

COMPARISON OF SHORT AND LONG-TERM OUTCOMES OF REPAIRS DONE WITH CONVENTIONAL SURGICAL METHODS AND FIBRIN-BASED TISSUE ADHESIVES IN DUODENUM PERFORATION MODEL IN RATS

SIÇANLARDA DUODENUM PERFORASYON MODELİNDE KONVANSİYONEL CERRAHİ YÖNTEMLER VE FİBRİN BAZLI DOKU YAPIŞTIRICILARI İLE YAPILAN ONARIMLARIN KISA VE UZUN DÖNEM SONUÇLARININ KARŞILAŞTIRILMASI

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Geliş Tarihi / Received: 19.07.2020
Kabul Tarihi / Accepted: 26.09.2020

Araştırma Makalesi/Research Article
DOI: 10.38065/euroasiaorg.222

ÖZET

Peptik ülser (PÜ), özofagus, mide ve ince barsakların asit-peptik aktivite ile karşılaşan mukozalarında oluşan kronik yaralardır. Hem PÜH komplikasyonu olan perforasyonun tedavisinde hem de morbid obezite hastalarının laparoskopik tedavisinde fistül oranlarının azaltılması için Fibrin bazlı doku yapıştırıcıları (FBDY) kullanılmaktadır. Bu deneysel çalışma ile minimal invaziv cerrahi yöntemlerde kullanılabilecek FBDY'nın PÜ komplikasyonu olan perforasyonda yara iyileşmesi üzerindeki etkisinin araştırılması amaçlandı.

Wistar Albino cinsi 72 adet dişi sıçan kullanıldı. Oluşturulan duodenal perforasyonun onarım şekline göre primer tamir (Grup 1), primer tamir ve omentoplasti (Grup 2) ve sadece FBDY ile onarım (Grup 3) uygulanarak 3 grup oluşturuldu. 4., 7. ve 22. günlerde yara patlama basıncı (PB) ve doku hidroksprolin düzeyi (HPD) ölçüldü. İstatistiksel anlamlılık $p < 0.05$ düzeyinde değerlendirildi.

PB 4.gün Grup 1 ve 2'nin patlama basıncı değerlerinin Grup 3'den ileri düzeyde anlamlı derecede yüksek saptandı ($p < 0,01$). Yedinci ve 22. gün patlama basınçları açısından 3 grup arasında anlamlı fark yoktu ($p > 0,05$). HPD 4. gün Grup 1 ve Grup 2'de Grup 3'den anlamlı derecede yüksek olarak saptandı ($p < 0.05$, $p < 0.01$).

PÜ perforasyonu cerrahisinde FBDY tek başına kullanıldığı zaman, klasik cerrahi yöntemlere göre erken dönemde daha güvensizdir. Tek başına kullanılması yerine diğer cerrahi yöntemlere destek amacıyla kullanılabilir.

Anahtar Kelimeler: Peptik ülser, Peptik ülser perforasyonu, Fibrin zamlak

ABSTRACT

Peptic ulcer (PU) defines the chronic wounds which develop in esophageal gastric and small intestinal mucosa that is exposed to acid-peptic activity. Fibrin-based tissue adhesives (FBTA) are used for reducing fistula rates both in treatment of perforation, a complication of PU disease and laparoscopic treatment of obese patients. This experimental study was conducted with the aim of investigating the influence of FBTA on wound healing in perforation, a complication of PU.

A total of 72 Wistar albino rats were used in the study. The animals were allocated to three groups as Group 1 (primary repair), Group 2 (primary repair and omentoplasty) and Group 3 (repair with only FBTA). Wound bursting pressure (WBP) and tissue hydroxyproline level (HPL) were measured on days 4,7 and 22. A p level of < 0.05 was accepted as statistically significant.

Levels of WBP were found to be higher in Group 1 and 2 as compared to Group 3 on day 4 ($p<0.01$). No significant difference was found among groups with regard to WBP on days 7 and 22 ($p>0.05$). Levels of HPL were found to be statistically significantly higher in Group 1 and 2 as compared to Group 3 on day 4 ($p<0.05$ and $p<0.01$).

The FBTA is less reliable than conventional surgical methods when used alone in PU perforation surgery. It may be used for supporting the other surgical methods instead of being used alone.

