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MINIREVIEWS

Role of endoscopic ultrasound in liver disease: Where do we stand in 2017?

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Abstract

Endoscopic ultrasound (EUS) was first introduced into medical practice in 1980s as a diagnostic imaging modality for pancreatic pathology. EUS has the unique advantage of combining ultrasound and endoscopy to obtain detailed information of the gastrointestinal tract. Over the past decade, the use of EUS in liver diseases has been increasing. EUS, which was initially used as a diagnostic tool, is now having increasing therapeutic role as well. We provide a review of the application of EUS in the diagnostic and therapeutic aspects of liver disease. We also look at the evolving future research on the role of EUS in liver diseases.

Key words: Endoscopic ultrasound; Liver disease; Portal hypertension; Liver lesions

Core tip: We have summarized the up-to-date literature on the emerging role of endoscopic ultrasound (EUS) in liver disease. This brief review summarizes both the diagnostic and therapeutic role of EUS in focal hepatic lesions, portal hypertension, liver abscess and hepatic cysts. We have also summarized the future research on this subject.

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INTRODUCTION

The evaluation of liver disease has been progressively changing over the last few decades with advancement of new technologies. Computed tomography (CT), conventional ultrasound and magnetic resonance imaging has have been the principal means for evaluating hepatic disease for long time[1].

Endoscopic ultrasound (EUS) was first introduced into medical practice in 1980s as a diagnostic imaging modality for pancreatic pathology[2]. It is distinctive in its ability to differentiate the histological layers of the gastrointestinal (GI) tract wall as well as the periluminal structures[3]. EUS has the unique advantage of combining ultrasound and endoscopy to obtain detailed information of the GI tract. With recent advances in technology, advanced physicians' training and the expanding use of EUS, its role has grown dramatically to include both diagnostic and therapeutic aspects in gastrointestinal, pancreatic and hepatobiliary tree disease[1].

In this review, we aim to summarize the application of EUS in diagnostic and therapeutic aspects of liver diseases. EUS performances in diagnostic and therapeutic aspects of liver disease include diagnosis and management of focal hepatic lesions, simple hepatic cysts, hepatic abscesses and portal hypertension. Limitations of EUS include limited access to the right hepatic lobe and increased risk of complications in those with anatomical alteration of the GI tract. Complications, although rare, can happen during EUS-guided fine needle aspiration (FNA) and include esophageal and duodenal perforation. We also look at the evolving future research on the role of EUS in liver diseases.

DIAGNOSTIC USE OF EUS, CONTRAST ENHANCED HARMONIC EUS, EUS-GUIDED FNA IN FOCAL HEPATIC LESIONS

Focal hepatic lesions are divided into benign lesions (such as hepatic cysts, focal nodular hyperplasia, regenerative nodular hyperplasia, abscess, adenoma or hemangioma) and malignant lesions (such as hepatocellular carcinoma, intrahepatic cholangiocarcinoma, biliary cystadenoma and metastatic liver disease)[4]. Those lesions were classically diagnosed with combination of conventional imaging such CT and transabdominal ultrasound and percutaneous liver. EUS was first used in liver imaging in 1997[5] and since then its use has become increasing popular.

EUS, especially when combined by cytology, has been used not for evaluating intra-abdominal masses only, but also for staging purposes[6-9]. In recent review by Srinivasan *et al*[4], EUS has shown superiority in detecting focal hepatic lesions compared with conventional CT and trans-abdominal ultrasound, especially for small lesions. A recent study comparing the diagnostic sensitivity of EUS and CT scan showed that of 574 patients, 14 had liver lesions that were visualized by EUS, however, only 3 of those 14 patients had their lesions visualized by CT scan prior to the use of EUS[10]. Another study by Awad *et al*[11] showed that EUS could detect additional hepatic lesions in 28% of patients with a history of known liver mass that were detected initially by CT scan. Similarly, other reports have shown that EUS can detect liver lesions that were missed by conventional imaging modalities[12]. Fuijii-Lau *et al*[13] proposed diagnostic criteria to differentiate between benign hepatic lesions and malignant metastatic lesions according to the lesion's characteristics on EUS. These criteria include lesion's shape, borders, echogenicity, homogeneity and size. These EUS criteria were applied to 200 patients who were diagnosed with malignancy using EUS-FNA. The authors concluded that EUS criteria may help in distinguishing benign from malignant hepatic lesions with a positive predictive value of 88%. The authors also suggested that the use of EUS criteria can guide the decision to perform EUS-FNA on a liver mass or not. The limitations of their study was that it was a signle center study and the EUS criteria was validated by one expert endosonosgrapher only.

The use of contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) for liver disease has evolved recently. Since the liver cells have a dual blood supply, CH-EUS is divided into three phases according to timing from contrast injection; arterial phase, portal phase and late phase[14]. According to contrast enhancement imaging, increased arterial enhancement and late-phase contrast washout indicate hepatocellular carcinoma, while peripheral-rim like hyper enhancement followed by subsequent washout is visualized in metastatic liver cancer[15]. In cases of hemangioma, peripheral nodular hyper enhancement associated with sustained enhancement in the late phase is usually visualized[15]. A comparable study by Liu *et al*[16] showed that CH-EUS is the same if not superior to CT scan in characterization and visualization of focal hepatic lesions.

The use of EUS was not limited to visualization only, but also in obtaining tissue biopsy for diagnostic purpose. EUS guided fine needle aspiration (FNA) has played a major role in revolutionizing the diagnosis of focal hepatic lesions. EUS-FNA is a minimally invasive procedure that is utilized for procurement of tissue

Table 1 Complication of endoscopic ultrasound guided fine needle aspiration compared with percutaneous fine needle aspiration

EUS guided FNA	Percutaneous FNA
Bleeding[18]	Bleeding[21,22]
Pain[18]	Severe pain[21]
Fever[18]	Punctured gall bladder[21]
Hemoperitoneum[23]	pneumothorax[21]
Death[23]	Syncope[21]
	Hemoperitoneum[24]
	Hypovolemic shock[24]
	Death[22]

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

of hepatic lesions. Currently, its use is limited to the left lobe, the proximal right lobe, the hilum and part of the intrahepatic biliary tract[17]. EUS-FNA has a theoretical advantage over classical percutaneous biopsy in patients with cirrhosis, since percutaneous approach may be difficult in these patients owing to the presence of ascites and coagulopathy[4]. Previous reports on the safety and efficacy of EUS-FNA have yielded encouraging results. In a survey by tenBerge *et al*[18], which included data from twenty-one centers of 167 cases of EUS-FNA of the lives lesions, it was shown that EUS-FNA was able to diagnose malignancy in 23 out of 26 (89%) of cases after a non-diagnostic trans-abdominal ultrasound guided FNA. Safety of EUS-FNA was also tested, with only 1% rate of major complication was reported. EUS-FNA was also shown to be safe with only 1% rate of major complications. Several other studies have shown the sensitivity of EUS-FNA for diagnosis of malignancy in liver lesions ranging from 82%-94%[19,20]. Table 1 sumarizes the complications of EUS guided FNA and percutaneous FNA[18,21-24].

EUS-GUIDED LIVER BIOPSY

Liver biopsy remains the cornerstone in the diagnosis of liver diseases[25]. Percutaneous liver biopsy was first described in 1923[26] before the transjugular approach was suggested in 1973[27]. Limitations of percutaneous approach are significant sample variability[25] and risk of adverse events that include pain at site of biopsy, bleeding, marked hypotension and pneumothorax[21]. The transjugular approach for liver biopsy entails accesses to the liver parenchyma through superior vena cava and hepatic vein, hence the liver capsule is not punctured[25]. This approach is preferred in those with coagulopathy, marked ascites and in morbidly obese patients[25]. Recently, EUS was used to obtain liver biopsy. EUS-guided liver biopsy (EUS-LB) was first described in animal studies in 2002[28], with favorable outcome and safety profile. EUS-LB in humans was described by Dewitt *et al*[29]. A case series of 21 patients who underwent a transgastric EUS guided Tru-cut biopsy with a 19-gauge needle. Histologic diagnosis was successfully obtained in 90% of specimens (19/21), however, only 71% (15/21) were helpful for clinical diagnosis. No adverse events were reported in any of the patients. In another retrospective study of 9 patients, Gleeson *et al*[30] were able to show that Tru-cut biopsy is safe and at the same time yields suitable tissue for diagnostic purposes of liver disease.

THERAPEUTIC EUS-FNA OF FOCAL HEPATIC LESIONS

Recently some case reports have highlighted the therapeutic role of EUS in liver lesions as well[31-34]. This includes the use of EUS to guide alcohol injection and laser ablation of hepatic lesions. Barclay *et al*[31] described a case of 3.3 cm metastatic liver lesion treated with multiple EUS-guided ethanol injections. Follow-up imaging showed a decrease in tumor size to less than 2 cm. Hu *et al*[32] also reported a patient with pancreatic adenocarcinoma with metastasis to retroperitoneal lymph nodes and left hepatic lobe. Following pancreatoduodenectomy and chemotherapy, patient underwent successful ethanol injection of left hepatic lesion with no significant post-procedure complications. Other examples of therapeutic intervention include EUS-guided Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:$Y_3Al_5O_{12}$) laser ablation of hepatocellular carcinoma[35].

THERAPEUTIC USE OF EUS IN SIMPLE HEPATIC CYSTS

Hepatic cysts are mostly asymptomatic, and estimated to occur in 5% of population[36]. The female: Male is approximately 1.5:1 among those with asymptomatic simple hepatic cysts (SHC) while it is 9:1 in those with symptomatic or complicated SHC[36]. SHC is generally diagnosed incidentally on abdominal imaging. Only 10%-16% of such cysts are symptomatic[4]. Symptoms are due to mass effect, rupture, hemorrhage and infection[36], and include abdominal pain, nausea, vomiting, early satiety, obstructive jaundice and hepatomegaly[4,36]. Management of SHC has varied over the years. Treatment options include surgical approach (open deroofing, laparoscopic deroofing, complete cyst resection and hepatectomy), percutaneous aspiration and sclerotherapy[4,36-40]. Prior reports have shown that percutaneous aspirations is associated with recurrence rate, as high as 100%, that can be seen as early as two weeks[38,40]. A recent systematic review by Wijnands *et al*[39] evaluated the role of percutaneous sclerotherapy in the management of SHC. The authors included 16 studies and reported cysts volume reduction ranged between 76% to 100% after a median follow-up period

of one to fifty-four months. In 10 of these studies, 72% to 100% patients reported improvement of symptoms, while 56% to 100% patients reported symptoms resolution. In regards to safety, three studies reported ethanol intoxication incidence, manifested as headache, nausea and flushing, with frequency of intoxication as high as 93%. The risk of intoxication increased with increased sclerotherapy duration, and increased volume of ethanol used[39].

In recent years, EUS guided ethanol lavage has emerged as a popular treatment modality of SHC. In 2014, Lee *et al*[41] did a single center retrospective cohort study comparing EUS guided and percutaneous ethanol lavage for treatment of large hepatic cysts. A total of 10 cysts were drained by percutaneous approach with placement of drainage catheter, while 8 cysts were drained using EUS guided ethanol lavage. In EUS-guided group, cysts were drained in a 1-step approach without the placement of a catheter. Both approaches were efficacious. Results revealed a 97.5% and 100% reduction in cysts size at 11.5-mo follow-up and 15-mo follow-up, respectively. The authors concluded that there is an excellent symptomatic and radiological response in both groups. EUS-guided approach is more effective for left liver lobe cysts while percutaneous approach is better in right sided liver cysts[41]. Despite positive results, further multi-center trials are needed to confirm these findings, since this was a single center study.

