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Effect of a 50-Hz Sinusoidal Electromagnetic Field on the Integrity of Experimental Colonic Anastomoses Covered with Fibrin Glue

Wpływ zastosowania kleju fibrynowego i zmiennego pola magnetycznego o małej częstotliwości (50 Hz) na integrację blizny pooperacyjnej w eksperymentalnym zespoleniu okrężnicy

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Abstract

Background. Low-frequency magnetic fields have been shown to affect biological processes. In this article the effects of 50-Hz sinusoidal magnetic field (MF) stimulation and application of fibrin glue on the healing of experimental colonic anastomoses were investigated.
Material and Methods. Twenty-eight rats were divided into four groups. Group 1 underwent 2-cm left colonic resection and primary anastomosis. Group 2 underwent normal resection anastomosis and the area was covered with fibrin glue. Group 3 underwent normal resection anastomosis and the rats were exposed to a 50-Hz sinusoidal MF. Group 4 underwent normal resection anastomosis, the anastomosis area was covered with fibrin glue, and the rats were exposed to a 50-Hz sinusoidal MF. Investigations included bursting pressure measurement, hydroxyproline content, and histopathological changes.
Results. Tissue hydroxyproline levels and anastomotic bursting pressures of groups 2, 3, and 4 were significantly higher than in group 1. Collagen deposition and fibroblast infiltration in groups 2, 3, and 4 had higher scores than in group 1. Furthermore, these results were significantly higher in group 4 rats than in the other groups. Histopathological examination of the anastomosis revealed significantly better healing patterns for group 4 than for groups 1, 2, and 3.
Conclusions. A 50-Hz sinusoidal MF stimulation and application of fibrin glue provided a significant gain in anastomotic healing in the large intestine. A combination of a 50-Hz sinusoidal MF and fibrin glue has significantly favorable effects on healing of experimental colon anastomosis (**Adv Clin Exp Med 2009, 18, 1, 13–18**).

Key words: colonic anastomosis, 50-Hz sinusoidal magnetic field, fibrin glue.

Streszczenie

Wprowadzenie. Wzrasta zainteresowanie skutkami oddziaływania pola magnetycznego o małej częstotliwości na różne procesy biologiczne. W prezentowanej pracy przedstawiono wyniki badań wpływu pobudzającego działania zmiennego pola magnetycznego (MF) o częstotliwości 50 Hz na rezultaty wykorzystania kleju fibrynowego w doświadczalnym zespoleniu okrężnicy.
Materiał i metody. Badaniom doświadczalnym poddano 28 szczurów, podzielonych losowo na 4 grupy. W grupie 1. wycięto dwucentymetrowy odcinek okrężnicy i zespolono ponownie metodą standardową. W grupie 2. wycięty obszar okrężnicy zespolono metodą standardową, a miejsce zespolenia pokryto klejem fibrynowym. W grupie 3. również dokonano zespolenia wyciętego odcinka w sposób standardowy, a następnie szczury poddano działaniu zmiennego pola magnetycznego MF o małej częstotliwości (50 Hz). W grupie 4. zespolone metodą standardową odcinki okrężnicy pokryto dodatkowo klejem fibrynowym, a następnie badane zwierzęta poddawano działaniu ta-

kiego samego pola magnetycznego. W każdej badanej grupie zwierząt wykonano pomiar ciśnienia rozrywającego w okrężnicy, oznaczono zawartość hydroksyproliny komórkowej oraz dokonano oceny zmian histopatologicznych.
Wyniki. Oznaczone ilości komórkowej hydroksyproliny oraz wartości ciśnienia rozrywającego w zespolonym odcinku okrężnicy były znacząco większe w przypadku grupy 2., 3., 4. w porównaniu do wyników uzyskanych w przypadku grupy 1. Poziom osadzonego kolagenu i naciekowych fibroblastów zaobserwowany w grupach 2., 3., 4. był większy niż w grupie 1. Wielkości te w 4. grupie badanych szczurów były ponadto znacząco większe w porównaniu do pozostałych grup badanych zwierząt. Badania histopatologiczne uzyskanego zespolenia okrężnicy wskazują na znacząco lepsze rezultaty wykonanego zabiegu w grupie 4. niż w grupach 1., 2., 3.
Wnioski. Jednoczesne zastosowanie kleju fibrynowego i zmiennego pola magnetycznego o małej częstotliwości (50 Hz) korzystnie wpływa na proces powstawania blizny pooperacyjnej w doświadczalnym zespoleniu okrężnicy u szczurów (**Adv Clin Exp Med 2009, 18, 1, 13–18**).

