

Title	Beta-D-Glucan Levels With Use of an Anti-adhesion Barrier Film in Pediatric Living Donor Liver Transplantation
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Beta-D-glucan Levels with Use of an Anti-adhesion Barrier Film in Pediatric Living Donor Liver

Transplantation

Abstract

Introduction: Serum beta-D-glucan (BDG) levels may increase with anti-adhesion barrier film (ABF) use during pediatric living donor liver transplantation (LDLT). It may affect detection of fungal infections after LDLT. We evaluate BDG levels after pediatric LDLT.

Methods: Pediatric patients who received an ABF during LDLT were included. Patients who may have had fungal infections prior to LDLT were excluded. One sheet of ABF was placed in the peritoneum during abdominal closure. Serum BDG levels before transplantation and on postoperative days (PODs) 1, 4, 7, 14, 21, and 28 and peritoneal fluid BDG levels on PODs 1 and 7 were measured.

Results: Sixteen patients received an ABF during LDLT. Median age at transplant was 1.9 years (range, 6–11 years). Median body weight was 12.6 kg (range, 6.8–39 kg). Indications for LDLT were biliary atresia (n=10) and other (n=5). Prior to transplantation, the mean serum BDG level was 3.8 pg/mL. Mean Serum BDG levels were 18.1, 38.3, 5.3, 3.8, 3.3, and 3.3 pg/mL on PODs 1, 4, 7, 14, 21, and 28, respectively. Mean peritoneal fluid BDG levels were 485.9 and 240.4 pg/mL on PODs 1 and 7, respectively. No clinical fungal infections were observed.

Conclusions: BDG levels were high in serum and peritoneal fluid after pediatric LDLT. Serum BDG levels normalized after POD 7. Careful interpretation of BDG levels until POD 7 is needed when an ABF has been used.

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Introduction

In most patients who have undergone laparotomy, adhesions are found at the time of subsequent surgery [1]. Anti-adhesion barrier film (ABF) is used to prevent adhesions. ABF can also be applied during pediatric living donor liver transplant (LDLT).

We used Seprafilm® (Genzyme Co., Cambridge, MA, USA), as the ABF. It is an absorbable translucent membrane composed of modified hyaluronic acid and carboxymethylcellulose that forms a physical barrier between adjacent tissues and prevents adhesion. It contains cellulose. Seprafilm® reduced the incidence, extent, and severity of postoperative adhesions safely and effectively in both animal model [2] and randomized clinical studie [3].

Invasive fungal infection is a severe complication in immunocompromised patients, especially patients with end-stage liver disease or after liver transplantation [4]. Beta-D-glucan (BDG) is a widely used marker to screen for and diagnose invasive fungal infections [5]. Serum BDG levels may increase with ABF use, which may affect detection of fungal infections after LDLT. We will report serum and peritoneal fluid BDG levels after pediatric LDLT.

Methods

Among patients who were under 18 years of age at the time of LDLT at our institution, those who received ABF during LDLT were included. Patients who may have had fungal infections prior to LDLT were excluded.

Seprafilm® was used as the ABF. One sheet (186.69m²) of Seprafilm® was placed into the peritoneum prior to abdominal closure. At least 1 drainage tube was placed in the abdomen at the time of closure. Patients were on tacrolimus-based immunosuppression and steroids according to our protocol.

BDG levels in serum and peritoneal fluid were measured with Limulus amoebocyte lysate reagent (Fujifilm Waco Chemicals, Osaka, Japan). Quantification of BDG was based on a kinetic turbidimetric limulus test [6]. Serum BDG levels were measured before transplantation and on postoperative days (PODs) 1, 4, 7, 14, 21, and 28. Peritoneal fluid BDG levels were measured on PODs 1 and 7.

Data were analyzed using the JMP version 11 software package (SAS, Cary, NC, USA). Continuous variables are presented as means with ranges and compared using the Student's t-test. A *P* value less than .05 was considered to be statistically significant.

Results

Existing diseases of patients included biliary atresia (n=10), Alagille syndrome (n=2), fulminant hepatitis (n=1), hepatoblastoma (n=1), progressive familial intrahepatic cholestasis type 2 (n=1),

and ornithine transcarbamylase deficiency (n=1). Median patient age at transplant was 1.9 years (range, .6–11 years). Mean patient body weight was 12.6 kg (range, 6.8–39 kg).

Serum BDG levels were plotted in Fig 1. The mean peak level was 38.3 pg/mL on POD 4.

Serum BDG levels returned to the normal range by POD 7.

The mean peritoneal fluid BDG level on POD 1 was 486 pg/mL (SD 447 pg/mL). The mean level on POD 7 was 240 pg/mL (SD 385 pg/mL). Peritoneal fluid BDG levels were high until POD 7. However, no information about levels after POD 7 was available because the drainage tube was removed.

The size of ABF was median 15cm²/kg (range, 4.8 -28 cm²/kg). it was decreased with patient body weight. The relationship between serum BDG levels on POD 4 and body weight was plotted in Fig 2. The regression line between serum BDG levels and body weight was $Y = -1.86x + 67$. The correlation coefficient was 0.34. Serum BDG levels tended to be higher in lighter patients. No complications related to ABF or clinical invasive fungal infections were observed.