THERAPEUTIC USE OF EUS IN LIVER ABSCESSES

Liver abscesses are defined as encapsulated collection of suppurative material within the liver parenchyma[42]. They are the most common intra-abdominal abscesses with a reported incidence of 8-20 cases per 100000 hospitalized patients per year in the United States[43]. Historically, pyogenic liver abscess has been managed with either surgical or percutaneous interventions[44]. Since 2001, the number of percutaneous procedures has doubled, while the number of surgical procedures has decreased by about 20%[45]. Percutaneous abscess drainage has a success rate of up to 100%[46], hence making it the first line drainage technique. On the other hand percutaneous drainage is associated with side effects including catheter dislodgment, subscapsular hematoma, drainage from catheter exit site[47], hepato-venous fisulas[48] and hepato-colic fistulas[49]. In recent years, EUS guided drainage for liver abscesses has emerged an alternative approach since it was first proposed by Seewald *et al*[50] in 2005. The authors reported a case of an 11 cm hepatic abscess within the left lobe of the liver that was successfully drained through trans-gastric approach using EUS with no complications or recurrence on follow-up. Since then, several other case reports and series have described successful EUS guided drainage of liver abscess *via* trans-gastric and trans-duodenal approaches[51-56]. In a retrospective report by Ogura *et al*[57], 27 patients who underwent either EUS-guided abscess drainage or percutaneous abscess drainage, the clinical success rate of EUS-guided group was superior to that of the percutaneous group, at 100% and 82%, respectively. Safety and hospital stay was also superior in EUS guided group[57]. Although this data is encouraging, more prospective studies are still needed to compare the safety and efficacy of both interventions.

EUS AND PORTAL HYPERTENSION

Diagnostic aspect

Portal hypertension is the hallmark of end stage liver disease or advanced fibrosis. Hepatic venous pressure gradient (HVPG) greater than 5 mmHg is defined as portal hypertension. Esophageal varices (EV) form when HVPG is greater than 10 mmHg and the chances of EV bleeding occurs when HVPG exceeds 12 mmHg[58,59]. Esophagogastroduodenoscopy (EGD) has been the cornerstone for diagnosis, surveillance and treatment of EV[60]. Over the last decade EUS has emerged as an important tool for evaluation of gastroesophageal varices[61].

EUS can effectively measure the size of EV by using the sum of the cross-sectional surface area of all the EV in the distal third of the esophagus[62]. While upper gastrointestinal endoscopy continues to be the gold standard in detecting EV, EUS has better sensitivity in detecting gastric varices[63]. In one study EUS was able to detect gastric varices twice more than conventional EGD[63]. Since EUS can detect vascular changes better, some experts believe that EUS can easily differentiate thickened gastric folds from small gastric varices that can be difficult to diagnose *via* EGD[64]. EUS like EGD can not only diagnose esophageal and gastric varices but can also predict the risk of bleeding. One report showed that the detection of hemocystic spots *via* EUS predicted the chance of variceal hemorrhage[65].

The other advantage of EUS is increased sensitivity in detection of collateral veins around the esophagus. These veins can be small in size, called peri-esophageal collateral veins, or large in size; para-esophageal collateral veins[61]. In one study from China, EUS was able to detect extra-luminal venous abnormalities in greater than 90% of patients with cirrhosis[66]. Some gastroenterologists argue that the early detection of gastroesophageal varices, and other venous abnormalities in cirrhosis *via* EUS might reduce the need of liver biopsy if the etiology of cirrhosis is clear, *e.g.,* alcohol use and long standing viral hepatitis[67].

The detection of collateral vasculature does not only have diagnostic significance, but also has prognostic value. Prior studies have shown that the presence of severe collateral and perforating veins can help predict

Table 2 Animals studies regarding endoscopic ultrasound-guided intrahepatic portosystemic shunt placement

Ref.	Animals	Type of needle	Success rate
Schulman *et al*[79]	5 pigs	19-G-needle	100%
Buscaglia *et al*[80]	10 pigs	19-G-needle	100%

the chance of recurrence of esophageal varices before and after treatment[68-70]. Konishi *et al*[70] performed a study evaluating the risk of recurrence of esophageal varices after band ligation based on presence of vascular structures around the gastric cardia detected *via* EUS. They reported that over 90% of patients with severe perforating veins seen on EUS prior to variceal band ligation had recurrence of varcies[70]. In another study by Masalaite *et al*[71], severe esophageal collateral veins seen during EUS were shown to be independent risk factors for recurrence of varices. This suggests that this subset of patients might need closer follow-up as compared to patients who do not have perforating veins.

Therapeutic aspect

Over recent years, EUS has found role in management and treatment of gastroesophageal varices as well. The role of sclerosing therapy under EUS guidance is becoming increasingly popular. One randomized trial from Brazil showed encouraging results demonstrating that EUS guided sclerotherapy was equally effective as compared to standard endoscopic sclerotherapy for esophageal collateral vessels[72]. Where treatment of esophageal varices *via* EGD continues to be the standard of care, bleeding from gastric varices continues to be a challenge for endoscopists around the globe. Gastroesophageal varices type 2 (GOV-2) are usually large in size and lead to significant bleeding. These varices cannot be effectively treated by band ligation, and therapy targeting the accompanying perforating and collateral veins is needed. Due to these challenges, EUS guided therapy with precise localization of these veins is becoming exceedingly popular[73]. The two common modalities include EUS guided cyanoacrylate injection and EUS guided coil embolization[73,74]. Lee *et al*[66] performed a study in which 54 patients with bleeding due to gastric varices underwent EUS every two weeks, with injection of cyanoacrylate until obliteration of gastric varices. The authors reported that this intervention lead to decrease in recurrence of bleeding and improved survival in this group of patients[66]. A multi-center study also compared the use of cyanoacrylate injection (CI) with EUS guided coil embolization (CE) for treatment of bleeding gastric varices[75]. The results of this study were promising and showed that both EUS guided CI and CE were effective in treatment of gastric varices, however, CE had less side effects and needed less number of sessions for eradication of gastric varices. EUS guided sclerosis has also been successfully used to treat bleeding rectal varices in some cases[76].

The role of EUS in portal hypertension seems to be growing even more. Recently an animal study reported comparable results of portal pressure gradient measurement by EUS guided manometer approach with interventional radiology guided portal pressure measurement[77]. The same group of investigators also performed a pilot human study in which 28 patients underwent EUS guided portal pressure measurement with a hundred percent success rate and no adverse events[78]. Whereas further studies with larger sample size are needed in this regard, EUS guided portal pressure measurement might be a breakthrough for gastroenterologists and hepatologists in taking care of patients with cirrhosis. Animal studies (Table 2) have also shown that EUS can potentially be used for creation of intra-hepatic portosystemic shunts[79,80]. Historically the intra-hepatic portosystemic shunt has been placed using a trans-jugular approach under angiography (TIPS). Although this procedure as suggested has been technically feasible in animals, major concerns should be addressed before its application in patients with advanced liver disease. Those concerns include high risk of bleeding, severe infections and technical difficulties in stent placement[81].

COMPLICATIONS OF EUS

Due to specific mechanical properties of echoendoscopes used for EUS and the evolving training of advanced endoscopy specialists, there is a low, and yet noteworthy risk of complications with EUS. Majority of the complications related to EUS occur during EUS-FNA[82]. The mortality associated with EUS and EUS-FNA is 0.02%[82]. The major adverse complication with EUS is perforation. Gastrointestinal perforation can happen, especially at areas of angulation and in the presence of unexpected anatomical changes[82]. A survey conducted in Germany, including 67 centers, reported 32 complications associated with EUS. Esophageal perforation occurred only in 8 of almost 85000 diagnostic EUS procedures[83]. Another survey among members of American endosonography club in 2002 reported 16 esophageal perforations that occured after almost 44000 EUS procedures were performed, and more than half of those occurred with endoscopists who had less than one year of experience performing EUS[84]. Duodenal perforations occur more frequently than esophageal perforation[82]. In a prospective EUS online registry, 10 events of gastrointestinal perforations in 13988 diagnostic EUS procedures were noted, with duodenal perforation accounting for 60% of these cases[82]. A survey by Lachter[85] investigated the mortality in patients who had a complication during EUS. The authors reported that 13 out of 18

(73%) fatalities resulted from duodenal tears causing retroperitoneal perforations, with four of those thirteen patients having duodenal diverticula.

CONCLUSION

The role of EUS has evolved greatly in recent years. Initially thought to be a great tool for diagnostics, EUS has now several therapeutic implications as well. Since expansion of EUS in liver diseases, it is emerging as a great tool for gastroenterologists and hepatologists to manage several liver related conditions. Focal hepatic lesions have always been a challenge for hepatologists. With recent advancements in EUS, it has shown superiority in detecting focal liver lesions as compared to conventional CT scan and ultrasound imaging modalities. Moreover, recently several therapies including EUS guided ethanol and EUS-guided Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:$Y_3Al_5O_{12}$) laser ablation are also used to treat focal hepatic lesions. Similarly, recent data is showing that EUS guided liver biopsy may potentially be more safer than percutaneous liver biopsy when done by an experienced endosonographer. In regards to portal hypertension, EUS can detect early changes of portal hypertension and hence provides early and accurate assessment of overall clinical status. Despite encouraging results from available data, further research including randomized control trials is needed, before the use of EUS can be generalized in liver diseases.

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MINIREVIEWS

Liver transplantation in the treatment of severe iatrogenic liver injuries

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Abstract

The place of liver transplantation in the treatment of severe iatrogenic liver injuries has not yet been widely discussed in the literature. Bile duct injuries during cholecystectomy represent the leading cause of liver transplantation in this setting, while other indications after abdominal surgery are less common. Urgent liver transplantation for the treatment of severe iatrogenic liver injury may-represent a surgical challenge requiring technically difficult and time consuming procedures. A debate is ongoing on the need for centralization of complex surgery in tertiary referral centers. The early referral of patients with severe iatrogenic liver injuries to a tertiary center with experienced hepato-pancreato-biliary and transplant surgery has emerged as the best treatment of care. Despite widespread interest in the use of liver transplantation as a treatment option for severe iatrogenic injuries, reported experiences indicate few liver transplants are performed. This review analyzes the literature on liver transplantation after hepatic injury and discusses our own experience along with surgical advances and future prospects in this uncommon transplant setting.

Key words: Urgent liver transplantation; Acute liver failure; Iatrogenic liver injury; Vascular injury; Surgical complication; Biliary injury; Tertiary referral center; Liver transplantation

Core tip: Liver transplantation may represent the only option to manage severe iatrogenic liver injuries. Despite

widespread interest, reported experiences indicate only a minority of liver transplants are performed, and the place of liver transplantation in this setting has not yet been widely discussed. Causes other than severe bile duct injuries during cholecystectomy are less common indications for liver transplantation. Urgent liver transplantation for the treatment of severe iatrogenic liver injury may require technically difficult and time-consuming surgical procedures. The centralization of complex surgery in tertiary centers and the early referral of patients with severe iatrogenic liver injuries are crucial.

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INTRODUCTION

At the end of the line, liver transplantation (LT) may represent the only curative and life-saving option to manage severe iatrogenic liver injuries. Whereas many recent articles have focused on different strategies in the multidisciplinary management of iatrogenic bile duct injuries (BDI) after cholecystectomy[1-4], the place of LT in the treatment of other severe iatrogenic liver injuries after hepatobiliary (HPB) surgery has not yet been widely discussed in the literature. This review analyzes the cases reported to date and discusses our own experience along with surgical advances and future prospects in this uncommon transplant setting.

TYPE OF INJURY

There are basically two main types of severe iatrogenic liver injury requiring urgent LT: Biliary or vascular injuries, or a combination of the two. Some patients were indicated for LT due to acute liver failure (ALF) resulting from vascular injury secondary to a first biliary injury or other less common severe iatrogenic liver injuries.

BDI and vasculobiliary injuries during cholecystectomy

The incidence of BDI during cholecystectomy varies from 0.1% to 0.3%, rising to 0.6% when considering the laparoscopic approach[5,6]. The type and extent of BDI play an important role in surgical planning for appropriate timing and treatment.