Keywords: Peptic ulcer, peptic ulcer perforation, fibrin glue

1. INTRODUCTION

Peptic ulcers (PU) are defined as the wounds which develop in the mucosa of the esophagus, stomach, and small intestines that are exposed to acid peptic activity (Roses, 2019:1120). Peptic ulcer differs from mucosal erosion because of the wound's influence on the submucosa and deeper layers. The lesions which develop in gastroenterostomies, in the ileum neighboring Meckel's diverticula, and in Zollinger-Ellison syndrome are evaluated under the heading of peptic ulcer disease (PUD) (Gökşen, 2002:973). Hyperacidity, impaired mucosal defense systems, decreased pylorus tone, reflux of duodenal content (mainly bile) into the stomach, and *Helicobacter Pylori* (HP) infection are responsible for disease development (Roses, 2019:1120; Kalafat 2001:119; Zittel 2000:84). Although surgical treatment is not widely used for PUD today, it is necessary for the treatment of the complications like hemorrhages which cannot be controlled endoscopically (15-35%), pyloric stenosis (1-2%), perforation (5-10%), and in the presence of an accompanying malignity (Kalafat 2001:119; Zittel 2000:84; Lipof, 2006:3248).

Minimally invasive methods like laparoscopy are safely used in surgery-requiring PUD, as in all fields of surgery (Siu, 2002:235; Sarıbeyoğlu, 2007:134). Many technical and suture-line supporters are used for reducing potential complications like fistula and bleeding, both in the treatment of perforation, which is a complication of PUD, and in the laparoscopic treatment of morbid obese patients. Supporting the repair site or stapler line by using FBTA is among these methods (Radosevich, 1993:133; Bedford-Turner, 1945:457).

Fibrin-based tissue adhesive (fibrin glue) is a material obtained by mixing purified-frozen and dried human fibrinogen and Factor (F-XIII) and the human or bovine thrombin calcium (F-IV)-anti-fibrinolytic agent aprotinin. Fibrin glue is widely used as a hemostatic agent and a surgical suture support in all surgical branches (Spotnitz, 1996:77; Ryo, 2006:33; Petersen 2004:327).

The present study was conducted with the aim of investigating the influence of FBTA, which can be used in minimally invasive surgical methods like laparoscopy and robotic surgery, on wound healing in perforation, a complication of PU.

2. METHODS

The present experimental study was conducted at Goztepe Education and Research Hospital after ethics committee approval had been obtained. A total of 72 female Wistar albino rats weighing 175-236 g were used in the study. Animals were divided to three groups with 24 in each according to the repair type of the created duodenal perforation (Photo 1). Primary repair was applied to the first group (Group 1), primary repair and omentoplasty were applied to the second group (Group 2) (Photo 2), and repair with only FBTA was applied to the third group (Group 3) (Photo 3). Six out of 24 rats in each group were separated as the control group, undergoing only explorative laparotomy. The remaining 66 rats were divided to three groups for measuring wound bursting pressure (WBP) and tissue hydroxyproline (HPL) values on days four, seven, and 22. Anesthesia was provided by the intra-peritoneal application of 100 mg/kg of Ketamin (Ketalar, Eczacıbaşı Drug Company, Turkey) and 10 mg/kg of Xylazin (Rompun amp, Bayer, Germany). The depth of the anesthesia was controlled with the cornea reflex and tail clamping method every 15 min. An explorative

