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ORIGINAL ARTICLE

Comparison of ıncisional hernia models ın rats: an experimental study

M. Sahin[1,5] · M. Saydam[2] · K. B. Yilmaz[3] · D. Ozturk[1] · P. Demir[4] · A. T. Arıkok[2] · M. Akinci[3] · M. T. Ozer[3]

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Abstract

Purpose Incisional hernia repair is a frequently performed operation worldwide. In this experimental study, our aim is to present the incisional hernia model after creating midline laparotomy and several type of defects on abdominal wall of the rats. Thereby, the method determined here may be used in future experimental incisional hernia repair studies.

Methods After approval, 32 male rats were randomly seperated into 4 groups of 8 animals each, and were operated to form an incisional hernia; Sham group, 5 cm incision group, 5 cm incision plus capitonnage group, and 5 cm incision plus 2×4 cm muscle excision group, respectively. On the 28th postoperative day after killing, the abdominal anterior wall of rats were removed for histopathological and biomechanic examination.

Results The incisional hernia size was found to be statistically different in at least one group ($p = 0.001$). The incisional hernia size in Group 4 was found to be significantly higher than Group 2 ($p = 0.001$). When the tension and elongation values were examined, there was a difference in at least one group ($p < 0.001$ and $p = 0.029$, respectively). Histopathological examination shows that the degree of inflammation and fibrosis varies significantly ($p = 0.001$ and $p = 0.002$, respectively).

Conclusion This study has lead us to believe that the rat model created by applying muscle excision from the midline of the abdomen is the ideal incisional hernia model that can be used in future experimental incisional hernia studies.

Keywords Incisional hernia · Rats · Experimental model · Ventral hernia · Abdominal wall

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✉ M. Sahin
drmutlu@gmail.com

1 Department of General Surgery, University of Health Sciences, Ankara Kecioren Training and Research Hospital, Ankara, Turkey

2 Department of General Surgery, University of Health Sciences, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

3 Department of General Surgery, University of Health Sciences, Ankara Gulhane Training and Research Hospital, Ankara, Turkey

4 Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkey

5 Kecioren Education and Research Hospital, General Surgery Clinic, Ankara, Turkey

Introduction

Incisional hernia, which is classified in the anterior abdominal wall hernias, is one of the most common problems which occur after surgical procedures performed on the abdomen. Therefore, one of the most frequently used procedures in general surgery is incisional hernia repair [1]. Various studies report the incidence of incisional hernias as being 12.7% to 23% [2–4]. Incisional hernia, which may occur following abdominal surgical procedures, leads to significant labor losses, morbidity, and negatively affects the quality of life. Due to their frequent occurrence and high morbidity, they continue to keep one of the major problems of surgery. The only treatment option for incisional hernia is surgery. In the treatment of incisional hernia, repairs take place with the help of different primary repair techniques and prosthetic materials [5]. To test different methods that can be used in incisional hernia repair, attempts have been made to develope various experimental models, to create incisional hernia in rats [6–9]. Previous studies have shown that fibroblast matrix signaling and collagen production reaches its peak on the 28th day of wound repair [7, 10]. Different experimental studies have determined the incision hernia formation rates as being 50%, 80% and 90%, respectively [6, 7, 9]. On the other hand, when the literature is reviewed, it is considered that there is a lack of optimal incisional hernia model that can be supported histopathologically and mechanically, especially in animal experiments, due to the failure to comply with the appropriate waiting times required for the formation of a full incisional hernia. To determine the most accurate result, the model used needs to form a hernia close to 100% and simulate standard surgical incisions.

The aim of the current research is to determine the optimal rat model study to create the highest incisional herniarate, after midline laparotomy. Thereby, the method determined here may be used in future experimental incisional hernia repair studies.

Materials and methods

Ethics committee approval was obtained for the study on 12.11.2018. The "resource equation" method was used to calculate the required sample size [number of rats) for the study [11, 12]. After power analysis, it was determined that a total of 24 rats were required, for comparing results obtained using 4 different methods. In addition 2 rats (with 30% reserve) per group were added, making the required total 32 rats to supply for possible losses. Thirty-three male Sprague–Dawley rats, weighing 250–300 g, were included in the study. The animals were randomly seperated into four groups of eight male animals each.