Discussion

Adhesions occur when tissue becomes damaged during surgery. Connective tissue is formed, which eventually results in tissue adhesions. Seprafilm®, an ABF composed of hyaluronic acid and carboxymethylcellulose, is an excellent anti-adhesion material and can be used safely in pediatric LDLT.

Since Becker et al reported the effectiveness of Seprafilm® for preventing abdominal adhesions [3], many clinical studies have evaluated the safety and effectiveness of Seprafilm® for patients undergoing major abdominal surgery [7, 8] and hepatobiliary surgery [9].

Infection remains the principal cause of morbidity and mortality among pediatric patients after LDLT. Although better outcomes have been reported after the introduction of novel antifungals, invasive fungal infections remain an important cause of mortality in patients with liver transplant[10]. Targeted microbiological cultures before administration of antimicrobials are recommended. The use of BDG could be considered if fungal infection is suspected [11].

An elevated serum BDG level is a biochemical marker of invasive fungal infection. However, several other situations also increase serum BDG levels, such as the release of BDG from unmodified cellulose-containing membranes during renal replacement therapy [12, 13]. Seprafilm® contains cellulose, which also may cause false-positive BDG values for invasive fungal infection.

We observed a wide range of serum BDG levels, ranging from peak levels that were nearly undetectable to levels 5-fold above the upper limit of normal. Peritoneal fluid BDG levels were higher than serum BDG levels. Furthermore, we observed a correlation between body weight and BDG levels. The amount of cellulose absorbed into the bloodstream was negatively correlated with body weight because the amount of Seprafilm® per body weight used decreased with body

weight. False positives were more commonly observed in younger patients.

Our data clearly demonstrate that the vast majority of patients have positive serum BDG levels in the first days after ABF administration. After 1 week, serum BDG levels decreased below the cutoff value in all patients. Thus, in the week after ABF administration, serum BDG levels have to be interpreted with caution. While negative results may be interpreted as usual, positive results within 1 week after ABF administration alone should not lead to a diagnosis of fungal infection. Clinicians should be aware of this 1-week interval when BDG levels can be falsely positive after ABF administration.

Conclusions

BDG levels in serum and peritoneal fluid were high after pediatric LDLT. Serum BDG levels normalized after POD 7. Careful interpretation of BDG levels until POD 7 is needed when ABF has been used.

References

1. Menzies, D., Parker, M., Hoare, R., et al., *Small bowel obstruction due to postoperative adhesions: treatment patterns and associated costs in 110 hospital admissions*. Ann R Coll Surg Engl, 2001. **83**(1): p. 40-6.
2. Lim, R., Morrill, J.M., Lynch, R.C., et al., *Practical limitations of bioresorbable membranes in the prevention of intra-abdominal adhesions*. J Gastrointest Surg, 2009.

- 13**(1): p. 35-41; discussion 41-2.
3. Becker, J.M., Dayton, M.T., Fazio, V.W., et al., *Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study.* J Am Coll Surg, 1996. **183**(4): p. 297-306.
 4. Righi, E., *Management of bacterial and fungal infections in end stage liver disease and liver transplantation: Current options and future directions.* World J Gastroenterol, 2018. **24**(38): p. 4311-4329.
 5. Levesque, E., Rizk, F., Noorah, Z., et al., *Detection of (1,3)-beta-d-Glucan for the Diagnosis of Invasive Fungal Infection in Liver Transplant Recipients.* Int J Mol Sci, 2017. **18**(4).
 6. Mori, T., Ikemoto, H., Matsumura, M., et al., *Evaluation of plasma (1-->3)-beta-D-glucan measurement by the kinetic turbidimetric Limulus test, for the clinical diagnosis of mycotic infections.* Eur J Clin Chem Clin Biochem, 1997. **35**(7): p. 553-60.
 7. Tang, C.L., Seow-Choen, F., Fook-Chong, S., et al., *Bioresorbable adhesion barrier facilitates early closure of the defunctioning ileostomy after rectal excision: a prospective, randomized trial.* Dis Colon Rectum, 2003. **46**(9): p. 1200-7.
 8. Diamond, M.P., *Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study.*

- Seprafilm Adhesion Study Group*. Fertil Steril, 1996. **66**(6): p. 904-10.
9. Yu, Y.D., Kim, D.S., Jung, S.W., et al., *Influence of anti-adhesive agent on incidence of bile leakage after liver resection: A prospective cohort study*. Int J Surg, 2016. **31**: p. 40-6.
 10. Husain, S., Tollemar, J., Dominguez, E.A., et al., *Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study*. Transplantation, 2003. **75**(12): p. 2023-9.
 11. Bassetti, M., Marchetti, M., Chakrabarti, A., et al., *A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts*. Intensive Care Med, 2013. **39**(12): p. 2092-106.
 12. Prattes, J., Schneditz, D., Pruller, F., et al., *1,3-ss-d-Glucan testing is highly specific in patients undergoing dialysis treatment*. J Infect, 2017. **74**(1): p. 72-80.
 13. Prattes, J., Schilcher, G., and Krause, R., *Reliability of serum 1,3-beta-D-glucan assay in patients undergoing renal replacement therapy: a review of the literature*. Mycoses, 2015. **58**(1): p. 4-9.