laparotomy was performed following abdomen shaving and cleaning with povidone iodine. The duodenum was reached by following the stomach. Full-thickness perforation foci with a diameter of three mm were created at the post-pyloric site of the duodenum by using a No. 20 scalpel. After observing and cleaning the duodenal content, these perforation foci were repaired with primary repair by using a 4-0 silk suture in Group 1, with primary repair and omentectomy in Group 2, and with 125 cc/cm² fibrin glue in Group 3. The abdomen was closed with 3-0 propylene suture material in accordance with anatomic planes. For post-operative care, each cage contained six subjects. All subjects were not fed orally but fed with 20 ml/kg of 10% dextrose solution (Eczacıbaşı-Baxter, Turkey) on the day of the surgery and on day following. A normal diet was started with oral feeding and water on post-operative day two. Subjects were euthanized by applying a four-fold greater dose of (20 mg/kg) diazepam (Diazem amp, Deva, Turkey) on days four, seven, and 22 post-operatively according to their subgroups. Resection was applied so as to contain four cm of healthy duodenal tissue in the proximal and two cm of healthy duodenal tissue in the distal after finding the duodenal perforation focus repaired with re-exploration. Care was given to keeping the adhesions between the repair site and the neighboring tissues together; errors that could occur during the measurement of bursting pressure were prevented. The duodenal end of the removed tissue was freely ligated, a pressure meter was placed at the side of the stomach, and air was inflated at a constant rate of six ml/min in a waterfilled container. The pressure value where the air bubbles were first noticed was recorded as "burst pressure" (Photo 4). Following burst pressure measurement, tissues were skeletonized so as to keep one cm of healthy tissue around the tissue repair area and were stored at -40° C in saline solution. The stored tissues were extracted at 120° C and treated with pure HCL (concentrated acid) at the Göztepe Desk of System Medical Laboratories Company. The preparation was centrifuged at 5000 rpm for 30 min, and the study material was obtained. In these materials, the tissue hydroxyproline levels were determined (mg/L/gr tissue) through the high-performance liquid chromatography (HPLC) method by using a Shimadzu device (made in Japan).

2.1. Statistical Analysis

Statistical analyses were done by using the NCSS 2007 and PASS 2008 statistical Software (Utah, USA) program. The Kruskal Wallis test was used for inter-group comparisons of the non-normally distributed parameters. The Mann Whitney U test was used for detection of the group that caused a difference in the parameters and in assessments according to two groups besides the descriptive statistical methods (mean and standard deviation). Spearman's correlation analysis was used for assessment of the relationships between the parameters. Results were evaluated at a 95% confidence interval, and a p level of <0.05 was accepted as statistically significant.

3. RESULTS

Burst pressure measurements on day four were found to be statistically significantly lower than the values on days seven and 22 in all groups ($p < 0.01$, Table 1 and 2). When the burst pressure values were compared among the groups, a significant difference was not detected between Group 1 and Group 2 on day four ($p > 0.05$), but burst pressure values were found to be significantly higher in Group 1 and Group 2 compared to Group 3 ($p < 0.01$, Table 1). When burst pressures on days seven and 22 were analyzed, a significant difference was not detected among the three groups ($p > 0.05$, Table 1 and 2).

In Group 1, the HPL levels on day four were found to be higher than the day seven measurements, but the difference was not statistically significant ($p > 0.05$). However, measurements on day four were significantly higher than the values on day 22 ($p < 0.01$, Table 3 and 4). In Group 2, the HPL levels on day four were found to be higher than the day seven measurements, but the difference was not statistically significant ($p > 0.05$). However, measurements on day four were significantly higher than the values on day 22 ($p < 0.01$, Table 3). In Group 3, HPL values on day four were found to be significantly lower than those on day seven and significantly higher than those on day 22 ($p < 0.01$).

On day 4, HPL values were significantly higher in Group 1 and Group 2 as compared to Group 3 ($p < 0.05$, $p < 0.01$, Table 3). When the day seven HPL value measurements were compared, they were found to be significantly lower in Group 1 as compared to Group 2 and Group 3 ($p < 0.05$, $p < 0.01$). No difference was found between the groups with regard to HPL measurements on day 22 ($p > 0.05$, Table 3 and 4).

4. DISCUSSION

Peptic ulcer perforation (PUP) is a severe complication seen in five to 11% of PU patients. Duodenal ulcer perforations are approximately 15 times greater than gastric ulcer perforations. An increase has been observed in the incidence of PUP despite developing diagnosis and treatment methods. While the use of non-steroid anti-inflammatory drugs, smoking, acute stress, and the use of steroid-based drugs are responsible for PUP development, an association was not observed between duodenal PUP and HP infection and hyperacidity (Santander, 1996:1549; Friedman, 1998:1696; Andersen, 2000:434; Kaya, 2000:11).