Słowa kluczowe: zespolenie okrężnicy, pole magnetyczne o małej częstotliwości, klej fibrynowy.

Anastomotic leakage is a most serious complication after colorectal surgery and is affected by many local and systemic factors [1, 2]. Many developments in surgical technique, antimicrobial therapy, bowel preparation, nutritional and pharmacological drugs and postoperative intensive care have diminished the incidence of anastomotic dehiscence after colorectal surgery; however, morbidity still remains high [1, 3].

Experimental data suggests that electromagnetic field (EMF) influences cell functions, including proliferation, apoptosis, permeability, and DNA damage [4, 5]. The exact mechanism of action of magnetic fields within the living system is not clearly defined. Studies have shown that EMF can modulate cell function and affect the production of extracellular matrix components. The molecular architecture of the extracellular matrix is critical to the functioning of connective tissues [6]. Additionally, various mesh sealing have also been studied, but with varying results [7]. There have also been experimental studies on reinforcement of sutured or stapled gastrointestinal anastomoses using liquid fibrin glue, with widely varying results [8–11]. Fibrin adhesives have three positive effects on wound healing: they decrease hematoma formation secondary to their hemostatic effect, are well adapted to tissues, and maintain a suitable media for fibroblast development [12]. For a while, fibrin adhesives have been used to adapt skin grafts to donor regions; recently, in Australia and Germany, they are used to strengthen anastomoses [12, 13].

The biochemical evaluation of anastomotic healing is performed by determining the level of a standard indicator hydroxyproline of new collagen synthesis in collagen tissue. The amino acid hydroxyproline is a unique characteristic of the alpha chains of collagen molecules, and is formed by hydroxylation of proline before the alpha chains are wrapped together, forming a triple helix. Generally, a low hydroxyproline level negatively affects wound healing [14]. Additionally, it was proposed that assessment of the anastomotic healing mainly depends on mechanical parameters, and bursting pressure is particularly of great value [15]. Therefore, the authors measured the tissue hydroxyproline content and bursting pressure to determine the effect of sinusoidal electromagnetic field stimulation and fibrin glue on wound healing.

This study was designed to investigate the effect of sinusoidal electromagnetic field stimulation and fibrin glue on colonic anastomosis healing.

Material and Methods

This study was conducted in laboratories of the Dicle University Faculty of Medicine Experimental Research Center (DUSAM) using 28 Spraque-Dawley rats weighing 250–280 g. The rats were fed standard pellet chow and tap water and were kept at room temperature and in a humidity-controlled environment. Rats were randomly allocated to one of four groups containing seven rats each. In group 1, a 2-cm left colonic resection and primary anastomosis were done. In group 2, normal resection anastomosis was done and was covered with fibrin glue. In group 3, normal resection anastomosis was done and the rats were exposed to a 50-Hz sinusoidal MF. In group 4, normal resection anastomosis was done, the anastomosis area was covered with fibrin glue, and the rats were exposed to a 50-Hz sinusoidal MF.

The abdomen was dissected under anesthesia (Ketamine 75 mg/kg *i.m.*, Ketalar®, Parke-Davis, Eczacibasi, Istanbul, and Xylazine HCl16 mg/kg *i.m.*, Rompun® 23.32 mg/ml, Bayer, Istanbul). The two-cm left colonic resection and primary anastomosis were done with separate 7/0 sutures (Prolene, Ethicon, UK) by a single-layer technique. Then the incision was closed with continuous 4/0 silk sutures.

Fibrin glue (Tisseel Kit; Immuno, Vienna, Austria) is a multicomponent adhesive consisting of two solutions: (a) a freeze-dried protein con-

centrate of human fibrinogen (120 mg/ml) reconstituted in a solution of aprotinin (3000 KIU/ml) and (b) a solution of thrombin (500 IU/ml) and calcium chloride (40 mmol/l). After preheating to 37°C, the components are reconstituted with the solutions and drawn into separate syringes. These syringes fit in a specially designed syringe holder (Duploject; Immuno, Vienna, Austria), enabling mixing and application of the two components simultaneously. On mixing and application, the fibrinogen is activated to form fibrin, and the solution is transformed into a rubber-like adhesive mass. For one anastomosis, 0.2 ml of fibrin glue was used, taking precautions to avoid dispersion of the glue into the peritoneal cavity.