Different systems have been proposed to classify and grade the severity of BDI. In 1982, Professor Bismuth[7] first classified postoperative bile duct strictures in a chapter of the "Blumgart book". He subsequently proposed a useful classification of biliary strictures based on the principles of surgical treatments[8]. Like the Bismuth classification, Strasberg's scale[9] incorporates other biliary injuries commonly encountered after laparoscopic cholecystectomy. To prevent bile duct injury, the Stewart-Way classification incorporates the mechanism of injury as well as its anatomy, separating resectional damage from stricture and providing a guide to pre-operative evaluation and biliary reconstruction[10]. Although other classifications of BDI after laparoscopic cholecystectomy have been reported and recently reviewed by Chun[11], the Strasberg scale remains the classification of choice for defining the types of BDI.

Some recently reported series on LT for cholecystectomy-induced BDI provide important insights. In 2011, Ardiles *et al*[2] analyzed their experience using LT as a definitive treatment for BDI, reporting data from a retrospective national survey performed in 18 LT centers over 20 years in Argentina. Among 2766 LT performed from 1990 to 2009, 19 (0.7%) were secondary to BDI arising during 16 cholecystectomies (open in 10, and laparoscopic in 6), two hydatid cyst resections, and one right hepatectomy. Seven patients had associated vascular injuries. The indication for LT was liver cirrhosis in 18 cases and ALF in the remaining one. No intraoperative mortality was reported but four patients died during the first month after LT, and another four died in the late postoperative period. The remaining 11 patients showed a good quality of life in the long-term follow-up and recipient survival rates at one, three, five and ten years were 73%, 68%, 68% and 45% respectively. The authors reported a higher rate of major post-operative complications (52%), according to the Clavien classification[12], compared with other etiologies and secondary biliary cirrhosis[13]. Interestingly, the significant decrease over time in the incidence of LT for this indication in their cohorts (3.1% of all LT in the period 1990-1994; and 0.2% in the period 2005-2009 - $P < 0.001$) reflects improvements in the prevention and management of BDI related to a multidisciplinary and specialized approach to injury-related complications.

In 2013, Parilla *et al*[4], on behalf of the Spanish Liver Transplantation Study Group, reviewed the indications and outcome of 27 patients with BDI after cholecystectomy and listed for LT in Spain over a 24-year period. Emergency LT for ALF was indicated in seven patients all after laparoscopic cholecystectomy. Two of them died while on the waiting list, one from multiorgan failure (MOF) secondary to BDI-related sepsis, and the other was anhepatic after a total hepatectomy required for massive liver necrosis. Another 20 patients underwent elective LT for secondary biliary cirrhosis after BDI (13 after open and 7 after laparoscopic cholecystectomy). Four of the five recipients who underwent emergency LT for ALF died within 30 d after LT, and the estimated overall five-year survival rate was 68%. The Spanish study confirms that BDI after laparoscopic cholecystectomy tends to be more severe than that after the open approach.

Very recently, an Italian group from Genoa reviewed the literature and reported another two cases of LT for

iatrogenic injuries among 12 patients referred to their tertiary center for the management of complicated cholecystectomy[14]. The timing for LT differed in this series. The first patient was transplanted after several endoscopic and radiological attempts to solve recurrent cholangitis that led to secondary biliary cirrhosis five years after BDI. He initially underwent open cholecystectomy with a biliary lesion described as type E2 (according to the Strasberg-Bismuth classification), and referred to the tertiary center five years after the first injury. Conversely, the second patient was listed for an emergency LT after a laparoscopic cholecystectomy converted to the open approach because of bleeding from the liver parenchyma. Eight days after surgery the patient had bile leaks and underwent endoscopic biliary stent placement complicated by a large intrahepatic hematoma and bleeding initially treated by right hepatic embolization. The patient required emergency surgical exploration and a total hepatectomy with temporary portocaval shunt (TPCS) was required to overcome the bleeding after a right hepatectomy. The intraoperative field showed a massive liver hematoma involving the right lobe, deep parenchyma lacerations, and a type D injury. After a two-day anhepatic bridging period the patient was successfully transplanted and underwent long-term follow-up. The same authors also described another patient with chronic cirrhosis who underwent LT after acute liver decompensation caused by open cholecystectomy for common bile duct lithiasis.

In addition to biliary damage, severe vascular iatrogenic injuries during HPB surgery can result in devastating complications. While the BDI rate after cholecystectomy is estimated up to 0.6% (6), and concomitant hepatic artery damage has been reported in 12%-47% of patients[15], isolated portal vein (PV) injury is uncommon. In 2011, Strasberg *et al*[16] published an analytical review of vasculobiliary injury in cholecystectomy, evaluating frequencies, causes clinical implications, and their management. A year later, the same team addressed the pathogenesis of "extreme" vasculobiliary injury and reported on outcomes after cholecystectomy for severely inflamed gallbladders in eight patients[17]. Unfortunately, one patient developed infarction of the bile ducts after injury to the proper hepatic artery and died of sepsis in the postoperative period after urgent LT. In author's opinion, in presence of inflammation a fundus-down cholecistectomy should be avoided for the prevention of extreme vasculobiliary injuries.

In 2013, Wang *et al*[15] analyzed the therapeutic strategies for iatrogenic PV injury after cholecystectomy, reporting their experience of 11 patients with vascular injuries in the absence of biliary damage. One of these patients, a 50-year-old woman, underwent LT due to chronic liver failure four months after the initial injury to the right branch of PV after an open cholecystectomy. In the authors' opinion, delayed diagnosis and treatment may have led to difficult vein repair and liver revascularization resulting in PV thrombosis and hepatic necrosis. They highlighted the major role of thrombolytic and anticoagulation therapy in the treatment of acute massive thrombus. We agree with them that an immediate attempt to repair severe PV injury should be preferred in a hemodynamically stable patient.

Other causes of severe iatrogenic liver injuries

Indications for LT to treat severe iatrogenic liver injuries after abdominal surgery or causes other than injuries during cholecystectomy are certainly less common, and very few cases have been reported.

In 2006, Huerta *et al*[18] described three lethal complications resulting from severe iatrogenic injuries during bariatric surgery performed in a high-volume bariatric center. They also described details of three cases of PV thrombosis that led to LT after two Roux-en-Y gastric bypass (RYGBP) procedures and one vertical banded gastroplasty. In the two cases of RYGBP, the porta hepatis was inadvertently stapled, while in the patient who underwent vertical banded gastroplasty the PV was divided and promptly reconstructed, but caused irreversible ischemic liver damage. Although the iatrogenic injuries were immediately recognized, a transplant surgeon consulted, and patients referred for emergency LT, the postoperative course was complicated by sepsis, MOF, and other severe medical complications resulting in the deaths of the patients. The authors claimed that PV ligation with immediate patient referral to a LT center for emergency transplant may improve the outcome in case of severe PV injury.

In 2009, the group from the University Medical Center, Nashville, Tennessee (United States) reported two cases of iatrogenic porta hepatis transection requiring an urgent two-stage liver LT[19]. In the first case, severe porta hepatis transection occurred during an open adrenalectomy in a 39-year-old woman with a history of cholecystectomy. Before transferring the patient to the authors' tertiary LT center, primary PV repair was attempted, and a Roux-en-Y hepaticojejunostomy performed, while the hepatic artery was left divided. Due to progression of the hepatic dysfunction and worsening hemodynamics, the patient underwent urgent total hepatectomy and portocaval shunt, and was listed for an emergency LT. In the other case, severe iatrogenic injury occurred during a laparoscopic cholecystectomy converted to an open operation to control a massive bleed and complete cholecystectomy before emergency transfer of the patient to the authors' tertiary center. A computed tomography (CT) scan showed infarction of the right hepatic lobe, transection of the right hepatic artery and right PV. Arterial perfusion of the left lobe was provided through a replaced left hepatic artery. A right hepatic lobectomy was planned and an urgent surgical re-exploration performed. Unfortunately, the extent of the

left PV injury precluded successful reconstruction of the PV flow and a total hepatectomy with a portocaval shunt was performed. The patient underwent LT 20 h later. We agree with the author that patients presenting with severe portal transection cannot be treated expectantly, and prompt radiological evaluation and surgical intervention are mandatory to attempt to restore hepatic flow. Hepatic resections should not be the only options entertained and LT should be promptly evaluated on a case-by-case basis.

Another case of severe hepatic injury resulting from an open right adrenalectomy was reported in the same year by Tessier *et al*[20] in a review of high-grade complications after adrenalectomy. The surgical procedure was complicated by an unrecognized injury to and ligation of the proper hepatic artery. Three months after adrenalectomy, the patient underwent a Roux-en-Y hepaticojejunostomy for the treatment of multiple liver abscesses, recurrent episodes of cholangitis and later a bleeding cholecysto-enteric fistula. The patient was ultimately referred to a tertiary center where LT was performed because of recurrent cholangitis and bile duct sclerosis.

Interestingly, in 2010 Di Benedetto *et al*[21], reported details of their experience in the treatment of severe injuries after transjugular intrahepatic portosystemic shunt placements in two cirrhotic patients where surgical and radiological attempts had failed to stop the bleeding after parenchymal and vascular rupture. Although the indications for LT were liver failure after artery embolization, and uncontrollable hemobilia, this experience highlights the ability of a tertiary referral center to offer LT as the only curative option.

OUR EXPERIENCE

Our tertiary referral center offers both a specialist HPB referral service and an abdominal organ transplantation service with more than 1800 LTs performed by the end of 2016. Out of 64 patients referred to our center with BDI after cholecystectomy only four underwent LT for secondary biliary cirrhosis, while the injuries were repaired by surgical operations or radiological and endoscopic approaches in the other cases. Another three patients were listed for LT to manage severe iatrogenic liver injuries occurring during HPB surgery.

The first case of life-saving LT performed by our institution has been described in detail elsewhere together with a full description of the surgical technique adopted[22]. A 46-year-old man was initially considered for a liver resection due to a giant symptomatic hepatic hemangioma arising from the caudate lobe with compression of the retrohepatic inferior vena cava (IVC), and thrombosis of the left and middle hepatic veins. An uncontrollable bleeding from the confluence of the suprahepatic veins occurred during the liver resection and a total hepatectomy with retrohepatic IVC resection after a venous-venous by-pass was carried out to overcome the hemodynamic instability. The extensive liver congestion excluded any attempt to proceed to an *ex-vivo* major hepatectomy, and a request for urgent LT was launched. A Dacron interposition prosthesis replaced the retrohepatic vena cava, and an end-to-side TPCS was performed between the recipient PV and the Dacron prosthesis. The LT was carried out with a side-to-side cavocaval anastomosis between the graft retrohepatic vena cava and the Dacron interposition graft. There were no postoperative complications, and the patient was discharged 26 d after LT.

The second patient was a 52-year-old woman referred to our center from another HPB tertiary center without a LT program. She had ALF resulting from a radiologically assisted hepatic artery embolization in a patient initially affected by bilobar intrahepatic calculosis treated by bile duct exploration and a Roux-en-Y hepaticojejunal anastomosis. Before referral, after surgical bile duct exploration an intrahepatic bleed occurred with a rapid deterioration of the patient's clinical status due to hemorrhagic shock. The CT scan showed a massive intrahepatic hematoma involving the right hepatic lobe and segment Ⅳ (Figure 1). After right hepatic artery embolization the bleeding stopped, but the patient developed severe ALF due to acute ischemic liver necrosis (Figure 2). After the patient was referred to our center, a conservative liver resection such as right extended hepatectomy was excluded because of the liver failure and the massive hepatic infarction extending to the left lobe. In our opinion, a liver resection could be a surgical option only when the hepatic infarction and necrosis is limited and liver function preserved, because any surgical or infectious complication after a major hepatectomy could represent a contraindication to proceed to LT. An urgent LT was planned and a liver graft from a deceased donor was immediately requested on a top priority basis from the Italian national organ sharing network. An AB0-compatible graft became available 16 h later, and the patient underwent LT. The intraoperative findings are summarized in Figure 3. Despite the huge right lobe hematoma extending to segment Ⅳ with signs of extrahepatic rupture, the hepatectomy was carried out with hemodynamic stability and a TPCS and a venovenous by-pass. The liver implant was performed in a piggy-back fashion, and a Roux-en-Y reconstruction carried out using the same intestinal loop created during the first surgery. The patient was transferred to the floor after two days spent in the ICU, discharged after 12 d, and alive three years after LT.