Surgery is still the preferred treatment method for PUP today although successful outcomes have been reported with conservative management by Wangenstein, Bedford-Turner, Fontaine, Berne-Donovan, & Crafts (18, 19). Initially, surgery was being performed as the definitive ulcer treatment, both for the repair of perforation focus and the prevention of recurrent ulcers. However, today, because of new understanding of HP bacteria as the causal agent, ulcer treatment involves eradication of this bacteria and development of acid-suppressing agents like H₂ receptor blockers and proton pump inhibitors. Definitive ulcer surgery is no longer being used except in case of special conditions (Gökşen, 2002:973; Lau, 1997:890).

Today, duodenal ulcer perforations may be successfully managed with endoscopic and laparoscopic methods. However, insufficiency rates of between two and five percent were reported for repair of the perforation focus in a larger series (Kaya, 2004:11). In recent years, bariatric and metabolic surgery have become quite popular. Because of innovative development of laparoscopic systems and auxiliary devices, laparoscopic surgery has come to be widely used. Sleeve gastrectomy, Roux-en-Y gastric by-pass, duodenal switch, and biliopancreatic diversion operations are the most common laparoscopic methods. Sleeve gastrectomy has particularly come into the foreground because of its provision of effective weight loss and its ease of application (Coşkun, 2016:2174). The most common complications from this method include bleeding at the stapler line and fistula (Aurora, 2012:1509).

Fibrin glues become activated as the result of mixing two main products. The first product is purified, frozen and dried human fibrinogen and FXIII, and the second product is a mixture of thrombin, FIV (Ca²⁺) and the anti-fibrinolytic agent aprotinin. Fibrin polymers are formed as the result of the reaction of the mixing of these two. These polymers are bound to fibroblasts, megakaryocytes, and platelets at the wound site and create a net around tissue collagen. Fibrinolysis develops beginning from the third day; degradation products strengthen connective tissue formation and neo-vascularization through encouraging the migration of fibroblasts and macrophages to the wound site (Peterse, 2004:327; Kaya, 2004:11). Hedelin et al. showed that local fibrin application increased collagen concentration of the wound through measuring the tissue hydroxyproline levels (Kaya, 2004:11). Theoretically, in wound healing in the gastrointestinal system, the first collagen synthesis begins within the first 10 hours following injury and maximizes between days five and seven, and gradually decreases thereafter. In the last phase of wound healing, the maturation phase, a balance occurs between collagen production and degradation. At the third week of healing, collagen destruction begins to exceed proliferation. The strength of wound tissue emerges as the result of the structural arrangement of the collagen present (Hüner, 2006:18). Hydroxyproline is a water-soluble amino acid which is found in only collagen tissue and used for the biochemical examination of collagen tissue. Detection of the tissue level of hydroxyproline provides relative information about the collagen production rate because the other fibrous tissues like elastin do not

contain significant amounts of hydroxyproline (Tolu, 1990:487). Also, in this experimental study, the maximum collagen production rate was reached on day four in the primary repair group and on day seven in the primary repair, omentoplasty, and fibrin glue groups. A reduction was detected on post-operative day 22.

The time to reach maximum hydroxyproline synthesis differs among authors. Irvin measured the HPL level in colon anastomoses by using a radioactive marking method and reached the maximum on day three (Irvin, 1973:457). Ahomen reached this value on day 10 after anastomosis (Jiborn, 1978:333). Scott et al. reached maximum values on post-operative day nine in the samples obtained from the incisions on line alba in a study conducted with rats (Scott, 1985:777). Goodson et al. reached this value on post-operative day seven (Goodson, 1987:205). The present study indicated that collagen synthesis reached maximum on post-operative day four in the primary repair group, and collagen synthesis was found to be lower compared to the other groups on day seven when collagen synthesis was expected to be maximum. In the subjects on which primary repair and omentoplasty were performed, collagen synthesis increased on post-operative day four and reached maximum values on day seven. Collagen levels on day seven did not differ significantly from the group to which fibrin glue was applied. In repair done with fibrin glue, tissue HPL levels were found to be significantly higher on days four, seven, and 22 compared to control groups ($p < 0.01$, $p < 0.05$, $p < 0.05$).