The EMFs was generated in a device previously designed by Vesper and Collages [17]. The sinusoidal MF was generated in a device designed by the present authors that has two pairs of Helmholtz coils of 70 cm in diameter in a Faraday cage (130×65×80 cm) that grounds the shielding against the electric component. This magnet was constructed by winding 125 turns of insulated soft copper wire with a diameter of 1.5 mm. The coils are placed vertically, facing one another. The distance between coils was 47 cm A pulsed current produced by a pulsed power supply (DAYM, Turkey) was passed through the device. The current in the wires of the energized exposure solenoid was 40 A for 1.5 mT, which resulted in a 50-Hz sinusoidal MF.

On the seventh postoperative day, 4 cm of the left colon was resected. One end of this segment was closed with a ligature and a catheter was secured to the other end. Inside a glass jar filled with water, air was pumped into the segment of colon at a rate of 2 ml/min by an infusion pump. Intraluminal pressure was monitored while the air was being pumped. The intraluminal pressure at which air leakage from the anastomosis occurred was recorded as the bursting pressure. A 2-cm segment of the colon including the anastomosis was resected, transsected longitudinally, and rinsed with saline to remove intestinal contents. One third of this sample was fixed in 10% formalin for histopathological examination. The remaining two thirds were kept wrapped in aluminum foil in the biochemistry laboratory for measuring tissue hydroxyproline.

Hydroxyproline levels were shown to indicate the amount of collagen in tissues [18]. The tissues (30–50 μg) were placed into hydrolysis tubes. Fifty mM potassium phosphate buffer, pH 7.0, and an equal volume of concentrated HCl were added to each tube and the samples were hydrolyzed at 110°C for 16 hours. The samples were oxidized with chloramine-T solution (pH 8.5) and Ehrlich's reagent was added. The color was allowed to develop at 60°C for 25 minutes and the absorbency at 560 mm was determined with Bergman and Loxley's method [40]. Total protein in the tissue homogenates was determined by the addition of trichloroacetic acid (TCA, 10% final concentration) to precipitate proteins and the sample was centrifuged at 2500 g for 10 minutes. The amount of protein in the sediment was determined with a protein assay kit based on the Lowry method (Bio-Rad, Hercules, CA, USA) [19].

A segment of each anastomotic ring was cut off for histological examination and fixed in 10% formaldehyde. The samples for histology were dehydrated and embedded in paraffin. From all paraffin blocks, 5-μm sections were cut and stained with hematoxyline-eosin. Verschoof, Van Gieson, and Masson's Trichrome staining were also done to assess the tissue reaction. The anastomoses were graded histopathologically in a blinded fashion. The parameters evaluated were inflammatory cell infiltrate (polymorphonuclear and mononuclear cells), fibroblast and blood vessel in growth, and collagen deposition (18). Each indicator was scored as: (0) = absent, (+) = mild, (2+) = moderate, and (3+) = intense.

Statistical Analysis

Data obtained from the study groups were expressed as the mean ± standard deviation. Differences in parameters among groups were examined using one-way analysis of variance (ANOVA) and post hoc analyses with the Tukey HSD test, while the histopathological parameters among the groups were examined using the Kruskal-Wallis test and *post hoc* analyses with the Tukey HSD test using SPSS for Windows, Release 10.0 (SPSS, Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered significant.

Results

The mean anastomotic bursting pressure values for the different groups are shown in Figure. 1. Group comparison showed that the mean anastomotic bursting pressure in group 4 was significantly higher than in the other groups ($p < 0.05$ for all). The mean anastomotic bursting pressures in groups 2 and 3 were significantly higher than in group 1 ($p < 0.05$ for all). The mean anastomotic bursting pressures in groups 2 and 3 were not statistically different ($p > 0.05$).

