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RAPID COMMUNICATION

Effects of primary suture and fib sealant on hemostasis and liver regeneration in an experimental liver injury

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Abstract

AIM: To investigate the effects of fibrin sealant on hemostasis and liver regeneration and intra-abdominal adhesions in an experimental liver injury.

METHODS: Thirty-six Wistar rats were randomly divided into primary suture group (n = 15), fibrin sealant group (n = 15) and control group (n = 6). A wedge resection was performed on the left lobe of the liver. In primary suture group, liver was sutured using polypropylene material, while fibrin glue was administrated on the liver surface in fibrin sealant group.

RESULTS: More intra-abdominal adhesions were observed in the primary suture group compared to the fibrin sealant group on 3rd (2.50 ± 0.5 *vs* 0.25 ± 0.5, P = 0.015), 10th (2.75 ± 0.5 *vs* 0.50 ± 0.6, P = 0.06) and 20th (1.75 ± 0.5 *vs* 0.70 ± 0.5, P = 0.015) postoperative days. Histopathological scores were better in the fibrin sealant group in comparison with the primary suture group on 3rd (8.75 ± 0.5 *vs* 6.75 ± 0.5, P = 0.006), 10th (7.50 ± 1.0 *vs* 5.5 ± 0.6, P = 0.021) and 20th (6.40 ± 1.7 *vs* 3.20 ± 1.6, P = 0.025) postoperative days.

CONCLUSION: Out data suggest that fibrin sealant is preferred over primary suture in appropriate cases including liver trauma since it causes less intra-abdominal adhesions while allowing shorter hemostasis time as assessed in experimental liver trauma.

Key words: Liver; Trauma; Fibrin sealant; Hemostasis; Regeneration

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INTRODUCTION

Liver injuries occur as a result of blunt and penetrating traumas and rarely due to some iatrogenic reasons. In blunt abdominal traumas, liver turns out to be the organ that mostly gets injured, with mortality rates varying from 10% to 15%. Eighty percent of the liver injuries are formed subsequent to penetrating wounds caused by fire guns or piercing, incisive tools. Acute bleedings and operative complications cause an increase in mortality and morbidity rates[1]. Fibrin glue has been used in a wide selection of surgical fields, such as thorax surgery[2-4], and otolaryngology[5], and neurosurgery[6], and cardiovascular surgery[7]. Besides this, in general surgery application of fibrin glue has been made for treatment[8,9] of anal fistulas and repair of inguinal hernia. Fibrin sealant can be used as a safe and appropriate treatment technique in liver injuries. However, its effects on liver regeneration and development of intra-abdominal adhesions yet remain unclear. In this experimental study, the early and late effects of the reparation techniques employing primary sutures and fibrin glues on an experimental trauma model are evaluated.

MATERIALS AND METHODS

The study was performed at the animal laboratory of Ministry of Health Ankara Training and Research Hospital, after obtaining an approval from the Ethics Committee. For the purposes of the study, 36 male albino Wistar rats were selected from ages varying between 18 to 20 wk and an average body weight of 160 g. Animals were fed standard rodent food and water. They were left hungry for 24 h during both the pre- and post-operative periods. Animals did not receive antibiotic prophylaxis. The experimental study was conducted under semi-sterile conditions.

Rats were randomly divided into three groups: (1) Primary suture group consisting of 15 rats; (2) fibrin sealant group consisting of 15 rats; and (3) control group (which was used only for bleeding time measurements) consisting of 6 rats. Anesthesia was induced with 75 mg/kg ketamin HCl and 5 mg/kg xylazine HCl (Rompun®)

