Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Automated low flow pump system for the treatment of refractory ascites: A multi-center safety and efficacy study

Pablo Bellot[1,11], Martin-Walter Welker[2], German Soriano[3,11], Markus von Schaewen[4], Beate Appenrodt[5], Reiner Wiest[6], Steven Whittaker[7], Radin Tzonev[8], Stoyan Handshiev[9], Chris Verslype[10], Christian Moench[2], Stefan Zeuzem[2], Tilman Sauerbruch[5], Carlos Guarner[3,11], Ekart Schott[4], Noel Johnson[7], Assen Petrov[8], Krum Katzarov[9], Frederik Nevens[10], Pedro Zapater[1,11], Jose Such[1,11,12,*]

[1]*Liver Unit, Hospital General Universitario de Alicante and Universidad Miguel Hernández, Elche, Alicante, Spain;* [2]*Klinikum und Fachbereich Medizin, Johann, Wolfgang Goethe-Universitat, Frankfurt, Germany;* [3]*Servicio de Patologia Digestiva, Hospital de la Sta. Creu I St. Pau, Barcelona, Spain;* [4]*Medizinische Klinik, Charité Hospital, Berlin, Germany;* [5]*Medizinische Klinik und Poliklinik I, Universitatsklinik Bonn, Germany;* [6]*Universitatsklinikum Regensburg, Germany;* [7]*Sequana Medical AG, Zürich, Switzerland;* [8]*Clinic of Internal Diseases, Tokuda Hospital, Sofia, Bulgaria;* [9]*Gastroenterology and Hepatology, Military Medical Academy, Sofia, Bulgaria;* [10]*Department of Hepatology, UZ Leuven, Belgium;* [11]*CIBERehd, Instituto de Salud Carlos III, Madrid, Spain;* [12]*Miguel Hernández University, Elche, Alicante, Spain*

See Editorial, pages 850–852

Background & Aims: Refractory ascites (RA) affects 10% of patients with advanced cirrhosis and ascites. Usual therapy includes large volume paracentesis, and in selected patients, a transjugular portosystemic shunt (TIPS). These therapies may be associated with increased morbidity: paracentesis may induce circulatory dysfunction and impair quality of life and TIPS may induce encephalopathy and is associated with increased mortality in patients with severe liver dysfunction. We present the results of a multicenter, non-randomized trial to assess the safety and efficacy of a new automated pump system for treatment of RA.

Methods: Forty patients at 9 centers (February 2010–June 2011) received an implanted pump for the automated removal of ascites from the peritoneal cavity into the bladder, from where it was eliminated through normal urination. Patients were followed-up for 6 months. The primary study outcome was safety. Secondary outcomes included recurrence of tense ascites and pump performance.

Results: Surgical complications occurred early in the study and became less frequent. The pump system removed 90% of the ascites and significantly reduced the median number of large volume paracentesis per month [3.4 (range 1–6) *vs.* 0.2 (range 0–4); p <0.01]. Cirrhosis-related adverse events decreased along follow-up.

Conclusions: The automated pump seems an efficacious tool to move out ascites from the peritoneal cavity to the bladder. Its safety is still moderate, but a broad use in different countries will improve the surgical technique as well as the medical surveillance. A prospective randomized clinical trial *vs.* large volume paracentesis is underway to confirm these preliminary results.

Keywords: Cirrhosis; Ascites; Refractory; Liver; Failure.

Received 20 July 2012; received in revised form 20 December 2012; accepted 20 December 2012; available online 11 January 2013

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2013.01.037.

* Corresponding author. Address: Liver Unit, Hospital General Universitario de Alicante, Av. Pintor Baeza, 12, 03010 Alicante, Spain. Tel.: +34 965 913 928; fax: +34 96 593 83 45.

E-mail address: such_jos@gva.es (J. Such).