Another patient, a 42-year-old woman, was referred to our center the day after a complicated Whipple procedure for an ampullary adenoma with subsequent total pancreasectomy due to pancreatic fistula and hemoperitoneum. After surgical re-exploration patient was transferred to the ICU. Liver function tests, lactate, and her hemodynamic conditions continued to worsen and a CT scan showed massive liver necrosis with multiple abscesses excluding any attempt to proceed to a liver resection. A request for an urgent LT was

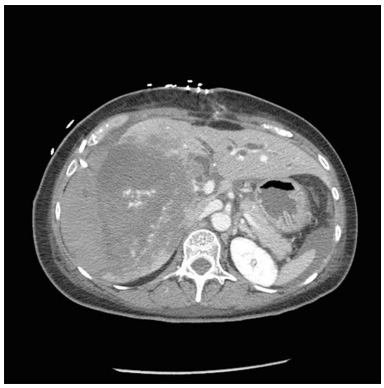

Figure 1 Computed tomography scan show a massive intrahepatic hematoma involving the right hepatic lobe and segment Ⅳ.

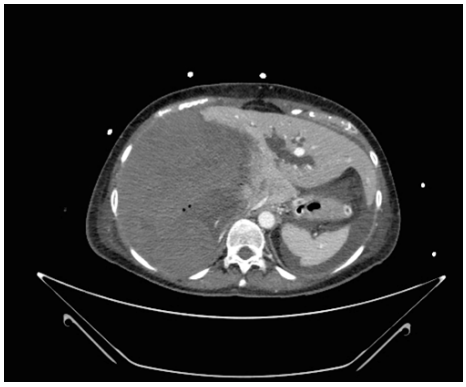

Figure 2 Computed tomography scan show the ischemic liver necrosis after the right hepatic artery embolization.

launched, and a compatible donor was available eight hours later. Recipient laparotomy revealed massive intestinal necrosis, and complete hepatic artery and PV thrombosis. These findings, associated with severe MOF and hemodynamic instability, made the indication for LT impracticable and futile. Unfortunately, the patient failed to overcome MOF and the available liver graft was connected to oxygenated hypotermic machine perfusion after 12:15 h of static cold storage before the transplant in a back-up recipient[23].

SURGICAL CONSIDERATIONS

Urgent LT to solve severe iatrogenic liver injuries may represent a surgical challenge requiring technically difficult and time-consuming procedures. Although a TPCS improves hemodynamic stability during LT, its role is still controversial and its use has remained limited since the technique was recommended in the early 1990s for recipients with portal hypertension caused by acute or subacute liver failure expected not to have adequate portosystemic collaterals[24]. A total hepatectomy and subsequent LT could be a useful strategy for patients presenting massive ischemic liver or exsanguinating hepatic injuries with uncontrollable vascular or parenchymal bleeding. In addition, urgent

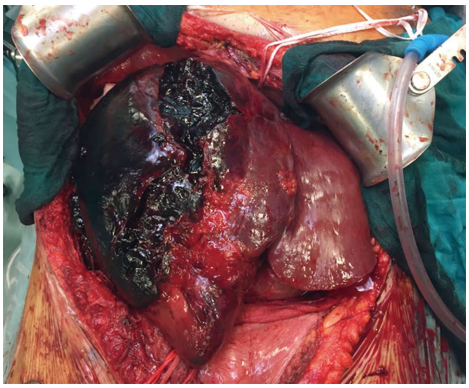

Figure 3 Intraoperative findings: A huge right lobe hematoma extended to segment Ⅳ with signs of extrahepatic rupture.

total hepatectomy and a TPCS may be performed awaiting a compatible deceased liver donor, or in the event of "toxic hepatic syndrome" secondary to massive hepatic necrosis. It is well known that total hepatectomy might improve the metabolic, coagulation and hemodynamic profiles of these patients while waiting for a suitable liver donor[21,25].

From a surgical point of view, portal blood could be shunted to the systemic circulation performing an end-to-side anastomosis between the main PV and the anterior wall of the anterior surface of the suprarenal IVC or performing a portosuprahepatic anastomosis[26].

Alternatively, an extracorporeal portocaval shunt-catheter connecting the PV to the femoral vein can be applied as described by the Munich transplant group[27] who reported the feasibility of this shunt technique, which does not require anticoagulation or an additional pump supply.

A venovenous by-pass may represent another possible option especially when a patient becomes hemodynamically unstable after a massive bleed and resection of the IVC required as previously reported by our Institution[22].

Vascular reconstruction in patients with severe iatrogenic injuries of hepatic hilum elements could be challenging, and extra-anatomical reconstruction with the use of arterial conduits remains an important tool in the transplant surgeon's armamentarium. Banked or freshly procured vascular grafts from deceased donors should be considered for supraceliac or infrarenal aortohepatic conduits.

The use of aortohepatic conduits using deceased donor iliac artery as an interpositional graft in LT have already been investigated and recently reviewed[22-30].

In addition to deceased arterial grafts, the use of cryopreserved arterial grafts as conduits has been recently proposed in living donor LT[31].

A recently published paper by Hibi *et al*[32] advised proceeding with caution in primary adult LT, where the placement of an aortohepatic conduit should be strictly limited because of the greater risk of late hepatic artery thrombosis and impaired graft survival.

Nevertheless, the use of arterial conduits could provide the only alternative option for graft vascularization during LT after severe iatrogenic injury of the hepatic artery. Baylor's group recently published their center experience after twenty years' follow-up of PV conduits in LT[33]. More than two thousand adult LTs were evaluated. All PV conduits were the donor's iliac vein procured during liver retrieval. PV conduits were required during the first LT in 35/2370 patients (1.5%). Long-term graft survival after LT using PV conduits was excellent and comparable to that of the control group (65% with the conduit *vs* 66% without the conduit at five-year follow-up, 58% *vs* 51% at ten years, and 48% *vs* 35% at 15 years). The authors reported excellent long-term results proving the longevity of the PV conduits using the donor's iliac vein. The reported results may also be applicable to other complex surgical settings such as severe iatrogenic vascular injuries requiring LT.

Resection and replacement of the IVC could occasionally be required during LT for severe iatrogenic injury of the liver or the vena cava. A variety of reconstruction strategies and materials including biological (autologous and heterologous) and synthetic grafts such as polytetrafluoroethylene (PTFE) and polypropylene (Dacron) have been reported to replace the vena cava[22]. Pulitanò *et al*[34] recently highlighted some important technical aspects in the use of biological tissues for IVC replacement. They reported advances in the use of glutaraldehyde-treated bovine pericardium and an autogenous peritoneo-fascial graft from a flap of parietal peritoneum backed by the posterior rectus sheath as alternatives to prosthetic IVC reconstruction. After 32 IVC reconstructions, the authors claimed that biological grafts allow greater flexibility and biocompatibility and long-term patency without permanent anticoagulation.

As previously mentioned for arterial and PV reconstructions, especially in LT centers, the use of cryopreserved banked or freshly procured venous allografts from deceased donors offers an option in IVC replacement. The use of allografts was first described long ago by Starzl *et al*[29] and is still common practice in the field of LT[28,29,35].

TIMING OF REFERRAL AND THE ROLE OF TERTIARY CENTERS

HPB surgery has had an extraordinary evolution and diffusion in recent years thanks to the success in reducing mortality and morbidity rates[36], especially in high-volume centers. A debate is ongoing on the need for centralization of complex surgery in tertiary referral centers. Clinicians are constantly reminded about the importance of early referral for patients with severe iatrogenic liver injuries to a tertiary center with experienced HPB and transplant surgery. Patients initially and repeatedly treated in non-specialist hospitals and referred for LT in the ALF setting have been reported to have worse outcomes[4].

The role of surgical experience in the repair process has been widely explored and demonstrated in the past[37]. In 2008, Silva *et al*[38] from the Queen Elisabeth Hospital, United Kingdom reported their experience as a specialist outreach service for on-table repair for iatrogenic BDI after laparoscopic cholecystectomy. They highlighted the role of this new kind of "travelling surgeon" reporting repeatable outcomes with no post-operative mortalities in 22 procedures avoiding transfer of the patient to a tertiary center, prolonged bile drainage, and a reoperation with a shorter hospital stay and a reduced risk of sepsis and liver failure. They also claimed that the proposed immediate approach has potential medicolegal advantages reducing the risk of litigation and costs.

Our experience highlighted the crucial role of a liver transplant program when referring a patient with complex and severe injuries after HPB surgery because LT may represent the patient's only curative option in a small number of cases.

FUTURE PERSPECTIVES

The literature lacks reports on severe iatrogenic liver injuries, likely because negative outcomes tend to be under-reported, and we have no information on those patients with severe iatrogenic liver injuries who died before referral to a tertiary center. This is detrimental to surgical education, and the topic was recently voiced by Cheah *et al*[39] who discussed improvement in care by close examination of "near-miss" cases.

Reported experiences on the place of LT in the treatment of severe iatrogenic injuries indicate few LTs are performed in this uncommon setting. Without an official comprehensive registry, it is exceedingly difficult to determine appropriate indications and long-term outcomes as detailed data are confined to individual case reports in the literature.

All the clinicians involved in the care of patients with severe iatrogenic liver injuries should clearly spell out information on their outcomes honestly and swiftly so that others can learn a lesson and not repeat the same errors.

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ORIGINAL ARTICLE

Basic Study

Novel synthetic adhesive as an effective alternative to Fibrin based adhesives

Pramod Kadaba Srinivasan, Vera Sperber, Mamdouh Afify, Hirokazu Tanaka, Kenji Fukushima, Babette Kögel, Felix Gremse, René Tolba

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Institutional review board statement: The governmental care and use committee (LANUV), Recklinghausen, NRW, Germany, granted official permission.

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Abstract

AIM

To compare a novel, fully synthetic, polyurethane based glue (MAR-1) to fibrin sealant in a partial liver resection rat model.

METHODS

After 50% resection of the lateral left liver lobe in male Wistar rats (n = 7/group/time point), MAR-1, Fibrin or NaCl was applied. After 14, 21 and 90 postoperative days, sealant degradation, intra-abdominal adhesions were scored, and histological examination of liver tissue was performed.

RESULTS

(Mean ± SEM) (MAR-1 *vs* Fibrin *vs* NaCl). Bleeding mass was significantly higher in NaCl (3.36 ± 0.51 g)

compared to MAR-1 (1.44 ± 0.40 g) and Fibrin (1.16 ± 0.32 g). At 14 and 90 d, bleeding time was significantly lower in MAR-1 (6.00 ± 0.9 s; 13.57 ± 3.22 s) and Fibrin (3.00 ± 0.44 s; 22.2 ± 9.75 s) compared to NaCl (158.16 ± 11.36 s; 127.5 ± 23.3 s). ALT levels were significantly higher in MAR-1 (27.66 ± 1 U/L) compared to Fibrin (24.16 ± 0.98 U/L) and NaCl (23.85 ± 0.80 U/L). Intrabdominal adhesions were significantly lower in MAR-1 (11.22% ± 5.5%) compared to NaCl (58.57% ± 11.83%). Degradation of the glue was observed and MAR-1 showed almost no traces of glue in the abdominal cavity as compared to the Fibrin (10% ± 5% 14 d; 7% ± 3% 21 d). Survival showed no significant differences between the groups.

CONCLUSION

Compared to Fibrin, MAR-1 showed similar hemostatic properties, no adverse effects, and is biocompatible. Further studies on adhesion strength and biodegradability of synthetic sealants are warranted.

Key words: MAR-1; Fibrin; Liver resection; Hemostasis; Polyurethane

Core tip: This study evaluates the effectiveness of a novel, polyurethane based, surgical adhesive on a liver resection model. This study will further help in better sealing of wounds in a trauma model in comparison to Fibrin glue.