Table 1 Findings obtained from experimental groups

Subgroup	Primary suture			FIbrin sealant			Control
	A	B	C	A	B	C	
Adhesion score	2.50 ± 0.5	2.75 ± 0.5	1.75 ± 0.5	0.25 ± 0.5 ($P < 0.015$)	0.50 ± 0.6 ($P < 0.06$)	0.70 ± 0.5 ($P < 0.015$)	-
Histopathologic score	8.75 ± 0.5	7.50 ± 1.0	6.40 ± 1.7	6.75 ± 0.5 ($P < 0.006$)	5.50 ± 0.6 ($P < 0.021$)	3.20 ± 1.6 ($P < 0.025$)	-
Bleeding time(s)		113 ± 78			59 ± 37 ([a]$P < 0.001$)		125.7 ± 74

A: Postoperative d 3; B: Postoperative d 10; C: Postoperative d 20. [a]Mann-Whitney *U* test, according to the control group.

im. Then the abdominal wall was shaved off all the hair and the skin was cleaned using Betadine® solution. The abdomen was then entered with a 3-cm median incision to resect a triangular piece with a side length of 1 cm from the inferior edge of the left liver lobe (approximately 4% of the overall liver weight). In the primary suture group, horizontal matrix sutures (6/0 polypropylene) were applied to repair the liver injury. In the fibrin sealant group, the liver surface was coated with fibrin sealant (Tissel Kit®, 2.0 mL, Baxter AG). The fibrin sealant kit contains proteins and thrombin, properly cooled and dried, as well as a $CaCl_2$ and aprotinin solution. Mixing these substances results in two components: a covering and a thrombin solution. After the administration of primary suture and fibrin sealant, both test groups underwent chronometric measurements to determine the bleeding times. Blood samples (1 mL) were taken from the inferior vena cava to detect AST, ALT and ALP values. Five rats from each of the two test groups were sacrificed by administration of ether anesthesia at high doses on 3rd, 10th and 20th postoperative days. Laparotomy was performed by an U-shaped incision curved to upwards. Development of intra-abdominal adhesions was then assessed in animals for qualitative aspects, which were defined formerly as the following phases: Phase 1: Avascular, transparent, thin adhesion; Phase 2: Partly vascular, medium thick adhesion distinguishable with blunt dissection; Phase 3: Vascular, barely thick adhesion distinguishable with sharp dissection[10]. Samples were taken from the recovering liver region.

Light microscopy was employed for the evaluation and scoring of hepatic regeneration based on the following criteria: 1 = necrosis, 2 = hemorrhage, 3 = cytoplasmic vacuolization, 4 = multinuclear large cells, 5 = fibro-vascular structures, 6 = inflammatory exudates. Scores ranging from 0 to 3 were interpreted as the following: 0 = absence of any of these parameters, 1 = slight levels, 2 = medium levels, and 3 = high levels attained by values for the same, which were processed for calculating the total histopathologic regeneration score[11]. Points calculated at high levels indicated that the regeneration had an immature character. Total histopathologic regeneration scores were calculated for each group. AST, ALT and ALP values were assessed as the liver enzymes indicating cellular damage.

Mann-Whitney *U* and Chi-square tests were used for statistical analyses when appropriate.

RESULTS

The mean bleeding times were 125.7 ± 74 s, 113 ± 78 s and 59 ± 37 s in the control group, primary suture group and fibrin sealant group, respectively, indicating that the bleeding time was significantly shorter in the fibrin sealant group as compared to the control group and primary suture group ($P = 0.001$). However, no significant difference ($P = 0.069$) in bleeding time was found between the control group and primary suture group. Results of the test groups are shown in Table 1.

In the primary suture group, tearing on the liver surface and bleeding were observed during the suturing procedure; abscess formation was noted on suture lines over the liver in one rat on d 3, in an another rat on d 10 and in two other rats on d 20 postoperatively. At the 10th and 20th postoperative days, wound regions could not be observed clearly due to intensive adhesions between the liver and the great omentum.

A second administration of fibrin sealant was required in two rats of the fibrin sealant group due to the separation of the wound surfaces on d 3. In this group, the sites of hepatic resection were proven to be indistinguishable from the normal parenchyma on the 20th postoperative day; and there was no abscess development in the any rat liver throughout the postoperative study period; few adhesions were observed between the liver and the omentum. Although the AST, ALT and ALP levels were found to be lower in fibrin sealant group on the 3rd, 10th and 20th as compared to the primary suture group, but the difference could not reach statistical significance.