Animal preparation process

Before the experimental study, the rats were kept in a standard cage for 7 days at a temperature of 21–24 °C with 50% air humidity. A 12-h auto-light/dark cycle was maintained. During the whole study, rats were provided with standard availability of food and water. Prior to surgery, a dose of ketamine (90 mg/kg) + xylazine (10 mg/kg) was administered via general anesthesia. Subsequently, the anterior abdominal wall was shaved with an electric razor and excess hair was removed. Surgical surface antiseptic solution (BATTICON® Adeka Drug and Kim. ÜR. San. Ve Tic. AS. Maslak/Istanbul/Turkey) was used to disinfection the surgical site. Before starting the surgical procedure, the rats were tested to see if the anesthesia was sufficient, after which the procedure was commenced. When it was found that the anesthesia was insufficient, an extra half dose of anesthesia was applied.

Four groups of eight rats were formed as follows:

Group 1: Sham group (SG): a 5 cm midline skin incision + 5 cm midline celiotomy was performed. Following this, using 3/0 rapid vicryl (Ethicon), the facia was sutured, with individual sutures being placed 0.5 cm apart. Subsequently, skin suturing was performed with 2/0 vicryl (Ethicon), with each suture being 0.5 cm apart. Finally, antibacterial skin spray with oxytetracycline was applied on the skin.

Group 2: 5 cm incision group (IG): a 5 cm midline skin incision + 5 cm midline celiotomy was performed. Subsequently, skin suturing was performed with only 2/0 vicryl (Ethicon), single sutures being placed at 0.5 cm spacings and without suturing the fascia. Finally, antibacterial skin spray with oxytetracycline was applied on the skin.

Group 3: 5 cm incision + 3-0 Capitonnage with rapid group (CG): a 5 cm midline skin incision + 5 cm midline celiotomy was performed. Subsequently, instead of suturing the fascia bilaterally, to prevent mutual adhesion and mending, 3/0 rapid vicryl (Ethicon) was used to continuosly capitonise it. Skin suturing was performed using 2/0 vicryl (Ethicon), with single sutures at 0.5 cm spacings. Finally, antibacterial skin spray with oxytetracycline was applied on the skin.

Group 4: 5 cm incision + 2 × 4 cm muscle excision group (MEG): a 5 cm midline skin incision was performed. After which a midline celiotomy was performed, with 2 × 4-cm-sized muscle tissue centering the incision line from all sides being removed (Online Image I). Subsequently, skin suturing was performed with only 2/0 vicryl (Ethicon), single sutures being placed at 0.5 cm spacings and without suturing the fascia. Finally, antibacterial skin spray with oxytetracycline was applied on the skin. Following the different surgical procedures mentioned above, a total of six rats died in the first 3 days due to wound dehiscence and bowel evisceration.

The distribution of these rats by groups was as follows:

- two rats from Group 2 on the second postoperative day,
- three rats from Group 3; two on the first postoperative day and one on the second postoperative day,
- one rat from Group 4, on the third postoperative day.

Whilst the rats were being monitored, no pathological condition was encountered after the fourth day. During controls, incisional hernia formation of different sizes were observed, in all of the rats in Groups 2, 3, and 4. The minimum 28-day period required to create an experimental incisional hernia was awaited. During this period, the rats were kept in a standard cage with 50% air humidity at a temperature of 21–24 °C. In the first 72 h, rats were administered an analgesic combination (acetaminophen and COX-2 inhibitor) to provide adequate analgesia, every 12 h. The 12-h auto-light/dark cycle was maintained. Rats were provided with standard food and water availability throughout the study. Apart from general anesthesia, care was taken to ensure that there was no other condition that would cause the animals any pain. On the 28th postoperative day, 26 rats were again administered general anesthesia, with a dose of ketamine (90 mg/kg) + xylazine (10 mg/kg). The midline of the abdomen was opened from the skin and subcutaneous xiphoid area to the lowest point. Preparation was made for tissue excision with the formation of at least 3 cm flaps to the right and left. The anterior abdominal wall was removed in en bloc style to have biomechanical and histopathological examination (Online Image II). All rats were killed by exsanguination while under general anesthesia at the end of the procedure.