Srinivasan PK, Sperber V, Afify M, Tanaka H, Fukushima K, Kögel B, Gremse F, Tolba R. Novel synthetic adhesive as an effective alternative to Fibrin based adhesives. *World J Hepatol* 2017; 9(24): 1030-1039 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i24/1030.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i24.1030

INTRODUCTION

Hemorrhage due to traumatic injury is one of the leading causes of death worldwide. It is estimated that hemorrhage is responsible for more than 35% of pre-hospital mortality and 40% of mortality in the first 24 h[1]. In case of abdominal trauma, the liver is one of the most commonly injured organs; anatomical position and its delicate parenchyma make it susceptible to injury and hemorrhage[2]. Despite modern surgical techniques, management of hemorrhage after liver trauma still remains a challenge, with major liver trauma resulting in high morbidity and mortality rates[3]. Furthermore, surgeries involving liver resection are known to be of high risk; nevertheless, it is the one of the curative treatment options for hepatocellular cancer patients[4].

Management of liver injury has progressed tremendously in the last three decades[2]. Advancement in biotechnological research has resulted in a variety of hemostatic agents[5]. These hemostatic agents are either biological or synthetic in nature[5]. They are based on components including cellulose, collagen, glutaraldehyde, fibrin, and dihydroxyacetone[5-7]. Fibrin sealants (also known as fibrin adhesive or glue) are the most widely used hemostatic agents as a complimentary adjunct in various surgical procedures. Fibrin sealants comprise of two components, human-thrombin and fibrinogen, usually plasma derived[5]. During application, these two components interact to form a stable fibrin clot[5]. However, most require 2 ℃-8 ℃ storage, extensive preparation, and, once taken out of refrigeration, have to be used within 9 h[6]. Notably, fibrin sealants are less effective in events of strong bleeding, as they can be washed away with blood or other liquids and there is a risk of re-bleeding, due to fibrin sealants' limited sealing strength[8,9]. Due to their biological origin, fibrin sealants are associated with risk factors including immune reactions, viral transmission, and potential embolism risk[6,10,11].

In the early forties, cyanoacrylate based glues were marketed under brand names, such as, Superglue and Krazy glue. Cyanoacrylate glues are neither biocompatible nor bioabsorbable[12]. Additionally, upon degradation, cyanoacrylates form cyanoacetate and formaldehyde, which are toxic to humans[5,12]. Other options for synthetic products include urethane based polymers, such as polyurethane. Polyurethanes (PUs) are known for their tensile strength of 4-60 MPa; thus, making them highly elastic[13]. Research has shown that several factors, such as hydrolysis and enzymatic action, contribute to their degradation[14]. Because of their non-biological components, there is no risk of virus transmission or antigenic reaction like with fibrin based adhesives.

The aim of this study was to evaluate MAR-1, determining hemostatic properties, functionality, and prevention of intra-abdominal adhesions, tissue compatibility as well as biodegradation. In comparison, we tested the clinically used fibrin sealant Beriplast® P (CSL Behring GmbH, Marburg, Germany) and Sodium Chloride (NaCl) as a control solution.

MATERIALS AND METHODS

MAR-1 and Fibrin sealant

MAR-1 is a polyurethane based sealant that consists of two different components: A isocyanate-functional polyester-ether pre-polymer and an amino-functional asparagine acid ester. This adhesive technology and its polyaddition reaction are well-known.

The two components were stored at 22 ℃ in a double chamber syringe and combined upon application (Adhesys Medical GmbH, Aachen, Germany). The Fibrin sealant used was the commercially available Beriplast® P (CSL Behring GmbH, Marburg, Germany), which consists of fibrin and thrombin mixed prior to application.

Animals and surgical procedure

All experiments were conducted in accordance with German Federal Law regarding the protection of animals and the DIRECTIVE 2010/63/EU on the protection of animals used for scientific purposes. The Guide for the care and use of laboratory animals (8th edition, NIH Publication, 2011, United States) was also followed. The governmental care and use committee (LANUV), Recklinghausen, NRW, Germany, granted official permission. Male Wistar rats weighing between 200-260 g were used. The animals were housed in Type 2000 rat filter top cages (Tecniplast, Hohenpreisenberg, Germany) under specific pathogen free (SPF)-conditions according to Federation of European Laboratory Animal Science Associations (FELASA) guidelines (www.felasa.eu), in a temperature (22 ℃) and humidity controlled environment (55% relative humidity) with a 12-h light/dark cycle and allowed food (standard rat diet, Ssniff-Spezial Diäten GmbH, Soest, Germany) and water ad libitum.

Sixty-three rats were randomly allocated to the following groups: MAR-1, Fibrin and NaCl. The groups were further classified into three time points: 14 d, 21 d, and 90 d. Rats received general anesthesia by inhalation of 1.5% isoflurane (Abbott GmbH and Co.KG, Wiesbaden, Germany) and administration of 0.1 mg/kg body weight Buprenorphine (Temgesic®, Essex Pharma GmbH, Munich, Germany) subcutaneously as analgesic. For perioperative anti-biotic prophylaxis, rats received 16 mg/kg bodyweight Cefuroxime s.c. (Fresenius SE and Co. KGaA, Homburg, Germany). Using a vessel loop for compression, 30% of the left lateral lobe was removed, and sealant was applied in an amount sufficient to cover the wound area. Pre-weighed gauze was placed under the liver lobe prior to resection. Post resection, the blood absorbed by the gauze was weighed and subtracted from the pre-weight of the gauze to calculate the bleeding mass. The animals were euthanized under anesthesia after 14, 21 and 90 d respectively.

μCT to visualize the biodegradation

μCT data was measured using Tomoscope 30 s Duo (CT-Imaging GmbH, Erlangen, Germany) using a protocol (HQD-6565-90-360) that took 720 projections (1032 × 1012 Pixel) in 90 s during one rotation with radiation dose of 421 mGy[15]. Several sub-scans were taken and reconstructed using a Feldkamp algorithm with a voxelsize of 70 μm × 70 μm × 70 μm and were assembled into one volume data set. Volumetric image data was analyzed and visualized using the Imalytics Preclinical Software[16].

Histological evaluation

Tissue samples of the liver were collected at the time when the rats were euthanized. The samples were immediately fixed in 4% neutral buffered formalin (Roti®-Histofix 4%, Roth, Karlsruhe-Germany), and then were shaken overnight on a shaker (Lab net, International Inc., United States). The specimens were processed in grading series of alcohol and xylene, embedded in paraffin and sectioned at 4-6 μm thin slices using a microtome and were stained with hematoxylin and eosin (H and E). Paraffin-embedded liver sections were used for H and E staining and analysed using a Leica DM 2500 microscope (Leica, Bensheim, Germany).

Immunohistochemistry was performed as per manufacturer's instructions. CD68 macrophages were identified by a 1:50 mouse monoclonal antibody from Dako (Glostrup, Denmark), pre-treatment of the fixed specimen with microwave three times, citrate-buffer pH 6, and as secondary antibody rabbit anti-mouse 1:300 from Dako (Glostrup, Denmark).

Serum analyses and hematology

Serum was withdrawn at 14, 21 and 90 d post operation and analyzed with a clinical chemistry analyzer (Ortho Clinical Diagnostics GmbH, Neckar-gemünd, Germany). Liver enzymes, ALT and AST were measured from serum. In addition, blood count of leukocytes (10^3/μL), erythrocytes (10^6/μL), platelets (10^3/μL), and hemoglobin were measured using the MEK6450K automatic cell counter (Nihon Kohden, Rosbach, Germany).

Statistical analysis

Statistical review was performed by Professor René Tolba. All results are expressed as mean ± SEM and the data was analyzed by Graph Pad Prism® Version 5 (Graph Pad, San Diego, CA, United States). Significance between different groups was measured with one-way analysis of variance (ANOVA) and posttest: Tukey-Kramer. Survival analysis was carried out by Kaplan-Meier curve and Mantel-Cox test. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Bleeding mass

Bleeding mass (Figure 1) was assessed in order to record the amount of blood lost after liver resection. After 21 d, NaCl (3.36 ± 0.51 g) showed significantly higher levels of blood loss in comparison to MAR-1 (1.44 ± 0.40 g) and Fibrin (1.16 ± 0.32 g) treated animals. However, there were no significant differences between the animals in 14 d (MAR-1: 2.08 ± 0.30 g; Fibrin: 1.02 ± 0.29 g; NaCl: 1.02 ± 0.29 g) and 90 d (MAR-1: 2.21 ± 0.44 g; Fibrin: 2.03 ± 0.28 g; NaCl: 3.04 ± 0.50 g) group.

Bleeding time

Duration of blood loss (Figure 2) was recorded to evaluate the bleeding time in different groups. NaCl (158.16 ± 11.36 s) (127.5 ± 23.3 s) showed significantly higher bleeding times on 14 and 90 d in comparison to MAR-1

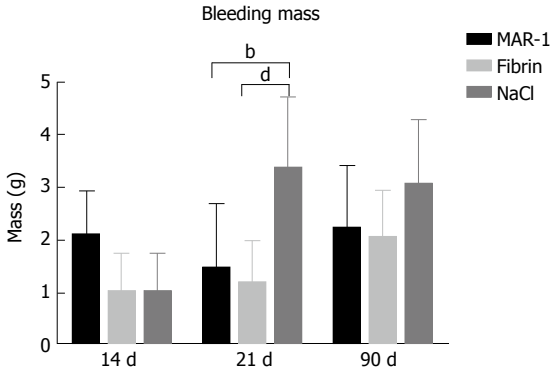

Figure 1 Amount of blood loss was measured at three different time points. $^{b}P < 0.001$ MAR-1 *vs* NaCl; $^{d}P < 0.01$ Fibrin *vs* NaCl in 21 d group ($n = 7$).

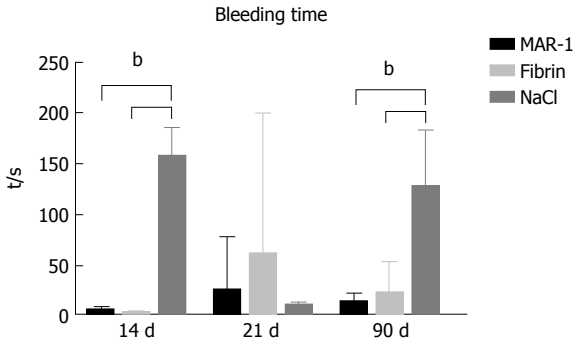

Figure 2 Bleeding time was recorded after liver resection. $^{b}P < 0.001$ MAR-1 and Fibrin *vs* NaCl in both 14 and 90 d group ($n = 7$).

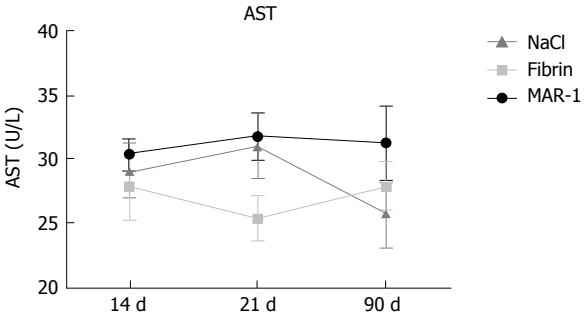

Figure 3 Aspartate transaminase release was measured after 21 and 90 post-operative days ($n = 7$). AST: Aspartate transaminase.

(6.0 ± 0.9 s) (13.57 ± 3.22 s) and Fibrin (3.0 ± 0.44 s) (22.2 ± 9.75 s) groups respectively. However, the groups showed no significance at 21 d time point (MAR-1: 25.33 ± 17.53 s; Fibrin: 61.16 ± 56.77 s; NaCl: 10.71 ± 1.19 s).