In the study by Kaya et al., HPL values examined after the repair of duodenal perforation in rats were found to be significantly lower in the primary repair and the primary repair and omentoplasty group compared to the group to which repair with fibrin glue was applied (Tolu, 1990:487). In the present study, HPL levels measured on post-operative day four were found to be significantly lower than the groups to which primary repair and primary repair and omentoplasty were applied ($p < 0.01$ and $p < 0.05$). On day seven, the values of the primary repair group were found to be significantly lower than the groups to which fibrin glue, primary repair, and omentoplasty were applied ($p < 0.01$ and $p < 0.05$). No difference was found between groups with regard to HPL levels on day 22. In light of these data, contrary to the results of the study of Kaya et al., the results of our study revealed that collagen synthesis on day four in the tissues of the rats to which fibrin glue for repair were applied was significantly higher than the control group but significantly lower than the other repair types. This result suggests that collagen synthesis begins on day four in the group repaired with fibrin glue but less than in the other groups. On day seven, tissue collagen synthesis was found to significantly increase in the fibrin glue group compared to the primary repair group. However, the values were not significantly different than the subjects to which were applied primary repair and omentoplasty. As seen, collagen synthesis reached the values of primary repair and omentoplasty group on day seven. On day 22, while tissue collagen synthesis of the subjects to which fibrin glue was applied were significantly higher than the subjects in control group, no significant difference was found when compared to the other groups. As reported in the study by Ozer et al., although collagen synthesis in anastomoses begins in the early period (approximately 12 hours), the mechanic resistance of the wound gradually decreases during the first two to four days. Wound resistance decreases 60 %, although it differs in various sites of gastrointestinal system. This results from the fact that collagenase enzyme activity is high during this period. Synthesis increased compared to collagen degradation beginning from day four. Wound resistance increased with the structural regulation of the collagen in the wound that entered the reconstruction phase (Özer, 2006:17). In inter-group comparison, while a significant difference was not detected between the primary repair and the primary repair and omentoplasty groups ($p > 0.05$), the values of these two groups were found to be significantly higher in the fibrin glue group ($p < 0.05$). When the day seven and day 22 results of the three groups were evaluated, while a significant difference was not found among three groups with regard to wound burst pressure ($p > 0.05$), a weaker mechanic resistance was found in the day four values of the fibrin glue group compared to the other groups.

In a study by Coskun et al. the fibrin glue applied to the stapler line following bariatric surgery was reported to trigger omental tissue's rapidly adhering to the stapler line and thereby reduced bleeding and leakage risk (Aurora, 2012:1509).

Fibrin-based tissue adhesives are used in different surgical procedures today. The FBTA may provide complete recovery in 41.7% of cases and partial recovery in 16.7% of cases when used in repair of peri-anal fistula (de la Portilla, 2019:1113). FBTA may be used in combination with platelet-rich plasma. This combination was reported to shorten the duration of wound healing following pilonidal sinus surgery and reduce pain in the post-operative period (Alamdari, 2019:234). On the other hand, fistula management could not be achieved in clinical and experimental studies conducted with fibrin-based filling materials. Use of fibrin filling materials after pancreatoduodenectomy does not reduce pancreatoduodenectomy fistula development (Schindl, 2018:811). This failure results from rapid and severe digestion of fibrin filling materials by the enzymes in the pancreatic fluid (Schindl, 2018:811). In our study, lower level of success of the fibrin glue group compared to the other groups resulted from the material being digested by pancreatic enzymes.

In light of these data, we detected that wound healing occurs more slowly in the fibrin glue group compared to the other groups in the early post-operative period. On day seven, the HPL values of the fibrin glue group were significantly elevated compared to the control groups, and burst pressure values reached those of the other two groups and even exceeded the values in the primary repair group. These results indicated that repair done with only fibrin glue started a slower recovery process compared to conventional surgical methods in the early post-operative period; however, recovery accelerated in the proliferation phase of wound healing and yielded similar results with the other methods.

5. CONCLUSION

In the subjects that underwent repair with only the fibrin glue, the wound healing being slower in the early period (day 4) compared to the subjects who underwent repair by using conventional surgical methods was verified with the lower values of HPL (an indicator of the tissue collagen synthesis rate) and the burst pressure. On days seven and 22 of wound healing, the collagen synthesis and burst pressure values of the fibrin glue group were close to the values of the conventional surgical method groups and even better than those of the primary closure method. Fibrin adhesives are less reliable than conventional surgical methods when used alone and should not be used in such a manner. We consider that a new generation fibrin adhesive that could be effective in the early period are needed because an early inadequacy in the repaired perforation focus could significantly influence morbidity and mortality. However, fibrin glue may be considered an auxiliary method for supporting the other methods because it did not yield different results in the late periods of wound healing.