Significantly more intra-abdominal adhesions were observed in the primary suture group compared to the fibrin sealant group on 3rd ($P = 0.015$), 10th ($P = 0.006$) and 20th ($P = 0.015$) postoperative days.

The mean histopathological regeneration scores indicated a significantly more wound immaturity in the primary suture group than in the fibrin sealant group on the 3rd ($P = 0.006$), 10th ($P = 0.021$) and 20th ($P = 0.025$) postoperative days. In the liver regeneration areas of necrosis and hemorrhage appeared to be less in the fibrin sealant group on the 3rd postoperative day ($P = 0.014$ and $P = 0.003$, respectively) as compared to the primary suture group. Cytoplasmic vacuolization was found to be significantly higher in primary suture group on the 20th postoperative day ($P = 0.014$) as compared to the primary suture group.

DISCUSSION

Deep hepatic sutures are known to prove inefficient in

stopping bleeding from the portal veins and branches of hepatic arteries as well as the posterior hepatic vein[12]. Recent studies tend to concentrate on investigating the risk of formation of intra-hepatic hematoma and abscess as well as the development of areas of necrosis dependent on parenchymal ischemia[12]. In the present study, the parenchymal suture group required a significantly longer duration for hemostasis (113 ± 78 s) than the fibrin sealant group (59 ± 37 s). We prefer using polypropylene sutures, a synthetic non-absorbable material known to have a more inert composition and pose lesser risk for infections. In some previous studies, it has been demonstrated that the thrombus generated after the administration of fibrin sealant may have less potential for the occurrence of the infection[13].

In the present study, the fibrin sealant provided shorter hemostasis times following the application. It was hard to re-find the operation area in fibrin sealant administered rats even on the 3rd postoperative day. In two rats, however, an extra fibrin sealant application was required to ensure the merging of the two surfaces, yet neither of these rats indicated any signs of secondary bleeding on surfaces of injured livers. Jacob *et al*[14] have recently reported that fibrin sealants are beneficial even in cases with prolonged hemostasis in rats with liver injuries. They demonstrated that fibrin impregnated collagens-enhanced survival compared to primary sutures, fibrin sealant was absorbed completely on d 28. In another study[15] performed on dogs, an efficient hemostasis was obtained using fibrin sealant in both superficial and profound injuries, no signs of hematoma or secondary bleeding were encountered and the fibrin sealant was completely absorbed within 6 wk of application. Chonn *et al*[16] administered the fibrin sealant in addition to performing surgery using standard surgical techniques subsequent to a liver injury created by infliction of an external blast effect. However, most of subjects in the control group required perihepatic packing, in the fibrin sealant administered group none of the subjects revealed a need for perihepatic packing and re-laparatomy[16]. Similarly, another study demonstrated that fibrin glue eliminated the need for packing after severe liver injuries[17]. Holcomb *et al*[18] attempted to apply the dry fibrin sealing dressing composed of concentrated fibrinogen, thrombin and calcium on polyglyconate mesh on pigs with grade V experimental liver injury. They consequently reported that dry fibrin sealing dressing provided a simple but quick and efficient control over hemorrhage without change of efficacy with neither hypothermia nor coagulopathy[18]. Moreover, several experimental studies have advocated the effectiveness of the novel fibrin sealant[19-21].

In this study, the highest incidence of abscess formation (33%) was observed in the primary suture group postoperatively, while no abscess was observed in the fibrin sealant group. This can be explained by the features of this technique which does not allow occurrence of any ischemic or blind areas or hematoma formation, and the fibrin sealant generates a quick and permanent sealing on blood and lymphatic veins by stopping fibrin exudation. According to the Dulchavsky's study, autologous fibrin gel possesses bactericidal properties in contaminated hepatic injuries[22]. Likewise, in the Taha's experimental study, the number of occurrences of abscesses was less extensive in the fibrin adhesive group than the suture group[23].