The mean anastomotic tissue hydroxyproline concentrations on the 7th postoperative day were statistically different among the groups ($p < 0.0001$)

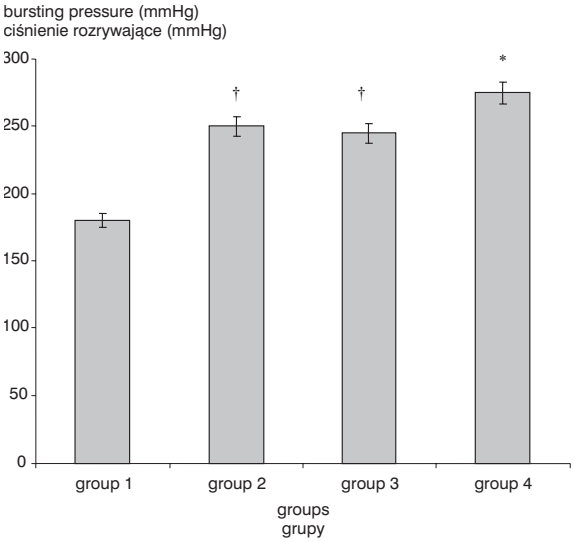

Fig. 1. Mean anastomotic bursting pressure in groups. * $p < 0.05$ compared with groups 1, 2, and 3, † $p < 0.05$ compared with group 1

Ryc. 1. Średnie wartości ciśnienia rozrywającego w okrężnicy wyznaczone w poszczególnych grupach badanych szczurów. * Różnica istotna statystycznie ($p < 0,05$) w porównaniu do grup 1, 2 i 3. † Różnica istotna statystycznie ($p < 0,05$) w porównaniu do grupy 1

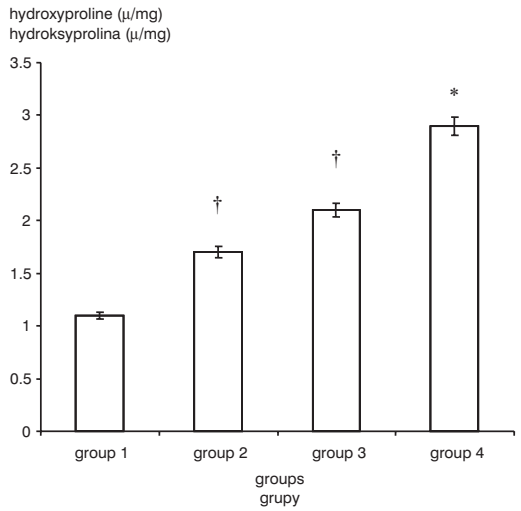

Fig. 2. Mean anastomotic hydroxyproline content in groups. * $p < 0.05$ compared with groups 1, 2, and 3, † $p < 0.05$ compared with group 1. Hydroxyproline content: μ/mg

Ryc. 2. Średnie wartości stężenia hydroksyproliny (μ/mg) komórkowej wyznaczone w poszczególnych grupach badanych szczurów. * Różnica istotna statystycznie ($p < 0,05$) w porównaniu do grup 1, 2 i 3. † Różnica istotna statystycznie ($p < 0,05$) w porównaniu do grupy 1

(Figure 2). The mean tissue hydroxyproline concentration in group 4 was significantly higher than in groups 1, 2, and 3 ($p < 0.05$ for all). The mean tissue hydroxyproline concentrations in groups 2 and 3 were significantly higher than in group 1 ($p < 0.05$ for all) and the mean hydroxyproline concentrations in groups 2 and 3 were not statistically different.

The histological findings of the colonic anastomosis are summarized in Tables 1. Groups 2 and 3 had higher scores for collagen deposition and fibroblast infiltration than group 1 ($p < 0.05$ for all). Additionally, the collagen deposition and the fibroblast infiltration were significantly increased on the 7th day in group 4 compared with the other groups ($p < 0.05$ for all). There were no significant differences in vascularization and inflammatory cell infiltrate among the groups ($p > 0.05$).

Discussion

Intestinal anastomotic insufficiency remains the most important cause of morbidity and mortality after gastrointestinal tract surgery. The study demonstrated a positive effect of sinusoidal MF stimulation and covering the anastomoses with fibrin glue on colon anastomotic healing in rats. Mechanical, histopathological, and biochemical parameters were improved.