Biomechanical examination

Tensile pressure and rupture pressure tests were applied to the removed parts first. To eliminate bias, the measurements of the materials were made by technicians in the pharmacy department, who were not familiar with the working groups. With the help of the device, "tensile strength" and "elastic coefficient" tests were performed and numerical data were recorded [13]. Tensile strength of the myofacial tissues resected from the rats were measured using a universal testing apparatus H5KS-Tinius Olsen Force Tester (PA, USA) fitted with 5 kN load cell and custom tissue clamps. Tissue samples were mounted on the clamps, left edge to the top clamp and right edge to the bottom clamp (Online Image III). Dimensions of tissue samples were recorded for use in calculating tensile strength. For rat myofacial tissue samples, 0.5-cm-long tissue was clamped to the tissue puller. The tissue was pulled until complete rupture at 300 mm/min, and force and extension were measured during the pulling. Peak force was the greatest force attained during pulling. Tensile strength is defined as peak force/tissue cross-sectional area. It is measured as unit of Newton/cm^2. The elongation amount was calculated and noted in milimeters.

Histopathological examination

The pieces of the abdominal wall samples were placed in fixative solution and taken to the pathological examination. The samples were immediately fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin or Masson's trichrome [6]. Then they were subjected to histopathological examination, with their inflammation, granulation and fibrosis states being examined microscopicly. Inflammation-granulation status was evaluated using three grades: grade 1: mild, grade 2: moderate and grade 3: severe. Fibrosis status was also evaluated using three grades: grade 1: mild, grade 2: moderate and grade 3: severe.

Statistical analysis

The suitability of numerical variables to normal distribution was examined using the Shapiro–Wilk test and coefficient of variation. The numerical variables examined in the study were summarized with a 95% confidence limit for minimum, maximum, median and median, while categorical variables were summarised with numbers and percentages. The Kruskal–Wallis *H* test was used to compare numerical variables in groups. In cases where significant difference was determined, Bonferroni (Dunn)-corrected binary comparison results were given. At the end of histopathological examinations, distributions in groups according to grades were compared using the Pearson Chi-square test. The level of significant difference was accepted as being $p < 0.05$. The IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) programme was used for statistical analysis and calculations. In the R program [14], "rcompanion" [15] package was used to obtain 95% confidence limits for the median.

Results

Descriptive information regarding the weight of 26 rats with tissue excision, the approximate measurements of hernia size and biomechanical test results, as well as comparison results of groups are given in Table 1. The box-and-whisker plots of weight, hernia size, tension and elongation in groups are given in Fig. 1, respectively.

In multivariate analysis, the hernia dimension in at least one group was found to be different from the others ($p = 0.001$). As a result of multiple comparisons, it was determined that the hernia size values obtained for Group 3 were not statistically different from the values obtained in Group 2 and those obtained in Group 4 ($p = 0.333$ and $p = 0.755$, respectively). However, the hernia size determined in Group 4 was found to be significantly higher than the values determined in Group 2 ($p = 0.001$). Whilst the median hernia size obtained in Group 4 was 8.0 cm^2 (95% GS 5.3–8.0), it was 3.0 cm^2 (95% GS 1.3–3.0) in Group 2 (Table 1).

When the tension and elongation values in the groups were examined, it was determined that there was a difference in both variables, in at least one group ($p < 0.001$ and $p = 0.029$, respectively) (Table 1). As a result of the bilateral comparisons made for the tension values, determined to have a significant difference in at least one of the groups. A statistically significant difference was found between Group 1 and Group 2, and Group 1 and Group 4 ($p < 0.001$ and $p = 0.024$, respectively) (Table 1).

The results of histopathological examinations show the distribution of the degree of inflammation and fibrosis to vary significantly in the groups ($p = 0.001$ and $p = 0.002$, respectively) (Table 2). In the comparison between the groups in terms of observation of inflammation grade 1, whilst there was a significant difference between Group 1

Table 1 Descriptive information regarding the weight, hernia size and biomechanical test results obtained from each group

Variables	Groups								Test statistics	
	Group 1 (SG*) ($n=8$)		Group 2 (IG□) ($n=6$)		Group3 (CG□) ($n=5$)		Group 4 (MEG□) ($n=7$)		χ^2	p
	Min; max	Median (lower–upper limit)	Min; max	Median (lower–upper limit)	Min; max	Median (lower–upper limit)	Min; max	Median (lower–upper limit)		
Weight (g)	405; 505	452.5 (440–475)	415; 590	462.5 (430–530)	435; 480	455 (435–470)	445; 615	525.0 (445–585)	6.167	0.104
Hernia size (cm^2)	–	–	1.3; 3.5	3.0 $^{\&}$ (1.3–3.0)	3.5; 6.0	5.3 $^{\&,\$}$ (3.5–5.3)	5.3; 10.0	8.0 $^{\$}$ (5.3–8.0)	13.667	**0.001**
Tension (Nm/cm^2)	13.40; 33.10	19.45 $^{\$}$ (14.90–21.20)	7.29; 8.74	7.78 $^{\&}$ (7.36–8.21)	7.86; 10.30	9.27 $^{\$,\&}$ (7.86–10.30)	5.07; 13.40	8.70 $^{\&}$ (5.07–10.20)	18.121	**<0.001**
Elongation	23.60; 51.90	39.68 (29.6–49.2)	19.46; 42.46	25.95 (21.0–37.7)	19.13; 29.33	25.03 (19.1–27.0)	14.18; 33.53	29.58 (14.2–33.0)	9.060	**0.029**