Aspartate transaminase

Aspartate transaminase (Figure 3) was measured as parameter for liver injury. There were no significant differences noticed in the groups at 14 (MAR-1: 30.37 ± 1.23 U/L; Fibrin: 27.83 ± 2.54 U/L; NaCl: 29.16 ± 2.12 U/L), 21 (MAR-1: 31.77 ± 1.80 U/L; Fibrin: 25.33 ± 1.70 U/L; NaCl: 31.00 ± 2.46 U/L) or 90 d (MAR-1: 31.28 ± 2.86 U/L; Fibrin: 27.90 ± 1.86 U/L; NaCl: 25.83 ± 2.71 U/L).

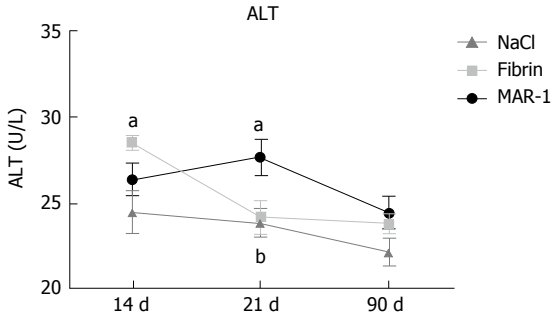

Figure 4 Alanine transaminase release was measure after 14, 21 and 90 post-operative days. $^{a}P < 0.05$ Fibrin *vs* NaCl after 14 d; $^{a}P < 0.05$ MAR-1 *vs* Fibrin; $^{b}P < 0.01$ MAR-1 *vs* NaCl after 21 post-operative days ($n = 7$). ALT: Alanine transaminase.

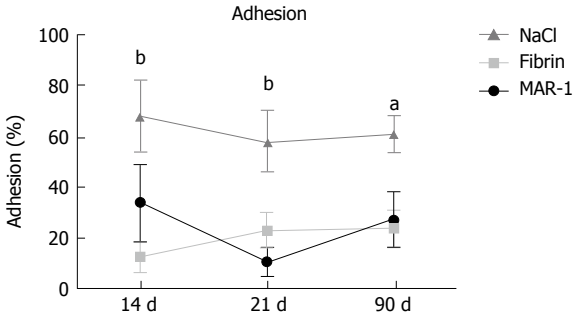

Figure 5 Percentage of tissue adhesion after 14, 21 and 90 post-operative days was tabulated. $^{b}P < 0.01$ Fibrin *vs* NaCl after 14 d, $^{b}P < 0.01$ MAR-1 *vs* NaCl after 21 d; $^{a}P < 0.05$ Fibrin *vs* NaCl after 90 d ($n = 7$).

Alanine transaminase

Alanine transaminase (Figure 4) release was measured as a parameter for liver parenchymal damage. Significant differences between the treatment groups were seen after 14 and 21 post-operative days. Fibrin (28.5 ± 0.42 U/L: 14 d) (24.16 ± 0.98 U/L: 21 d) showed a significantly higher release of ALT compared to NaCl (24.5 ± 1.23 U/L: 14 d) (23.85 ± 0.80 U/L: 21 d) group after 14 d. Meanwhile, MAR-1 (26.37 ± 0.92 U/L: 14 d) (27.66 ± 1 U/L: 21 d) showed significantly higher levels after 21 d in comparison to both NaCl and Fibrin treated animals.

Adhesions

Intra-abdominal adhesions (Figure 5) were visualized and the extent of adhesions was evaluated. After 14 d, Fibrin (13.33% ± 6.1%) treated animals showed significantly lower percentage of adhesions in comparison to NaCl (68.33% ± 14.24%). MAR-1 (11.22% ± 5.5%) showed significantly lower adhesion compared to NaCl (58.57% ± 11.83%) after 21 d. After 90 d, Fibrin group (24% ± 7.29%) showed significantly lower levels of adhesions compared to NaCl group (61.66% ± 7.03%). Whereas, there were no significant differences found between Fibrin and MAR-1 groups at any given time point.

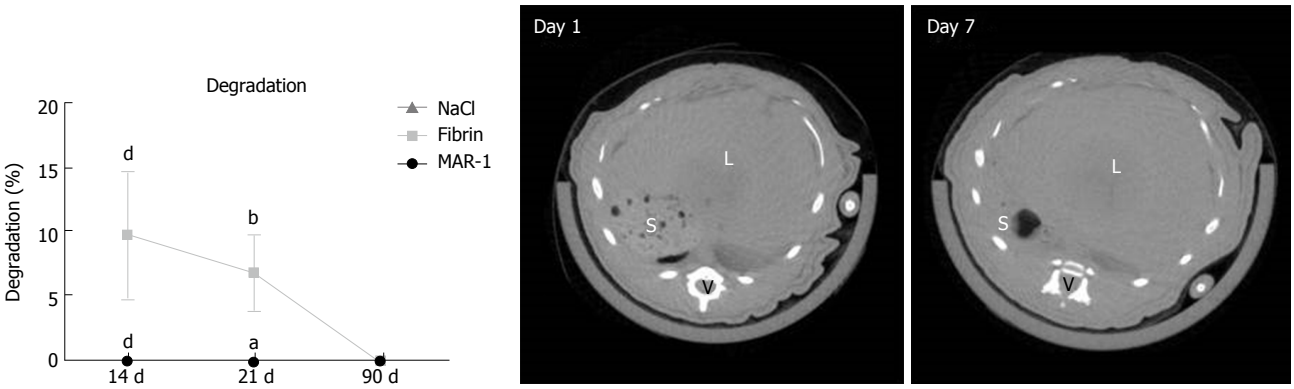

Figure 6 µCT scans of MAR-1 rat on day 1 and day 7. Percentage of adhesive degradation was evaluated after 14, 21 and 90 post-operative days. $^{d}P < 0.001$ Fibrin *vs* MAR-1 and NaCl after 14 d; $^{b}P < 0.01$ Fibrin *vs* MAR-1; $^{a}P < 0.05$ NaCl *vs* Fibrin 21 d ($n = 7$). L: Liver, S: Stomach, V: Vertebra.

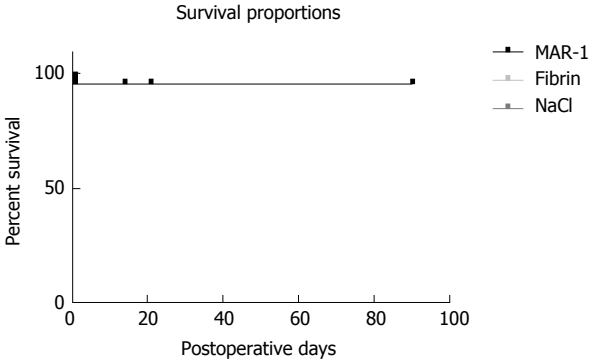

Figure 7 Survival proportions between the treatment groups were calculated during 14, 21 and 90 post-operative days. $P = 0.9906$ as per Mantel-Cox test ($n = 7$).

Degradation

µCT scans were performed on day 1 and day 7 to visualize the glue. Interestingly, due to its hydrogel like properties, the glue could not be distinguished from the liver tissue in the µCT images (Figure 6). Degradation of MAR-1 and Fibrin were noted and compared to NaCl treatment. MAR-1 (0% ± 0% at all time points) and NaCl (0%) were absent or negligible compared to Fibrin (10% ± 5% 14 d; 7% ± 3% 21 d; 0% 90 d). Fibrin glue levels were significantly higher compared to MAR-1 and NaCl groups after 14 and 21 d. Fibrin glue was completely metabolized after 90 d.

Survival rate

Percentage survival (Figure 7) was calculated for each treatment group. MAR-1 showed a survival percentage of 95.83% in comparison to Fibrin with 95.65% and NaCl with 95%. As per Mantel-Cox test, the *P* value was 0.9906 and there was no statistical significance seen between MAR-1 and other the groups.

Histopathology

Histopathological evaluation (Figure 8) was performed on the tissue section after 90 post-operative days. There was a slight inflammation due to foreign body reaction in both MAR-1 and Fibrin groups. The reaction zone showed granulation tissue along with some collagen structures. A dense collagenous fibrotic tissue along with histiocytic inflammation was noticed. Whereas, in MAR-1 and Fibrin treated animals inflammation was noticed initially; however, the reaction was absent after 90 d. In case of NaCl treated animals, a thicker liver capsule was seen and occasional inflammation due to bleeding remnants.

CD68

Immunohistochemical staining is an ideal tool to identify the presence of CD68 positive cells (Figure 9). It specifically stains macrophages as well as Kupffer cells, Giant cells, and Monocytes. This helps in recognizing cell proliferation in tissues. The CD68 cell count at 14 d (8.6 ± 1.0, 9.0 ± 1.0 AU, 6.8 ± 0.8 AU), 21 d (5.4 ± 0.6 AU, 5.6 ± 0.67 AU, 2.4 ± 1.0 AU), and 90 d (1.6 ± 0.5 AU, 2.4 ± 0.6 AU, 2.4 ± 1.0 AU) showed no significant differences within the groups.

Elastic van Gieson

Elastic van Gieson staining (Figure 10) protocol specifically stains elastic fibers, which helps in differentiating between normal and pathological elastic fibers. Due to the chemical reaction in the staining process, the elastic fibers and cell nuclei are stained black, collagen fibers are stained red, and other tissue elements including cytoplasm are stained yellow. We noticed the width of the reaction zone along with the proliferative tissue reduced with time and there were no significant changes noticed in the structural integrity.

Hematological parameters

Leucocytes, Erythrocytes, Hematocrit, and Platelets were measured and the groups showed no significant differences (Table 1). However, Hemoglobin levels (Table 1) were measured in all the groups. There was a significant difference noted between Fibrin (11.69 ± 0.21 g/dL) and NaCl groups (12.48 ± 0.17 g/dL) at baseline level. Whereas, MAR-1 (12.09 ± 0.29 g/dL) showed significantly lower haemoglobin levels compared to NaCl group (13.68 ± 0.26 g/dL).

Table 1 Leucocytes in 103/μL; Erythrocytes in 106/μL; Hemoglobin in g/dL; Hematocrit in %; Platelets in 103/μL; (mean ± SEM); 1-way ANOVA, Posttest: Tukey Kramer

		MAR-1	Fibrin	NaCl	*P* value
Leucocytes	0 d	7.48 ± 0.33	6.82 ± 0.30	7.26 ± 0.39	NS
	14 d	6.78 ± 0.66	7.18 ± 0.67	8.65 ± 0.75	NS
	21 d	7.56 ± 0.75	7.20 ± 0.72	6.23 ± 0.50	NS
	90 d	6.11 ± 0.78	5.76 ± 0.52	5.41 ± 0.32	NS
Erythrocytes	0 d	5.71 ± 0.09	5.68 ± 0.07	5.68 ± 0.08	NS
	14 d	6.07 ± 0.17	6.48 ± 0.20	6.03 ± 0.18	NS
	21 d	6.33 ± 0.14	7.03 ± 0.10	6.50 ± 0.17	NS
	90 d	7.58 ± 0.19	7.51 ± 0.12	7.72 ± 0.17	NS
Hemoglobin	0 d	12.29 ± 0.14	11.69 ± 0.21[a]	12.48 ± 0.17[a]	[a]$P < 0.05$
	14 d	12.09 ± 0.29[b]	13.13 ± 0.43	13.68 ± 0.26[b]	[b]$P < 0.01$
	21 d	13.08 ± 0.22	13.84 ± 0.28	14.17 ± 0.28	NS
	90 d	14.14 ± 0.33	13.88 ± 0.18	13.90 ± 0.29	NS
Hematocrit	0 d	35.09 ± 0.48	34.59 ± 0.30	34.05 ± 0.42	NS
	14 d	35.66 ± 0.96	38.30 ± 0.94	35.13 ± 0.50	NS
	21 d	35.50 ± 0.76	36.98 ± 0.62	36.31 ± 1.02	NS
	90 d	39.69 ± 0.91	39.26 ± 0.55	39.75 ± 0.94	NS
Platelets	0 d	923 ± 32	960 ± 42	998 ± 30	NS
	14 d	907 ± 67	985 ± 63	1035 ± 34	NS
	21 d	1104 ± 50	1024 ± 57	970 ± 41	NS
	90 d	924 ± 42	874 ± 25	916 ± 48	NS

[a]$P < 0.05$; [b]$P < 0.01$.

