in tensile strength, antibacterial activity, cytotoxicity as well as tissue and wound healing effect. It can be related to the nature of copper sulfate, particles scale, uniform particle sizes and similarly uniform particle dispersion on surface and in the bulk of catgut. The mean maximum tensile strengths for CSNPs@Catgut was more than two times higher than simple catgut. It was related to creation of a semi nanocomposite after adding $CuSO_4$ to catgut because of good merging of particles and suture. Results also showed an obvious effect of nanoparticles on antibacterial properties of the suture. It can be depended on antibacterial nature of copper sulfate as well as high surface area of attached nanoparticles to catgut. The result of cytotoxicity test also did not show any difference between the CSNPs@Catgut and catgut. Finally, the new suture with decreasing intensity of inflammation and bleeding leaded wound healing process to good situations and made itself as a reliable candidate for wound management.

CONFLICT OF INTEREST

There is no conflict of interest among the authors.

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