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Table 1. Comparison of burst pressures by days in groups

Groups Burst Pressure value (mmHg)

	4th day Mean+SD (Median)	7th day Mean+SD (Median)	22th day Mean+SD (Median)	⁺⁺ <i>p</i>
Group 1	73.3±12.11 (75)	236.6±21.6 (240)	296.7±8.16 (300)	0.001**
Group 2	84.16±9.17 (80)	265.83±31.05 (277.5)	300.00±0 (300)	0.001**
Group 3	37.50±6.12 (40)	257.5±37.17 (265.5)	285.0±36.74 (300)	0.001**
	⁺ <i>p</i>	⁺ <i>p</i>	⁺ <i>p</i>	
Group 1-Group 2	0.157	0.075	0.317	
Group 1-Group 3	0.004**	0.292	0.902	
Group 2-Group 3	0.003**	0.868	0.317	

⁺⁺ Kruskal Wallis test, ⁺Mann Whitney U test

p*<0.05, *p*<0.01

Table 2. Post Hoc assessment of burst pressure levels

	4 th – 7 th day ⁺ <i>p</i>	4 th – 22 th day ⁺ <i>p</i>	7 th – 22 th day ⁺ <i>p</i>
Group 1	0.004**	0.003**	0.003**
Group 2	0.004**	0.002**	0.002**
Group 3	0.003**	0.003**	0.030*

⁺Mann Whitney U test

p*<0.05, *p*<0.01

Table 3. Comparison of hydroxyproline levels by groups in days

Groups Tissue hydroxyproline levels (mg / L/gr. tissue)

	4th day Mean+SD (Median)	7th day Mean+SD (Median)	22th day Mean+SD (Median)	⁺⁺ <i>p</i>
Group 1	305.66±22.07 (308.5)	264.7±106.9 (262)	58.66±19.05 (62.0)	0.003**
Group 2	353.3±49.19 (343)	582.7±232.7 (500.5)	63.16±35.5 (57.0)	0.001**
Group 3	265.3±29.43 (259)	637.3±204.5 (561.0)	63.7±24.3 (64.5)	0.001**
	⁺ <i>p</i>	⁺ <i>p</i>	⁺ <i>p</i>	
Group 1- Group 2	0.108	0.016*	0.936	
Group 1- Group 3	0.024*	0.004**	0.749	
Group 2- Group 3	0.004**	0.423	1.0	

⁺⁺ Kruskal Wallis test, ⁺Mann Whitney U test

p*<0.05, *p*<0.01

Table 4. Post Hoc assessment of hydroxyproline levels

	4 th – 7 th day ⁺ <i>p</i>	4 th – 22 th day ⁺ <i>p</i>	7 th – 22 th day ⁺ <i>p</i>
Group 1	0.521	0.004**	0.004**
Group 2	0.054	0.004**	0.004**
Group 3	0.004**	0.004**	0.004*