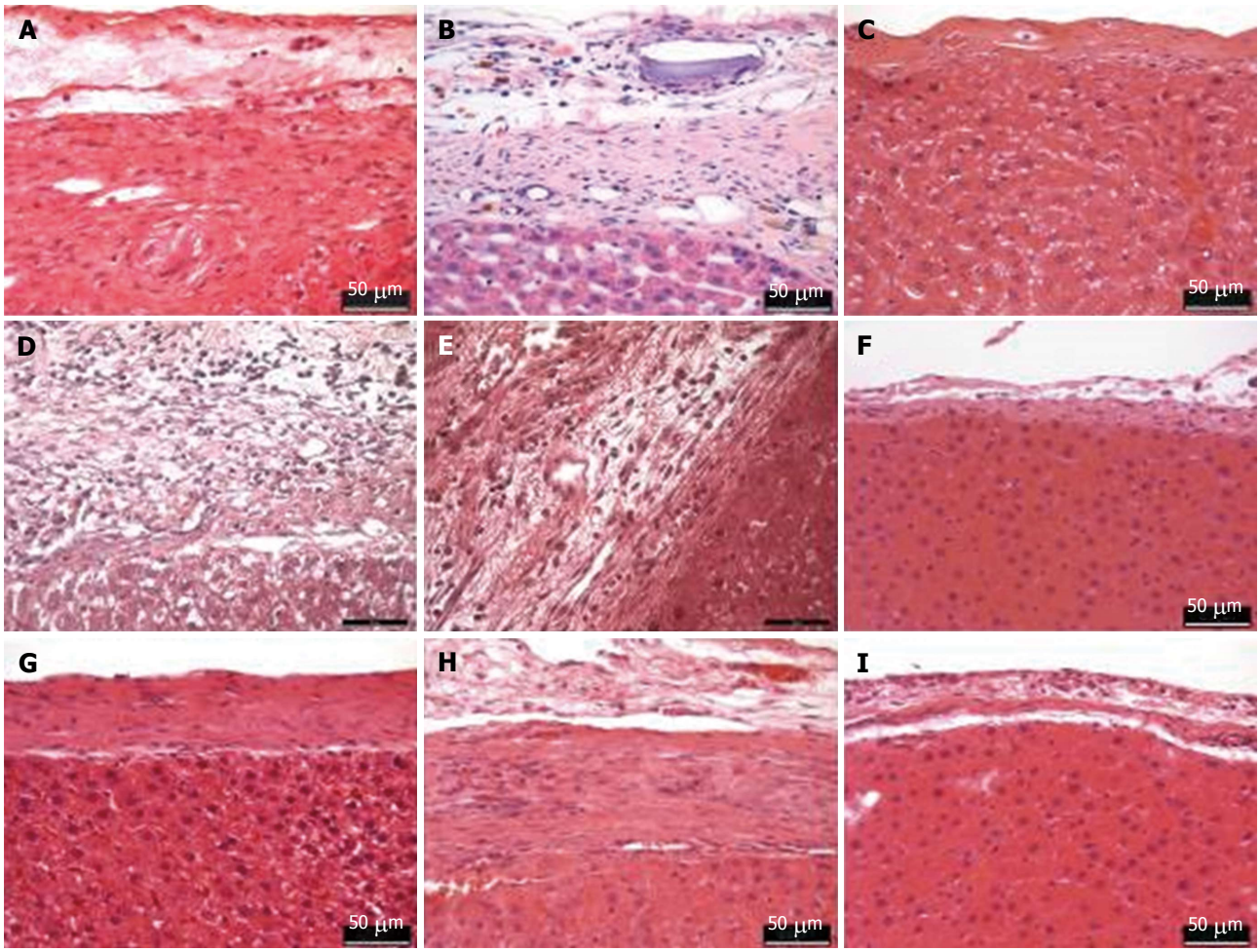

Figure 8 Histopathological evaluations of H and E stained liver tissue section shows the resected area and structural intergrity at different time points, MAR-1 (A: 14 d, B: 21 d, C: 90 d); Fibrin (D: 14 d, E: 21 d, F: 90 d); NaCl (G: 14 d, H: 21 d, I: 90 d).

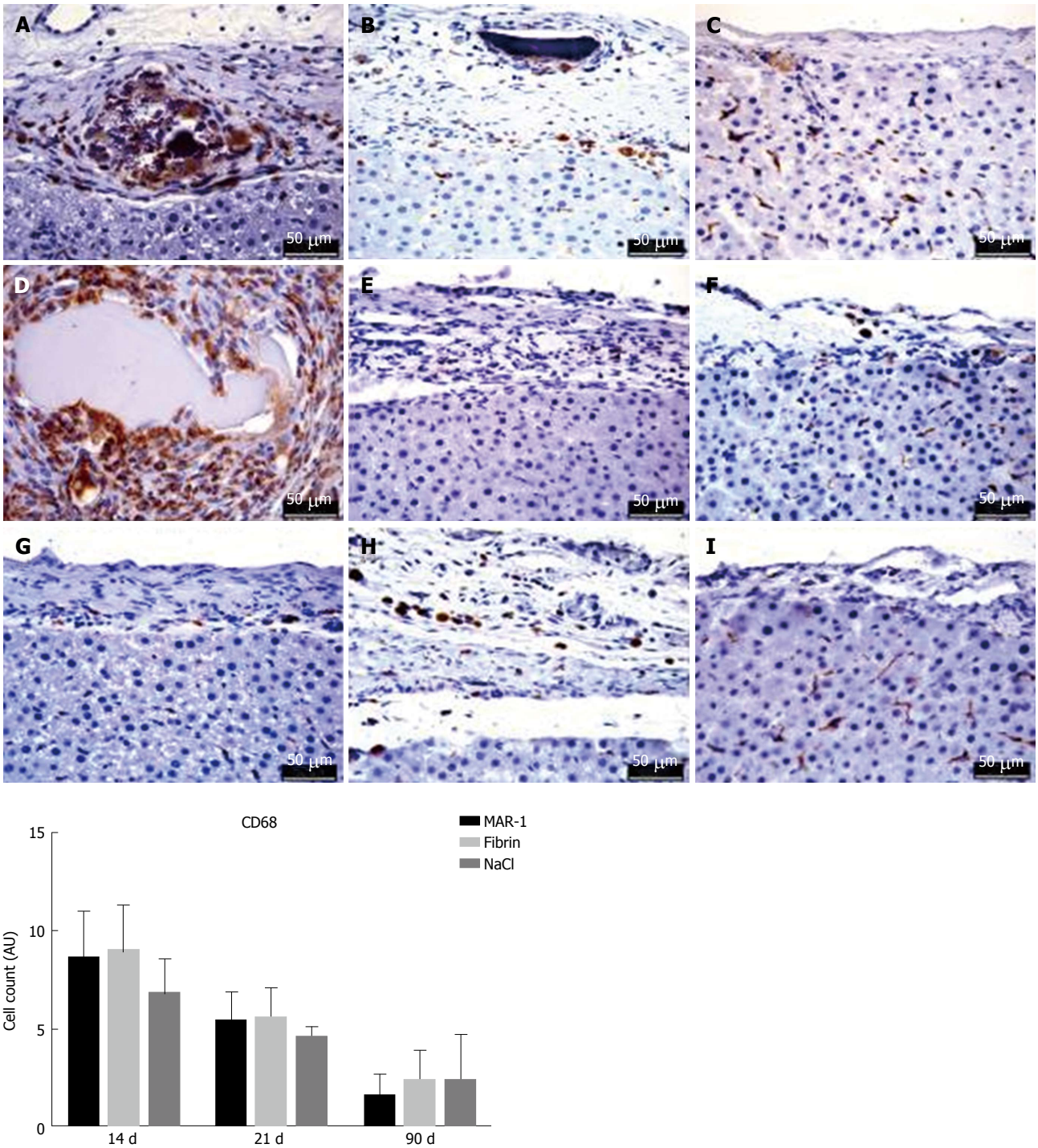

Figure 9 Immunohistochemical staining for CD68 shows a few darkly stained positive cells. The graph represents the CD68 positive cell count with no significant differences between the groups, MAR-1 (A: 14 d; B: 21 d; C: 90 d); Fibrin (D: 14 d, E: 21 d, F: 90 d); NaCl (G: 14 d, H: 21 d, I: 90 d).

DISCUSSION

According to WHO 2010 database, 5.8 million deaths due to injuries were recorded worldwide[17]. A quarter of these were due to trauma and hemorrhagic shock due to injuries; thus, making it a leading cause of death across the globe[1,17]. Liver injury is most commonly observed in abdominal trauma cases[18]. Apart from trauma, liver resection in hepatocellular carcinoma patients carries a high risk of hemorrhage[19]. Hemorrhage during liver surgery is directly associated with extensive use of vascular occlusion techniques, which leads to post-operative complications and eventually hepatic failure[19]. During liver surgery, it is vital to minimize bleeding, especially from small blood vessels of liver parenchyma, in order to prevent intraoperative blood loss and to better visualize the surgical field[19].

In this study, we compared the efficacy, haemostatic properties, and biocompatibility of a novel, polyurethane based synthetic adhesive, MAR-1, with that of

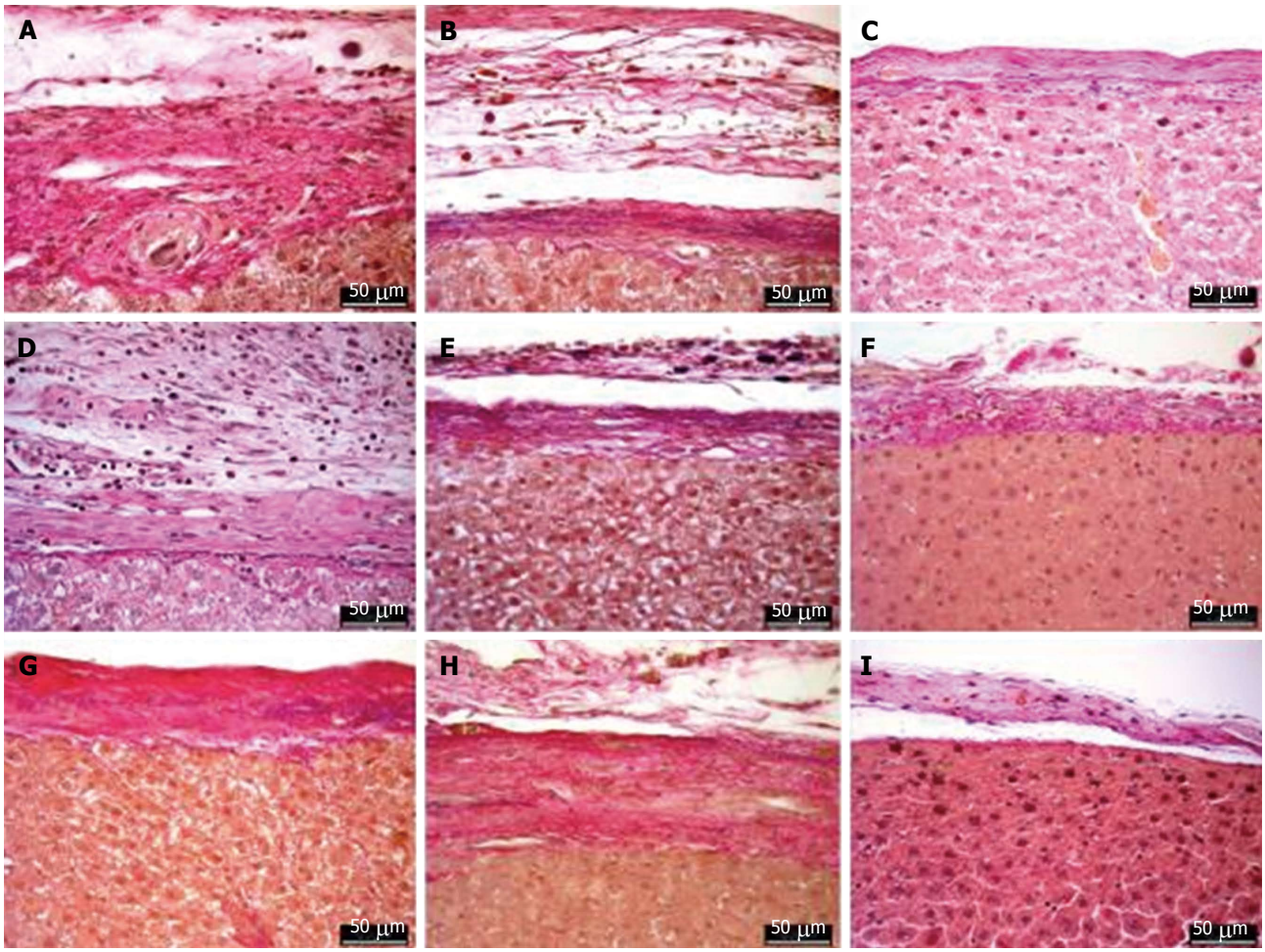

Figure 10 Elastic van Gieson staining shows the resected area and proliferative tissue, MAR-1 (A: 14 d, B: 21 d, C: 90 d); Fibrin (D: 14 d, E: 21 d, F: 90 d); NaCl (G: 14 d, H: 21 d, I: 90 d).

