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ORIGINAL ARTICLE

Effectiveness of porcine dermal collagen in giant hernia closure in patients with deleterious fascia constitution after orthotopic liver transplantation

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Summary

Incisional hernias (IHs) occur universally after orthotopic liver transplantation (OLT). This study aimed to investigate the effectiveness of porcine dermal collagen (PDC) as a closing aid in giant hernias after OLT in a prospective trial. If direct closure (DC) was not feasible due to the hernia size and abdominal wall constitution, a PDC mesh was implanted. All patients from the PDC and DC groups were followed prospectively for 24 months. IH recurrence rates served as the primary endpoint, and the development of infections and wound healing disorders served as the secondary endpoints. Recurrence rate was 21% (4/19) in DC patients and 12% (2/16) in PDC patients ($P = 0.045$). Implant site infections occurred in five of PDC and one of DC patients ($P < 0.05$). All of them were managed with antibiotics; two of the PDC patients required surgical drainage. Histological analysis of PDC mesh biopsies indicated good angiogenesis and integration of the PDC into the abdominal wall. PDC was effective in our study for incisional hernia repair, and our results compared favourably with those of patients in whom direct hernia closure was feasible.

Introduction

Orthotopic liver transplantation (OLT) remains the treatment of choice for patients suffering from end-stage liver diseases [1]. Incisional hernias (IHs) following OLT reportedly occur at an incidence of up to 35% [2]. Various factors influencing the high IH numbers have been reported, such as the extensive use of diathermy, bad abdominal wall constitution pre-transplantation or immunosuppressive regimens [3–5]. The evidence regarding closure techniques for IHs following major abdominal surgery or following OLT is scarce, and prospective controlled studies are still required [6–8]. Recent analysis suggested laparoscopic closing techniques to be superior to open methods [9]. However, in some patients, those techniques are not feasible due to their abdominal wall constitution.

IHs were classified in 2009 by the European Hernia Society according to their width and location [10]. In accordance with this classification, recommendations for appropriate closure techniques have been made [11]. IHs that occur under immunosuppression have been classified as Grad 2 hernias with high risk for infections or present

contaminated conditions – so since then, the use of a biological implant to repair the hernia is recommended. Despite these recommendations, various methods for IH closure have been used to date, especially in immunosuppressed patients [12,13].

Porcine dermal collagen (PDC) is a cellular porcine dermis graft that has been shown to be effective for wound closure, albeit with controversial results for abdominal wall reconstruction [14,15]. Data on PDC integration into the abdominal wall in immunosuppressed patients are still lacking [16]. Some studies have suggested potential benefits for the use of dermal meshes in IH closure in transplanted patients [17–20].

The aim of this study was to evaluate the effectiveness of PDC for the closure of IHs after OLT in situations where direct closure was not possible in this special patient cohort. The results were compared to direct closure reinforced by a synthetic onlay mesh in a patient population following OLT. This study was approved by the ethics board of the Medical University of Graz (EK Nr: 24-034 ex 10/11).

Patients and methods

Patients with a primary IH >10 cm in diameter after OLT and who were admitted to the Department of General Surgery of the Medical University of Graz for a routine repair were invited to participate in this study.

Prior to the operation, patients underwent an abdominal ultrasound to confirm the hernia size. All patients underwent closure and provided written informed consent for closure using a PDC mesh as well as direct closure (DC).

The closure technique depended on two factors: tension-free achievability of direct closure and abdominal wall thickness and strength. If feasible, hernias were closed directly using an onlay mesh placement. In these patients, sublay placement of a mesh is not preferred given that a strict sublay position is typically not possible due to the location of the hernia (slanting incision just below the patient's ribs). PDC was only used if DC was not achievable. Patients were followed 24 months postoperatively as DC or PDC patients.

Closing technique used at liver transplantation

In our centre, a subcostal incision is used for liver transplantation. In this study, patients had subcostal incisions only, without extensions to the midline. In all patients, running sutures with a nonabsorbable filament (PDS 2.0, Ethicon, Vienna, Austria) were applied using the small bite technique on the fascia to achieve optimal closure at the time of OLT. IHs were diagnosed at clinical presentation and confirmed on ultrasound as described above.