p values were found significant for hernia size, tension and elongation values (bold)

SG*: Sham group; IG□: 5 cm incision group; CG□: 5 cm incision + 3–0 capitonnage with rapid group; MEG□: 5 cm incision + 2 × 4 cm muscle excision group

min; max: minimum; maximum; lower–upper limit range: median 95% confidence limits of median, c2: Kruskal–Wallis test statistic, &, $: Dunn's binary comparison results

and Group 2 ($p<0.05$), other binary comparisons were not found to be statistically different ($p>0.05$). The distribution of 2nd degree inflammation was similar in the groups ($p>0.05$). Grade 3 inflammation was only found in Group 1. When similar comparisons were made for the degree of fibrosis, it was found that whilst there was no 3rd degree inflammation observed in Group 1, 83.3% of Group 2, 80.0% of Group 3 and all of Group 4 had fibrosis grade 3 (Online Image IV). In relation to the degree of fibrosis, difference was only observed in Group 1.

Discussion

An incisional hernia specifically describes a hernia, often in the middle of the abdomen, that occurs after a prior incision was made during a prior operation. In addition, a certain period of time must pass for incisional hernia formation after the operation. When we examine literature about the animal experimental studies related to this subject especially, it was seen that this waiting period was not complied with. Animal models prior to clinical trials are essential for biocompatibility and strength assessment in the long term [16]. Since there is no standardization in existing animal models, it has been argued that standards that can compare clinical suitability and effectiveness should be defined [17]. Thus, it was decided to conduct this study to create an ideal incisional hernia model, especially for further studies based on the incisional hernia or with additive interventions. Physiopathologically, during this period, a problem occurs especially in the healing of the fascial layer, and therefore, the intraabdominal organs hernateout of the abdomen in a hernia sac. Of course, patients who develop incisional hernia frequently after abdominal operations are those with obese and additional chronic diseases. It normally takes weeks or months for this to happen. However, to perform hernia repair experimentally, it is necessary to develop an incisional hernia model that will shorten this period. For this purpose, many studies have been done before and some important results have been obtained.

Following the deterioration in facial healing, only after 28th day, incision hernia formation can be mentioned when fibroblast matrix signal and collagen production reaches its peak [7, 10]. However, in some experimental studies in the literature, it has been claimed that after a celiotomy was applied to rats, abdominal fascial repair was performed using different surgical methods within the same session, with incisional hernia repair being performed on them [18, 19]. The procedure performed here can be defined as a fascial repair of a laparotomy in the same session. Because, a hernia is a subsequent opening of a laparotomy, and a development of a defect, due to the problems in the healing process. Once fascial contraction reaches the maximal level