⁺Mann Whitney U test

p*<0.05, *p*<0.01

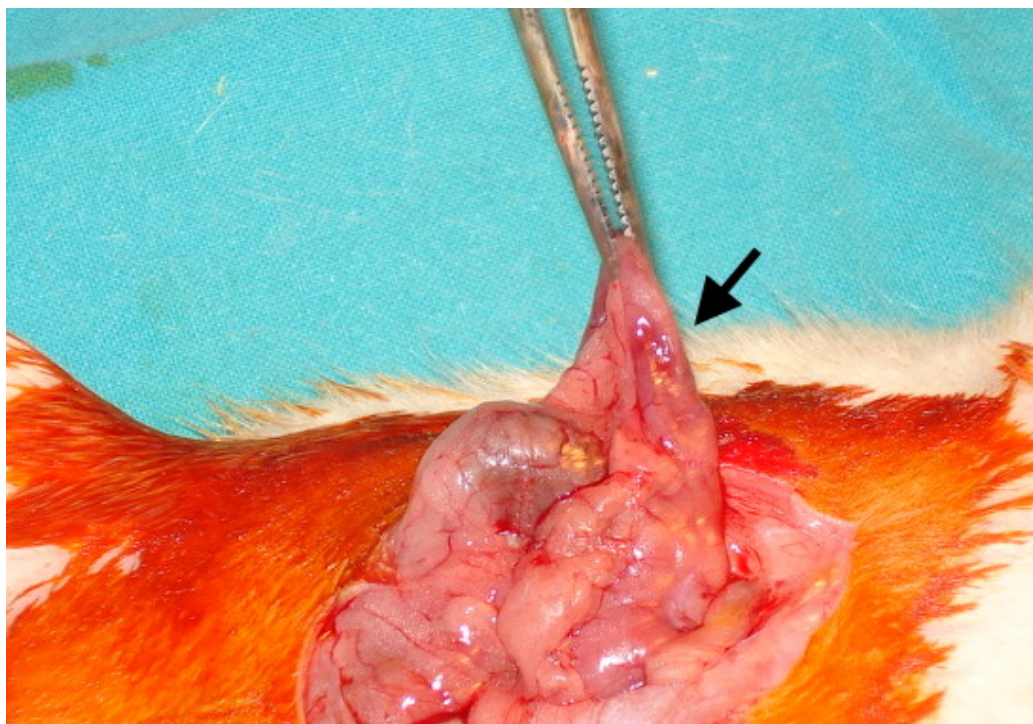


Photo 1. Creation of duodenum perforation

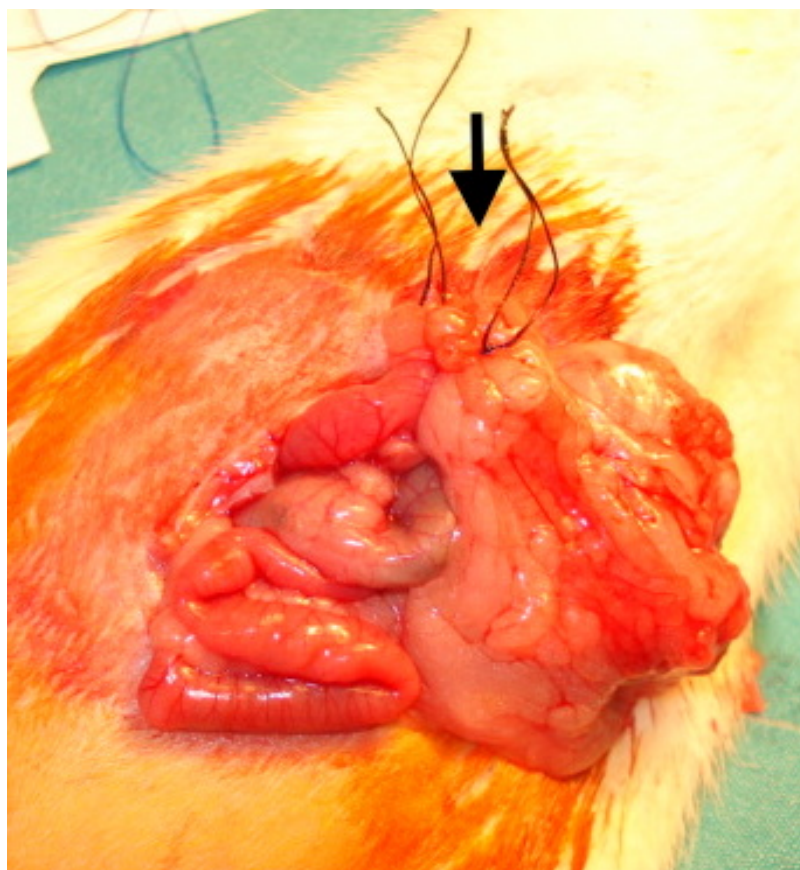