Dulchavsky's study with fibrin gel has demonstrated a significant improvement in adhesion formation and intra-abdominal abscess rate as compared with suture hepatorrhaphy[22]. The grade of adhesions found between the liver and omentum was observed to be drastically lower in the fibrin sealant group, the reason of which was attributed to minimal tissue damage and non-existent ischemia in liver parenchyma ensured with this technique[22].

The results obtained in this study are in compliance with those of past studies showing completion of liver, spleen and renal regeneration on d 30 following fibrin sealant administration[11]. Wound healing appeared to be completed at a high extent based on the findings of macroscopic evaluations in this group on d 20. The histological findings obtained also showed that hepatic healing was at higher rates in the fibrin sealant group than in the other groups. Tovar *et al*[11] investigated the effects of fibrin sealant administration on hemostasis and hepatic healing after hepatectomy. Fibrin sealant administration technique provided a faster hemostasis, while the hepatic recovery in the same group revealed to be quicker compared to hot air coagulation and primary suture techniques[11]. The results of this study are in agreement with those obtained in our experimental study. Previous studies demonstrated that plasminogen activators had an important additive role in liver regeneration by their contribution on remodelling of the liver[24,25]. Contrary to the presence of aprotinin in the fibrin sealant kit which is known as an plasminogen inhibitor, no negative effect on hepatic healing was observed. Vice versa, hepatic healing was more rapid than the other group. We believe that further studies need to be performed on this particular issue.

Kohno *et al*[26] compared the efficiencies of microcrystal collagen dust versus the fibrin sealant following an elective hepatic resection in 62 patients. They encountered bile leakage in two patients, and secondary hemorrhage in one patient in the collagen group, while no such complications were observed in fibrin sealant administered group[26]. Even though the study of Figueras *et al*[27] could not justify the influence of fibrin sealant, many clinical studies are available in the literature showing the useful effects of fibrin sealant in prevention of bile leakage after hepatic resection[27-31].

In conclusion, fibrin sealant may be preferred over to primary suture in appropriate cases of liver trauma, due to the shorter bleeding time, faster regeneration and lesser intra-abdominal adhesions by its use. However, more studies focusing on the clarification of the effects of this product on liver regeneration are needed to check the validity of these results.

COMMENTS

Background

Liver injuries occur as a result of blunt and penetrating traumas and rarely due to some iatrogenic reasons. In blunt abdominal traumas, liver turns out to be the organ that mostly gets injured. Acute bleedings and operative complications cause an increase in rate of mortality and morbidity.

Research frontiers

Fibrin sealant can be used as a safe and appropriate treatment technique in

liver injuries. There were many clinical and experimental studies in the literature showing the useful effects of fibrin sealant in prevention of bile leakage and in shortening bleeding time after hepatic resection and liver injury. However, the effects on liver regeneration and development of intra-abdominal adhesions yet remain unclear.

Innovations and breakthroughs

In this experimental study, more intra-abdominal adhesions were observed in the primary suture group compared to the fibrin sealant group. Hepatic healing was faster and liver abscess was not observed in the fibrin sealant group postoperatively. Minimal tissue damage and non-existent ischemia in liver parenchyma ensured with application of this technique.

Applications

Fibrin sealant can be used clinically in appropriate cases including liver trauma or hepatic resection.

Terminology

The fibrin sealant kit contains proteins and thrombin, properly cooled and dried, as well as a calcium chloride and aprotinin solution. Mixing these substances and covering the tissue surface result a thrombin solution.

Peer review

In this experimental study, the authors revealed that fibrin sealant causes less intra-abdominal adhesions and faster hepatic healing while allowing shorter hemostasis time compared to the primary suture as assessed in experimental liver trauma. Therefore, fibrin sealant can be preferred over primary suture in appropriate cases, including liver trauma.

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