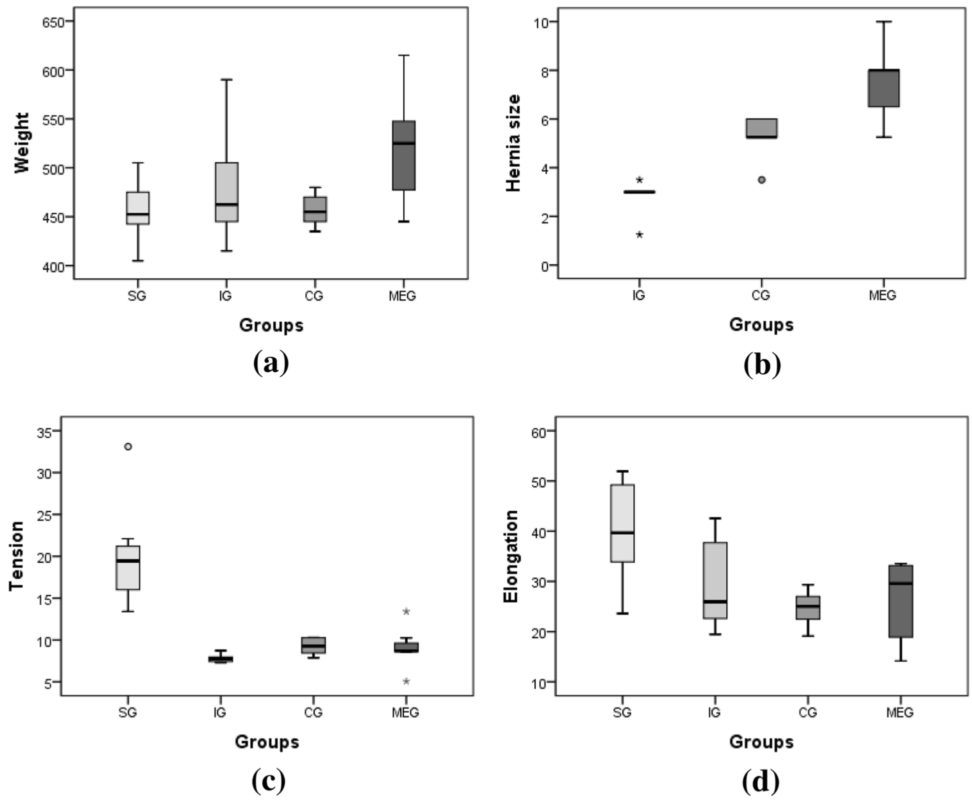

Fig. 1 **a**–**d** The box-and-whisker plots of weight, hernia size, tension and elongation in groups, respectively

Table 2 Histopathological examination results in each group [*n*: (line %)]

Groups	Inflamation			Fibrosis		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Group 1 (SG*) ($n=8$)	0 (0.0)[a]	1 (12.5)[a]	7 (100.0)[a]	4 (50.0)[a]	5 (50.0)[a]	0 (0.0)[a]
Group 2 (IG$^{\square}$) ($n=6$)	4 (66.7)[b]	2 (33.3)[a]	0 (0.0)[b]	0 (0.0)[a]	1 (16.7)[a]	5 (83.3)[b]
Group 3 (CG$^{\square}$) ($n=5$)	3 (60.0)[a, b]	2 (40.0)[a]	0 (0.0)[b]	0 (0.0)[a]	1 (20.0)[a]	4 (80.0)[b]
Group 4 (MEG$^{\square}$) ($n=7$)	4 (57.1)[a, b]	3 (42.9)[a]	0 (0.0)[b]	0 (0.0)[a]	0 (0.0)[a]	7 (100.0)[b]
χ^2; p	22.062; **0.001**			20.601; **0.002**		

p values were found significant in terms of inflammation and fibrosis (bold)

SG*: Sham group, IG$^{\square}$: 5 cm incision group, CG$^{\square}$: 5 cm incision + 3–0 capitonnage with rapid group, MEG$^{\square}$: 5 cm incision + 2 × 4 cm muscle excision group

χ^2: Pearson's Chi-squared test result; [a,b]: Each degree shows differences between groups

at postoperative 28th day, it is the most suitable day for the formation of the ideal incisional hernia model.

It is obvious that the application of muscle excision to rats in Group 4, does not exactly mimic normal surgical procedures. Criticism may arise as to this procedure being an 'abdominal wall resection model' rather than an 'incisional hernia model'. In other words, this model can be said to reflect an abdominal wall defect, aquired after combat surgery or post-extensive tumor resection. An explanation of why such an approach was taken, should ensure that it is better understood. Months, or years may pass for an incisional hernia to develope in humans. In this rather long time, the muscle tissues gradually contract. By applying muscle excision to the rats, muscle contraction status that would normally occur over a long period of time, was achieved within a month. If a longer period of time was taken before these rats were killed, hernia sizes would probably have been even larger in size. Therefore, in the future, when plans are made for different studies on incisional hernia repair, a 28-day study period is believed to be the ideal time period for the ideal model and one which we will be using. One of the most important things to keep in mind when developing this model is finding a model which allows the rats to best adapt and has the highest survival rate.