Surgical procedure in DC patients

After a preoperative single injection of 1.5 g cefuroxime as antibiotic prophylaxis, the hernia repair was performed with interrupted stitches using the small bite technique. A prolene mesh (Ethicon) was placed using the onlay technique and fixed using Vicryl 1/0 sutures (Ethicon). Therefore, the hernia was not only closed directly, but closure was reinforced by the polypropylene mesh placed in an onlay position. A 14 French Redon drainage was placed above the mesh. All patients received subcutaneous interrupted sutures with Vicryl 2/0 sutures (Ethicon). The skin was sutured intracutaneously, and sterile dressings were applied.

Surgical procedure in PDC patients

After a preoperative single injection of 1.5 g cefuroxime as antibiotic prophylaxis, the hernia repair was performed with a cross-linked PDC mesh (Permacol, Covidien, Brunn am Gebirge, Austria) placement using bridging technique. The mesh was fixed using interrupted stitches with monofil filament (Prolene 1.0, Ethicon). A 14 French Redon drainage was placed on top of the mesh. All patients received subcutaneous interrupted sutures with Vicryl 2/0 sutures (Ethicon). The skin was sutured intracutaneously, and sterile dressings were applied.

Study course

Hernia recurrence served as study endpoint. The patients were followed throughout their hospital stay with routine blood draws and laboratory monitoring of the inflammatory response, namely via white blood cell counts and C-reactive protein levels. Patients were released from the hospital after full recovery and received follow-up every 6 months for 12 months on an outpatient basis with a clinical examinations and ultrasonographies.

Detection of hernia recurrence

Recurrence was diagnosed if the patient presented with a symptomatic herniation or a herniation was detected via abdominal ultrasonography. In the case of recurrence and subsequent reoperations, biopsies of the PDC grafts were obtained, and vessel ingrowth was measured to depict the integration of the mesh into the patient's abdominal wall.

Detection of infections at the implant site

In case of elevations of inflammatory response parameters, fever or the development of redness above the implant site an abdominal ultrasound was performed to

detect fluid masses above the implanted mesh or closed hernia.

Statistics

Statistical analysis was performed using SPSS 19.0 (IBM, Vienna, Austria). To evaluate differences between groups, the chi-squared test for categorical data and the *t*-test for continuous variables were used. Correlations were performed using the Spearman rank or the Pearson correlation coefficient where appropriate. The development of an IH served as an endpoint.

For survival or time-to-event analysis, the Kaplan–Meier method was used.

A sample size calculation was performed using the published recurrence rates of incisional hernias in immunosuppressed patients. For immunosuppressed patients, recurrence rates of 10–36% after primary incisional hernia repair with nonbiological and biological meshes were reported [17,21]. A *P*-value of 0.05 was used for the calculation, and the relative risk was estimated based on both recurrence rates ($R = 3.6\%$). The sample size of each group was calculated using an alpha of 5% (0.05) and a beta of 20% (0.2), thereby generating a power of 80% with a constant of 7.85. The calculated sample size for each group is 15 patients.

Results

In our centre, at median, 26% (15–31%) of our OLT patients developed incisional hernias during the past 10 years ($n = 63$). Forty-one patients were invited to participate in the present study. Of these patients, 35 participated (four patients had hernias with a diameter < 10 cm, and two patients refused). In 19 patients, a DC was achievable (DC patients), and 16 patients received a PDC mesh (PDC patients).

The immunosuppressive regimen at the time of IH diagnosis and repair consisted of mycophenolate mofetil (1000 mg BID for all patients) in combination with tacrolimus (9/16 of PDC patients and 10/19 of DC patients; 6–8 ng/ml target trough levels) or mTOR (mammalian target of rapamycin) inhibitors (7/16 of PDC patients and 9/19 of DC patients; 4–7 ng/ml target trough levels); three patients (1/16 of PDC patients and 2/16 of DC patients) additionally received 5 mg of prednisolone daily. The immunosuppressive therapy was not altered throughout the hernia repair, but the target trough levels of mTOR patients were maintained as low as possible.

The PDC and DC patient groups were comparable at baseline. The median age was 54 years for the PDC patients and 56 years for the DC patients (range PDC: 35–67 years; range DC: 36–69 years; $P = 0.063$). At the time of the first intervention, the PDC and DC patients displayed a median BMI of 27 kg/m^2 and 28 kg/m^2 ($P = 0.08$), respectively. At the time of hernia recurrence detection, the PDC patients exhibited increased BMI values compared with the DC patients (PDC patients: 29 kg/m^2; DC patients 25 kg/m^2; $P = 0.045$, Table 1).