Anastomosis healing is a complex and dynamic process and various factors, such as inflammation, collagen synthesis, angiogenesis, matrix deposition, and remodeling steps, have been shown to affect the healing of anastomoses [22–27]. The effects of electromagnetic fields on several processes related to cell physiology and proliferation are currently being investigated. Receptors on the cell surface are important interaction sites for extracellular signals, such as hormones and cytokines, and the specific interaction between extracellular signals and their receptors is usually the initiation of signal transduction [22]. Some studies showed that electromagnetic fields could activate the signal transduction pathways which are usually related to receptors [28–30]. However, the initial site for electromagnetic fields interacting with a cell or receptor is unclear. Devary et al. [31] found that ultraviolet light may activate the stress-activated protein kinase pathway through the cellular membrane, and Rosette and Karin [32] confirmed that growth factor and cytokine receptors are the sites from which ultraviolet light activates the stress-activated protein kinase cascade.

It is obvious that covering the anastomosis with fibrin sealant protects the anastomosis and stimulates neoangiogenesis and fibroblast activity [10]. Additionally, it is essential to note that the

Table 1. Histological evaluation of colonic anastomosis on 7th postoperative day

Tabela 1. Ocena histopatologiczna zespolenia okrężnicy u badanych szczurów dokonana w 7. dniu po operacji

Parameters (Wskaźniki)	Groups (Grupy)			
	group 1	group 2	group 3	group 4
Vascularization	2.00 ± 0.81	2.00 ± 0.57	1.42 ± 0.53	2.57 ± 0.53
Inflammatory cell infiltrate	3.00 ± 0.81	1.85 ± 0.89	2.28 ± 0.95	1.42 ± 0.78
Fibroblast	0.85 ± 0.69	1.71 ± 0.48†	2.00 ± 0.57†	2.42 ± 0.28*
Collagen deposition	0.57 ± 0.5	2.57 ± 0.53†	2.00 ± 0.57†	3.14 ± 0.37*

Values are expressed as mean ± *SD*. * $p < 0.05$ compared with groups 1, 2, and 3, † $p < 0.05$ compared with group 1.

Wartości wyrażono jako średnia ± *SD*. * Różnica istotna statystycznie $p < 0,05$ w porównaniu z grupami 1, 2 i 3, † Różnica istotna statystycznie $p < 0,05$ w porównaniu z grupą 1.

fact that fibrin glue stimulates neoangiogenesis and fibroblast proliferation was also demonstrated in a previous study [33]. Kanellos et al. [10] showed that covering colonic anastomoses with fibrin glue protected the anastomoses from the immediate postoperative intraperitoneal injection of 5-FU and prevented leakage of the anastomoses. In contrast, in the 5-FU group, in which the rats were injected with 5-FU without covering the anastomoses with fibrin glue, the rupture rate increased by up to 37.5%. This difference was statistically significant. Fibrin glue, which makes a water-resistant covering, constitutes a physical barrier around the anastomosis. It thus prevents dehiscence of the anastomosis in the postoperative period. Additional sealing has been advocated in normal and high-risk colonic anastomoses in patients as a method to prevent anastomotic leakage [34]. However, in another study, Nordentoft et al. [35] revealed that the healing, strength, and complication rate after sealing with a collagen patch coated with fibrin glue components were equal to those in unsealed anastomoses.

Hydroxyproline level at the site of anastomosis healing is an indirect biochemical parameter that reveals information about the basic element of anastomosis healing, i.e. collagen metabolism [36]. On the other hand, the mechanical indicator of this metabolism is the anastomotic bursting pressure. Sealing with fibrin glue has resulted in increased levels of both hydroxyproline and bursting pressure. Hydroxyproline levels at the anastomotic site on day 7 in the fibrin glue group and in the rats exposed to a 50-Hz sinusoidal MF were higher than the levels measured on day 7 in the control group. Furthermore, in the rats exposed to a combination of a 50-Hz sinusoidal MF and fibrin glue the levels were significantly higher than in the other group.

As conclusions, a 50 Hz sinusoidal MF stimulation and fibrin glue provided a significant gain in anastomotic healing in large intestine. Additionally, a combination of A 50 Hz sinusoidal MF and fibrin glue has significantly favorable effects on healing of experimental colon anastomoses.

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