Fibrin, which is a clinically used medical adhesive.

Fibrin sealants mimic the coagulation cascade, which depends on various factors such as enzymes, proteins, and co-factors[20]. Polyurethane-based adhesives mainly react with the amino groups of proteins in the tissue, which enables the formation of urea linkages and eventually adhesion[12]. Polyurethanes are known to activate platelets, which enhances the blood clotting process[21]. Moreover, polyurethanes have demonstrated strong thrombogenic properties due to their hydrophobic nature, this promotes the proteins to adhere and initiate the coagulation cascade[12]. We measured the bleeding mass and time to assess the capacity of these sealants to stop bleeding after liver resection. The results showed no significant differences between the two sealants and the results were comparable. However, we noticed a significant difference between MAR-1, Fibrin and NaCl groups, this clearly showed the effectiveness of a sealant in minimizing blood loss, thereby reducing the bleeding time. On the other hand, liver parenchymal enzymes, AST and ALT, were measured and we noticed no significant changes in AST levels throughout the time course; whereas, a significant increase in ALT levels were seen in MAR-1 group after 21 d, in comparison to Fibrin and NaCl groups. AST and ALT levels are routinely measured to assess the functionality of liver and their ratio between the concentrations is of clinical relevance. AST/ALT ratio of 2:1 or more is considered as a sign of liver damage. The elevated ALT levels in the MAR-1 group was probably due to repeated manipulation of the liver lobe during the surgical procedure. Nevertheless, the values were within the physiological range and did not increase at a later time point.

Depending on the origin of thrombin in the fibrin sealants, severe immune reactions have been observed, leading to anaphylactic shock in some cases[22-24]. When extracted from human pooled blood, it carries a high risk of viral contamination[25,26]. Despite improved methods of viral inactivation[27], it still carries a risk of parvovirus infection[28]. Whereas, MAR-1, the polyurethane based adhesive, showed no adverse reaction in this study. Polyurethanes in general are considered biocompatible and biodegradable; they are polymers consisting of urethane links[13]. Research has

shown that polyurethanes containing biodegradable diisocyanates degrade into non-cytotoxic decomposition products[13,29,30]. After 14 d, the quantity of MAR-1 was either negligible or absent in the abdominal cavity, suggesting the rapid and efficient degradation of the glue. These results were significant in comparison to Fibrin glue, which was present even after 21 d. Nevertheless, both the glues were efficiently degraded by the end of 90 d. Meanwhile, it was difficult to visualize MAR-1 with the help of μCT, which can be attributed to its hydrogel like properties causing low contrast to the adjacent liver tissue. Studies have suggested that degradation of polyurethanes was mainly dependent on the polyester polyol composition[13,31,32]. Polyurethanes exhibit great versatility in their polymeric properties. Rapid degradation of MAR-1 proves its biocompatibility without any adverse effects. This also supported the previously established properties of polyurethanes such as toughness, durability, elasticity, biocompatibility, which is not achieved by any other available material[33].

Intra-abdominal adhesions are commonly noticed after abdominal surgery. Their incidence is estimated at 67%-93%, which affects the final outcome of the surgery[34]. When a foreign body is introduced into the abdominal cavity it leads to fibrosis and adhesion formation[35]. Demirel *et al*[36] showed that fibrin sealant drastically reduced adhesions in comparison to primary suture. In general, polyurethanes have been known to exhibit strong adhesion to the tissue[37], as mentioned earlier, their interaction with the amino acids results in the adhesion of the glue to the tissue[12]. We noticed the formation of adhesions during the time course; however, there were no significant differences between MAR-1 and Fibrin treated animals. However, significantly more adhesions were noticed in NaCl group compared to MAR-1 group. These results supports our hypothesis, which is the biocompatibility and non-inferiority of MAR-1 compared to Fibrin glue, the clinical gold standard. Furthermore, the survival rate showed no significant differences between the groups. Meanwhile, the histopathological examination revealed a few structural changes, however, the tissue sections failed to show any significant differences between the groups.

In summary, MAR-1 has been shown to be non-inferior to Fibrin in terms of effective and safe sealing of a liver in a resection model. Based on the obtained results, MAR-1 is biocompatible and showed no adverse effects. We agree that further research is needed to study the chemistry and biodegradability. Nevertheless, MAR-1 is ready to be used in its current form as a topical wound sealant. Moreover, due to the fully synthetic nature, there is no risk of increased immune reactions or viral transmission like with Fibrin.

ACKNOWLEDGMENTS

The authors thank Mr. Pascal Paschenda for his skillful technical assistance.

COMMENTS

Background

Despite advanced surgical techniques, hemostasis after liver trauma is a major cause for morbidity and mortality. Fibrin glue is the current gold standard for managing hemostasis; however, there are some disadvantages like production costs, allergic reactions, and storage conditions. In this study, the authors introduce a novel, polyurethane based, synthetic adhesive, which is biocompatible and controls bleeding effectively.

Research frontiers

Hemostasis in trauma and surgery is of prime importance, their study primarily focuses on management of blood loss during surgical and trauma procedures.

Innovations and breakthroughs

Novel polyurethane based adhesive, MAR-1, helps in managing blood loss effectively in rat partial liver resection model. This study shows variety of parameters, which plays an important role during traumatic situations.

Applications

Partial liver resection model in rats is an established model for liver trauma studies. Results from this study shows the effectiveness of fully synthetic, polyurethane based novel adhesive. This model provides all the necessary information to study the application of surgical adhesives.

Terminology

MAR-1: Medical adhesive revolution-1 is a novel polyurethane based adhesive; PU: Polyurethanes.

Peer-review

The manuscript is well-written and the data shown in the manuscript was understandable.

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LETTERS TO THE EDITOR

Lurking epidemic of hepatitis C virus infection in Iran: A call to action

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Abstract

Despite having a relatively low prevalence in the Iranian general population, the burden of hepatitis C virus (HCV) infection is on the rise, and hepatitis C is predicted to be the most important leading cause of viral hepatitis-related mortality in the near future in Iran. The recent population-based epidemiological studies have revealed the predominant role of injecting drug use in increasing prevalence of HCV infection. Undoubtedly, new management paradigm is required to drive down the rising wave of hepatitis C in Iran. Priority should be given to young injecting drug users as the cornerstone of the lurking epidemic of HCV infection in Iran.

Key words: General population; Injecting drug user; Epidemiology; Hepatitis C virus; Iran

Core tip: Iran is known as a low-endemic country for hepatitis C virus (HCV) infection, while the recent population-based epidemiological studies have revealed the increasing burden of HCV infection in the Iranian population. The asymptomatic nature of HCV infection and the undiagnosed HCV-infected injecting drug users have fueled this increase. Obviously, the current management paradigm is inadequate if control of HCV infection is aimed to be achieved.

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TO THE EDITOR

Less than 0.5% of the population, as many as 186500 patients are infected with hepatitis C virus (HCV) in Iran[1]. The majority of HCV-positive patients have been infected by injecting drug use, equivalent to 75% of the HCV-infected population[2]. The burden of HCV infection shows a rising trend, and HCV infection is projected to be the most important leading cause of viral hepatitis-related mortality in the near future in Iran[1,3]. Obviously, the current management paradigm is inadequate if control of HCV infection is aimed to be achieved.

Mandatory screening of all blood donors for hepatitis C resulted in a remarkable decrease in the prevalence of HCV infection[1,2,4,5]. In view of the success in the Iranian Blood Transfusion Organisation, the talk of HCV elimination has been intensified. However, all hopes came to knot due to rising wave of HCV infection among injecting drug users (IDUs), those whom the control of HCV transmission among is the most difficult. The shared use of drug paraphernalia and lack of awareness among young IDUs regarding the risk of acquiring HCV infection *via* needle-sharing are the root cause of the increasing prevalence of HCV infection among IDUs community[1]. At the same time, the asymptomatic nature of HCV infection and the undiagnosed HCV-infected IDUs would accelerate this increase[1].

The recent changes in the genotype distribution of HCV have also fueled this epidemic[6]. High rates of mutation in HCV genome have resulted in the emergence of seven major genotypes and at least 67 subtypes[7]. Each geographic region has a distinct genotypic pattern, which depends on the predominant mode of transmission, risk factors, life style, the source of infection, disease transmission patterns and age distribution in that particular region[8,9]. These genotypic patterns are not constant, change overtime and influence the epidemiology of HCV infection in that region[10,11]. The most prevalent subtype in Iran is 1a, followed by 3a and 1b. Over the last decade, however, a gradual decrease in the frequency of subtypes 1a and 1b and an increase in subtype 3a have been reported due to changes in the routes of transmission of HCV from blood transfusion to injecting drug use[6,9-12]. These changes should be taken in to consideration to establish better strategies for managing the silent epidemic of hepatitis C in Iran.

Another challenge is treatment of HCV-infected population. Despite having poor tolerability, prolonged treatment course and frequent side effects, interferon (IFN)-based therapy is still recommended as the first-line therapy in Iran due to affordability and local availability[3,9]. Annually, 2.4% of the Iranian HCV-infected population is treated by pegylated IFN plus ribavirin, with approximately 58%-78% of patients showing a sustained virological response (SVR) depending on the HCV genotype[2]. Introduction of IFN-free direct-acting antivirals (DAAs) has revolutionized the treatment course of HCV infection due to superior rates of SVR, favorable tolerability, fewer side effects and shorter treatment period[13-15]. However, in reality, the restricted accessibility and high price of DAAs outweigh these benefits. Recently, the production of a domestic DAA, the combination of daclatasvir and sofosbuvir, with health insurance coverage has been announced in Iran, paving the way for low-cost access to DAAs and subsequently widespread use of these drugs in the near future[1,3]. This domestically produced DAA, Sovodak, has shown favorable SVR rates in Iranian patients infected with genotypes 1 or 3 HCV, the most predominant genotypes in Iran, providing an opportunity to improve the treatment rate and subsequently eliminate HCV infection in the future[1].

These challenges in the management of hepatitis C epidemic cannot be neglected any longer. Resent changes in the epidemiology of HCV would demand changes in health policies, prevention and management strategies. In view of the success of the transfusion-safety measures implemented in the Iranian Blood Transfusion Organization[4,9], screening of high-risk populations for hepatitis C, new therapeutic strategies with an emphasis on timely diagnosis and treatment, expansion of harm-reduction interventions, public education regarding the risk of HCV infection, as well as comprehensive cooperation and mobilization of health care providers are required to drive down the rising wave of HCV infection in Iran once again. Priority should be given to young IDUs as the cornerstone of this silent epidemic. Furthermore, national health policies should be prioritized in a way to curb the lurking epidemic of HCV infection once and for all.

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