The IH diameter did not differ significantly between the PDC and DC patients (PDC: 19 cm [11–23] and DC patients: 16 cm [12–21]; $P = 0.054$). The median size of the implanted PDC meshes was 20 × 30 cm (13–25 × 25–32 cm).

Postoperative infections above the mesh occurred in 23% (4/16) of the PDC patients and in 4% (1/19) of the DC patients ($P < 0.025$) following hernia repair. All infections were managed with administration of antibiotics, and two of the PDC patients required surgical drainage (Table 2).

Table 1. The baseline characteristics of the included patients.

	PDC patients ($n = 16$)	DC patients ($n = 19$)	*P*-value
Age (years)	54 (35-67)	56 (36–69)	n.s.
Gender, male (%)	28%	35%	n.s.
BMI (kg/m^2)	27 (19–29)	28 (23–30)	n.s.
Immunosuppression	MMF – 100% (16/16)	MMF – 100% (19/19)	n.s.
	Tac – 56% (9/16)	Tac – 53% (10/19)	n.s.
	mTOR – 44% (7/16)	mTOR – 47% (9/19)	n.s.
	Prednisolone 6% (1/16)	Prednisolone – 10% (2/19)	n.s.
Indications for OLT	Alcoholic cirrhosis – 75% (14/21)	Alcoholic cirrhosis – 69% (13/19)	n.s.
	HCV cirrhosis – 25% (7/21)	HCV cirrhosis – 31% (6/19)	n.s.
IH diameter (cm, median, range)	19 (11–23)	16 (12–21)	n.s.
Time since liver transplantation (months, median, range)	9 (6–12)	7 (5–11)	n.s.
PDC size (median, cm, range)	20 × 30 (13–25 × 25–32)	–	–

MMF, mycophenolate mofetil; Tac, tacrolimus; HCV, hepatitis C-related cirrhosis; BMI, body mass index; IH, incisional hernia; PDC, porcine dermal collagen.

Table 2. Both groups were followed for 24 months. Significantly more infections occurred in the PDC patients compared with patients after direct closure of the hernia. Nevertheless, the PDC patients showed less recurrence rates after mesh implantation.

	PDC patients (n = 16)	DC patients (n = 19)	P-value
BMI (kg/m^2)	29 (25–31)	25 (23–29)	0.045
Postoperative infections (%)	23% (4/16)	4% (1/19)	0.025
Recurrence rate (%)	12% (2/16)	21% (4/19)	0.045
Time to recurrence (months)	5 (3–10)	7 (4–13)	0.035

The recurrence rate was 21% (4/19) among the DC patients and 12% (2/16) among the PDC patients (P = 0.045). The median interval between the discovery of the incisional hernia and the first intervention was 9 months in PDC patients (6–12 months) and 7 months in the DC patients (5–11 months; P = 0.053 between PDC and DC patients). Recurrence was managed surgically by re-operation and re-implantation of the mesh in PDC patients. In the DC patients, a PDC mesh was implanted during the second operation in two cases. During re-operation, biopsies from the previous *in situ* PDC were obtained to examine the mesh integration into the patient's fascia after implantation (Table 2). Three patients who had a PDC and developed recurrence received sirolimus as an immunosuppressant, and one patient received tacrolimus.

The risk of infection after PDC closure was sevenfold higher compared with DC (OR: 7.1875, CI 95%: 0.7653–67.521, P = 0.084). The risk of developing a recurrent hernia was fivefold increased for the DC patients compared with the PDC patients in the present study (OR: 5.418, CI 95%: 0.5540–52.869, P = 0.1465).

All recurrences were treated surgically. None of the patients displayed further signs of recurrence until the end of follow-up at 24 months.

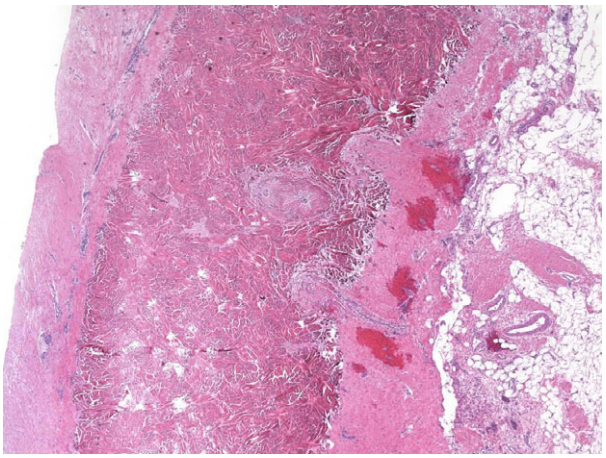

Figure 1 HE staining of a biopsy of an implanted PDC from an OLT patient. Blood vessel ingrowth is visible throughout the entire mesh.