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; HE, hepatic encephalopathy; RA, refractory ascites; HRS, hepatorenal syndrome; LVP, large volume paracentesis; AF, ascitic fluid; PPCD, post-paracentesis circulatory dysfunction; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; SAEs, serious adverse events; DSMB, Data Safety Monitoring Board; MELD, Model for End-Stage Liver Disease; NSAIDs, non-steroidal anti-inflammatory drugs.

Introduction

Ascites is a common complication among patients with late-stage liver disease and is the leading reason for hospitalization among patients with cirrhosis [1]. The first-line therapy for ascites includes dietary salt restriction and the use of diuretics [2]. Yearly, up to 10% of patients with cirrhosis and ascites become refractory to diuretic therapy [3] due to intolerance or because maximum dosages are insufficient to remove ascites [3]. The prognosis for these patients is uniformly poor if the underlying disease cannot be treated by liver transplantation. It is estimated that in the EU and US combined more than 100,000 patients will develop RA annually by 2020 [4].

The first-line treatment for patients with RA is large-volume paracentesis (LVP), a procedure where a needle is inserted into the patient's peritoneal cavity to remove the ascitic fluid (AF) [5]. This procedure is easy to perform and safe in most instances. However, complications are not completely absent, may present with delay [6] and be severe enough to compromise the life of patients [7]. LVPs larger than 5 L are usually followed by albumin

Table 1. Baseline clinical demographic data (n = 40).

Age (range)	59 (34-80)
Sex (male/female)	28/12
Etiology of cirrhosis	
Alcohol	17 (43%)
Hepatitis	10 (25%)
NASH	2 (5%)
Criptogenetic	6 (15%)
Other	5 (12%)
Child-Pugh (A/B/C)	0/30/10
MELD score (points)	12.6 ± 4.0
Child-Turcotte-Pugh score (points)	8.5 ± 1.1
INR	1.37 ± 0.26
Serum bilirubin (μmol/L)	31.9 ± 16.8
Serum albumin (g/L)	31.9 ± 5.0
Serum sodium (mEq/L)	136.2 ± 4.8
Serum creatinine (μmol/L)	103.6 ± 31.4
Median number of paracentesis procedures in month prior to implant (25^{th}/75^{th} percentil)	3.38 (2.21/4.81)

infusion to decrease the risk of post-paracentesis circulatory dysfunction (PPCD), a clinical situation that leads to an increased number of hospital admissions and risk of mortality [8]. Further, albumin infusion is costly, especially when considering that most patients with RA need an LVP every two weeks and sometimes more frequently.

In selected patients, a transjugular intrahepatic portosystemic shunt (TIPS) is an alternative to serial LVP [9]. This procedure creates a shunt between portal and suprahepatic veins, thereby reducing portal hypertension and ascites recurrence rate. However, the incidence of new or worsening encephalopathy following TIPS is 20–31% [10,11]. TIPS cannot be applied in some patients with advanced liver disease (mostly Child-Pugh C), congestive heart failure and/or severe pulmonary hypertension, due to an increased risk of mortality, or in patients with portal thrombosis or inadequate anatomy of the portal and hepatic veins.

Both these current therapies have disadvantages that could result in increased morbidity or contraindications that preclude their application. In response to clinical need, an automated approach has been developed to remove ascites from the peritoneal cavity into the urinary bladder where it can be eliminated through normal urination. The aim of the Pioneer Clinical Study here reported was to assess the safety of automated low-flow removal of ascites and to determine whether the requirement for paracentesis could be reduced.

Patients and methods

Between February 2010 and June 2011, forty patients were implanted with the ALFApump system in 4 countries with the following distribution: 9 in Spain (Barcelona 5, Alicante 4), 23 in Germany (Frankfurt 9, Berlin 5, Bonn 5, Regensburg 4), 6 in Bulgaria (Sofia Tokuda 4, Sofia Military 2), and 2 in Leuven; Belgium. The study was approved by the appropriate regulatory agencies and ethics committees for each participating institution and was registered on a public website (www.clinicaltrials.gov, registration number NCT01030185). Written consent was obtained from each patient. All study patients were implanted with the Automated Low-Flow Ascites Pump (ALFApump®) system from Sequana Medical AG, Switzerland.