One of the most important points in the formation of the ideal incisional hernia model is to provide the ideal muscle tensile strength level. When we examined the different rat incisional hernia models in the literature [6, 7, 9], we found that the tensile strength values were similar to the values we measured in Group 3 and Group 4. While the median value of tensile strenght in the 3rd group was 9.27 (7.86–10.30) Nm/cm^2, the median value in the 4th group was calculated as 8.70 (5.07–10.20) Nm/cm^2. Compared with other studies on this subject, it was thought that quite ideal values were obtained in this study.

In the literature, we have observed that in many experimental incisional hernia rat models, where attempts were made to create hernias, they commenced with a paramedian incision, with 3 × 6-cm skin flaps being removed. Then the fascia incision was made from the midline and using various methods, attempts were made to create an incisional hernia [6–9]. It is obvious that this skin flap method is performed so that the rats do not harm themselves after the operation. However, as this flap removal method is incompatible with the methods normally used in surgery, and as it is believed incisions made need to be exactly the same as the incisions in humans, it was decided that for the purposes of this study, groups would be formed accordingly.

Having considered that the suture material to be used was as important as the incision made, the sutures to be used on the skin and fascia were very carefully selected. There were several reasons why vicryl was preferred as a skin suture. As polypropylene has a hard structure, it was predicted that the movement of the rats would be restricted and cause pain; which could cause them to damage the suture line and hence harm themselves. Silk, on the other hand, may cause rats to gnaw the suture line and thus lead to open abdomens, as it is more allergic than vicryl. Skin clips were not used because in the experimental study by Burcharth et al. the rats were able to remove them, resulting in open abdomens [9]. Therefore, for the purposes of this study, non-allergic and multifilament vicryl sutures were preferred for use in both fascia and skin.

An attempt was made to identify the reason for the loss of more rats in Group 3 (CG), that is, the capitonnage with rapid group. It is thought that due to the pain caused by compression in the muscle tissue during capitonnage, even though oral intake of analgesic water was provided, the rats gnawed their abdominal areas due to pain and opened their midline skin incisions. This lead to bleeding and sepsis due to open abdomens and in turn lead to their deaths. It was thought that capitonnage would speed up the formation of fascial contraction and help create an appropriate incisional hernia model. According to the statistical calculations, although it is meaningful in terms of hernia size, it is not an ideal model because of the large number of rat loss, thought to be due to pain.

In fact, there was no statistically significant difference between Group 3 and Group 4 in terms of hernia size. The results with regards to fibrosis and inflammation of the tissues for these two groups were also very similar. Again, when the tension and elongation ratios were compared, no statistically significant difference was observed. However, the excess number of rat deaths in Group 3, may be a major factor in not preferring this group for further studies.

Histopathological differences between the groups were exactly as we expected. As the muscle tissue of the rats in Group 1 were sutured after celiotomy, inflammation resulting from the suture material was at a maximum level. Inflammation levels in the other groups, were at similar levels to each other. Again, as we expected, fibrosis status was at the highest level in Group 4, due to maximum muscle contraction. The fourth group (MEG) on which muscle excision was performed, was statistically the most ideal incisional hernia group in terms of both hernia size and tension and elongation values. Rats in this group passed the 28-day observation period quite uneventfully, despite the large ventral hernias that developed visually in the days immediately following the operation. Although the possibility of high numbers of rat loss due to spontaneous bleeding from fascial muscle tissues was feared, they had quite a good postoperative process. During the operation performed on the day the study. Acording to these results, the most appropriate incisional hernia model is the fourth group. Considering both hernia size, elongation and tension values and histopathological features, it is seen that the fourth group is the ideal hernia model.

Conclusion

Incisional hernia, is the leading serious post-abdominal surgery complication to occur in the long term. Even though the only treatment for this complication is surgery, the high recurrence rate after incisional hernia surgery is an indication that there is a lot of work to be done in terms of understanding and application in this area. For this reason, with the thought that establishing an ideal rat model to be used in experimental resarch is important, an attempt was made to do so, using various models. It is believed that the rat hernia model of created by applying muscle excision (MEG), from the midline of the abdomen, is the ideal incisional hernia model that can be used in future experimental incisional hernia studies.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval Ethics committee approval for the study was obtained with the decision of the Ethics Committee of Health Sciences University Gulhane Animal Experiments Local Ethics Committee dated 12.11.2018 and numbered ETİK-2018/38.

Human and animal rights The study including animal participants has been performed in accordance with ethical standards of the Declaration of Helsinki and animal rights ethics.

Informed consent For this type of study, formal consent is nor required.

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