The histological findings indicated vessel ingrowth with visible nuclear material in the mesh of the PDC patients. Both mesh biopsies exhibited evidence of an implant inflammatory response and tissue integration at the hernia defect site. The PDC mesh displayed complete cellular penetration (Fig. 1).

Discussion

The implantation of biological meshes for the treatment of abdominal wall defects is a widely recognised option, especially in patients with deleterious abdominal wall consistency. Additionally, these materials possess demonstrated bacterial and human protease resistance [10,22] and promote vessel ingrowth and early revascularization after implantation [23]. PDC meshes might also be able to prevent the development of biological niches above the implanted mesh – another advantage compared with synthetic meshes [19]. The above reasons serve as the rationale for the use of these meshes in immunosuppressed patients, such as orthotopic liver transplantation (OLT) patients. In the present study, we demonstrate that vessel ingrowth and mesh integration were evident in biopsies from patients who experienced recurrent hernias.

All patients who experienced postoperative infections at the mesh site also developed recurrent hernias. Although mesh site infections were rare among DC patients, these infections were also linked to the development of a recurrent hernia. Based on the records of all hernia recurrence patients, a postoperative elevation in the inflammatory response parameters was observed in all of the patients, even if surgical treatment was not required at the implant site. These findings indicate that the most crucial time point after PDC implantation in immunosuppressed patients is the early postoperative period. Given that similar results were observed among DC patients with an onlay mesh, this finding might also be true for immunosuppressed patients. We hypothesize that those infections weaken the abdominal wall at the implant site, and although fully healed, its capacity to reconstitute might not be the same at those sites.

A potential limitation of the present study is that our primary goal in hernia repair is to achieve a direct closure, combined with an onlay mesh reconstruction. A biological mesh was only used if direct repair was not possible. Another limitation, the onlay positioning, was our sole choice due to deleterious abdominal wall fascial constitution in this patient cohort, often combined with fascial necrosis at the primary suture points, which is attributed to the patients' immunosuppression and pretransplantation conditions like marasmus and massive ascites. The pre-

sented technique was confirmed by a recent review that showed onlay mesh reconstruction as most frequent repair technique after OLT [24]. Additionally, in the present study, we did not compare a direct closure but a reinforced one with an implanted PDC. This means that this study also investigated potential differences between synthetic and biological meshes in OLT patients. Therefore, this analysis adds an additional information on recurrence rates and postoperative courses between patients with biological implants and synthetic implants after OLT. Although PDC patients experienced higher postoperative infection rates, recurrence rates were lower in PDC patients, which confirms a potential value of PDC placement in OLT patients.

Biological meshes were created to add initial strength to the abdominal wall. These meshes should act as a framework to enhance regeneration and ultimately allow the abdominal wall to replace the mesh with native tissue [25]. Proper mesh integration through fibroblast ingrowth should lead to complete tissue remodelling [26]. Recently, a discussion on the use of various biological mesh types, for example, cross-linked versus non-cross-linked meshes, has evolved [27,28]. In transplanted patients, the use of a cross-linked mesh with consistent tensile strength appears to be more feasible than the use of a non-cross-linked mesh. We can underline this as the meshes were used to bridge large abdominal wall defects in the present study; they integrated properly into the abdominal wall and showed lover recurrence as compared to data shown in the literature.

To the best of our knowledge, no prospective investigation on the use of PDC in patients after OLT exists to date. Although only used for a highly selected high-risk patient group after OLT (immunosuppression, giant hernias with deleterious abdominal wall constitution and the impossibility of direct closure), which might be considered as limitation of the present study, PDC was effective for IH repair, and our results compared favourably with those of patients in whom DC was feasible. Therefore, we conclude that cross-linked PDC meshes are useful in transplanted patients with detrimental abdominal wall structures and should be considered, despite their cost, as closing aids in patients in which direct closure is not feasible to achieve definitive results.

Authorship

GW, TR, DK, and FI: performed the study. HC and DW: wrote the paper and analysed data. HB and MW: collected data. HJM, GW, and DW: designed the study. PK: contributed substantially in editing the revision of the upper mentioned manuscript by contributing to the revised statistical as well as results part.

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