Photo 2. Repair with primary rafi and omentoplasty

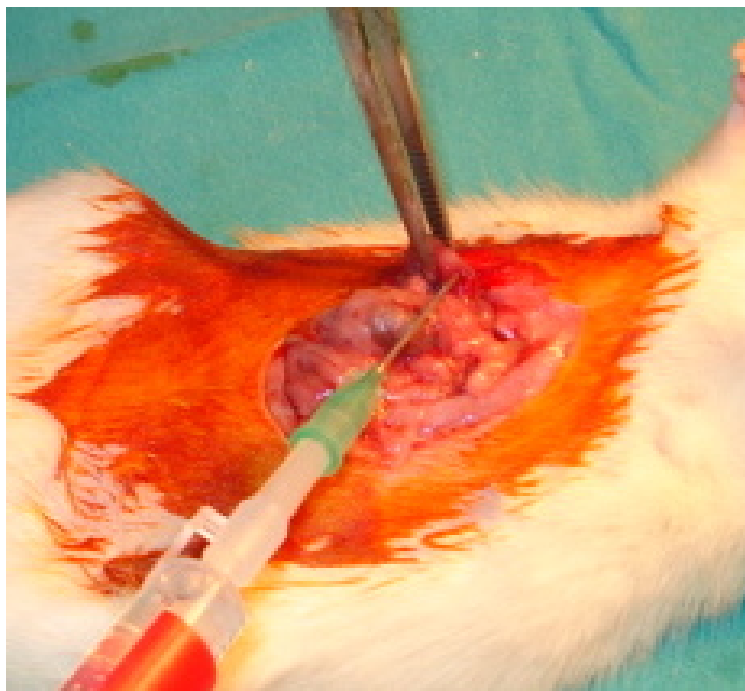


Photo 3. Repair with Fibrin glue

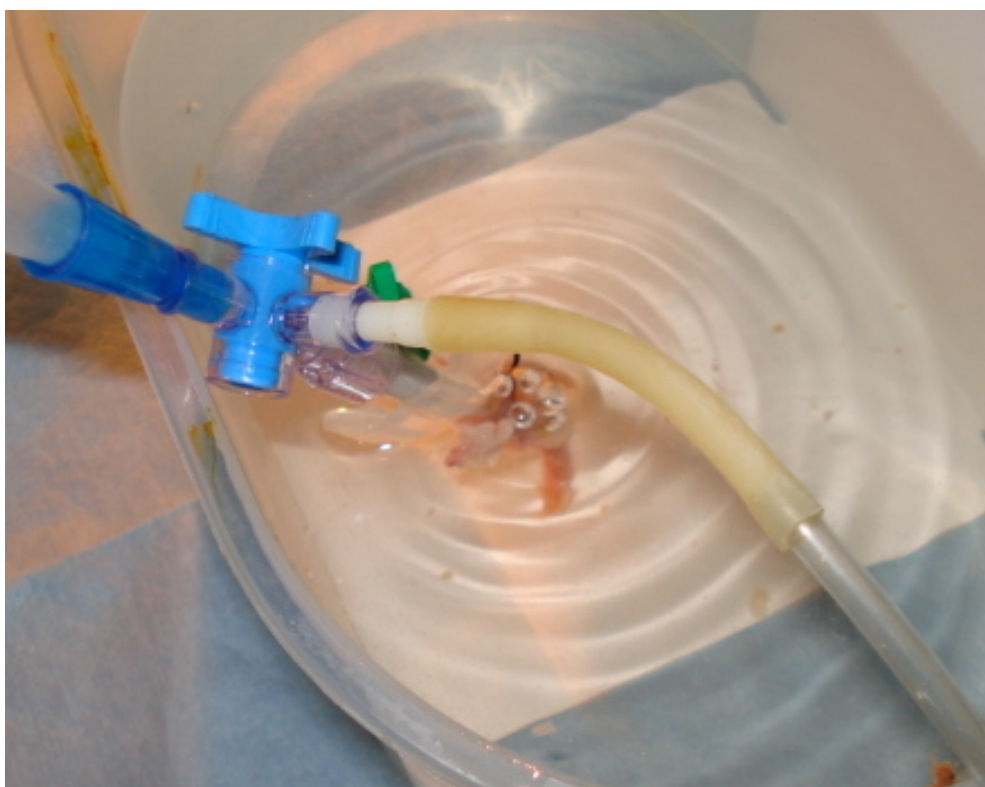


Photo 4. Burst pressure measurement