Patients

Patients with cirrhosis and RA were considered as candidates for implantation of the ALFApump system. Patients were eligible if they had recurrence of ascites within 4 weeks of paracentesis, despite treatment with a maximum of 160 mg/day of furosemide and 400 mg/day of spironolactone (or equivalent doses of loop-acting and distal-acting diuretics), or intolerance related to diuretic-induced complications; expected survival of greater than 6 months; serum creatinine levels $\leqslant$2.0 mg/dl for at least 7 days before study entry; total bilirubin levels $\leqslant$5 mg/dl and minimum 18 years of age. Patients were excluded if they had active systemic or local infections, such as spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), or cellulitis; malignancy, including hepatocellular carcinoma; evidence of extensive ascites loculation; portal hypertension-related gastrointestinal bleeding or hepatic encephalopathy in the two weeks prior to the inclusion in the study; obstructive uropathy or any contraindications for general anesthesia.

The primary outcome of the study was safety, as evaluated by the incidence and severity of device and procedure-related serious adverse events (SAEs). Secondary outcomes included the requirement for paracentesis, pump system function and incidence of hemodynamic derangement. After confirmation of eligibility, the patient's medical history and baseline measurements, which consisted of vital signs, physical examination, review of medications and basic blood chemistry were recorded. Pre-implant medical history and baseline parameters are shown in Tables 1 and 2. Follow-up assessments were performed at weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24. At each follow-up visit, subjects had a history and physical examination performed and a blood test to assess liver and renal function. An independent Data Safety Monitoring Board (DSMB) reviewed all SAEs, and made recommendations that were incorporated into the protocol. Thereafter, patients were divided into two subgroups, termed Cohorts I and II, according to having received the pump before or after recommendations of the DSMB (Table 3).

ALFApump system description and implantation procedure

The ALFApump system is a subcutaneously implanted battery-powered device that moves ascites from the peritoneal cavity into the urinary bladder where it is eliminated through normal urination. It has internal sensors that monitor the pressure in the peritoneal cavity and bladder in order to prevent pump operation when the peritoneal cavity is dry, and pathological bladder distension if the bladder becomes full. The ALFApump activates every 10–15 min and moves 10–30 ml of AF into the bladder depending on the programmed amount. The ALFApump is inactive during night time, to prevent filling the bladder whilst the patient is asleep. The only patient interaction required is to periodically recharge the ALFApump battery wirelessly through the skin, requiring 20–30 min/day.

All implant procedures were performed under general anesthesia. Placement of the ALFApump system (Fig. 1) was by minimally invasive surgical techniques employing three small incisions; 1 cm incision for the bladder catheter, 2 cm incision for the peritoneal catheter and 4 cm incision for the pump. Insertion of the bladder catheter was done using a modified Seldinger technique, placement of the peritoneal catheter was done under visual guidance. All pumps were placed on the right side; catheters were tunneled from the distal incisions to the pump pocket where the pump was anchored using two suture holes. The mean surgical implantation time was 68 (±39) min. All patients received perioperative prophylaxis before and after the surgical procedure with the administration of amoxicillin/clavulanic acid 2 g iv previous to the procedure, which was continued for 2–3 more days according to the physician criteria.

Table 2. Pre-implant cirrhosis-related co-morbidities.

Pre-implant co-morbidity	Number of patients (%)
Oesphageal varices	27 (68)
Diabetes mellitus	19 (48)
History of hepatic encephalopathy	14 (35)
History of renal dysfunction	14 (35)
History of spontaneous bacterial peritonitis	9 (23)
History of gastrointestinal haemorrhage	8 (20)
History of urinary tract infection	5 (13)