Combined treatment of refractory ascites with an alfapump (R) plus hernia repair in the same surgical session: A retrospective, multicentre, European pilot study in cirrhotic patients

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Original Article

Combined treatment of refractory ascites with an alfapump® plus hernia repair in the same surgical session: a retrospective, multicentre, European pilot study in cirrhotic patients.

Short title: alfapump® for cirrhotic refractory ascites plus hernia repair

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Abstract

Introduction: The treatment of symptomatic hernia in cirrhotic patients with refractory ascites is critical but challenging. The objective of this study was to assess the feasibility and safety of the implantation of alfapump® combined with concomitant hernia repair in cirrhotic patients with refractory ascites.

Methods: Using data from six European centres, we retrospectively compared patients treated with alfapump® system implantation and concomitant hernia repair (the combined treatment group (CT group, n=12)) or with intermittent paracentesis hernia repair (the standard treatment group (ST group, n=26)). Some patients of the ST group had hernia repair in an elective setting (STel group) and others in emergency (STem group). The

endpoints were requirement of peritoneal drainage, the rate of infectious complications, the in-hospital mortality, the length of stay, paracentesis-free survival.

Results: Post operatively, none of the patients in the CT group and 21 patients (80 %) in the ST group underwent peritoneal drainage for the evacuation of ascites fluid ($p<0.0001$). The overall incidence of infectious complications was not different between groups but there were fewer infections in the CT group than in the STem group (33% vs 81%; $p=0.01$). There was no difference for in-hospital mortality. The length of stay was shorter in the CT group ($p=0.03$). Paracentesis-free survival was significantly better ($p=0.0003$) in the CT group than in the ST group.

Conclusion: Implantation of alfapump combined with concomitant hernia repair seems feasible and safe in cirrhotic patients however some adverse events must be known.

Keys words: refractory ascites; alfapomp; hernia

INTRODUCTION

Ascites is the most frequent complication of cirrhosis, and has a two-year mortality rate of 50% [1]. The condition becomes refractory to treatment in 10% of patients [2], for whom the median survival time is 6 months [3-5]. Twenty percent of cirrhotic patients with refractory ascites develop a hernia, 10 times more than in the general population [6]. The resulting chronic increase in intra-abdominal pressure, portal hypertension and malnutrition lead to an elevated frequency of umbilical and inguinal hernias [6-9].

Surgical treatment of an asymptomatic hernia remains a difficult situation and surgery is avoided whenever possible, due to the elevated associated mortality and morbidity rates, which can be as high as 8.3% and 21% respectively in cirrhotic patients with ascites [10-12]. However, the morbidity and mortality rates associated with the emergency treatment of a complicated hernia (mainly for rupture or strangulation or ulceration) and the risk of severe complications in the absence of treatment have prompted physicians to perform elective treatment in patients with maintained hepatocellular function and controlled ascites [11, 13-16] as the morbidity rate associated with elective surgery (about 15%) is similar in compensated cirrhotic patients and non-cirrhotic patients [14]. Moreover, for patients on a liver transplant waiting list, it is preferable to perform surgical repair at the same time as transplantation [17, 18].

Control of ascites before and after surgical hernia repair is essential, in order to avoid ascites fluid leakage and tension on the scar wall and promote wound healing [14, 16]. To this end, a peritoneal drain is often left in place for a few days. In the long term, the risk of hernia recurrence is 45% for poorly controlled ascites and 4% for controlled ascites [10]. Although repeat paracentesis is currently the first-line treatment for refractory ascites, this approach can lead to severe complications, such as haemorrhage (in 1%), perforation of the small intestine (0.4%) or fragmentation of the catheter in the abdominal wall (0.2%) [19, 20]. Decreasing the portal vein pressure with a surgical portosystemic or peritoneovenous shunt has been recommended as a means of controlling ascites and thus facilitating surgical hernia repair. Although these shunts are effective for refractory ascites, their use has been limited by numerous complications. Similarly, a transjugular intrahepatic portosystemic shunt (TIPS) can be envisaged in a select subset of patients [21].

An automated low flow pump system (alfapump®, Sequana Medical AG, Zürich, Switzerland) is an innovative medical device that drains the ascites fluid into the urinary bladder at a low flow rate, thus avoiding the sudden hemodynamic changes associated with paracentesis. It has been evaluated in studies without hernia repair during the same procedure [22, 23].

The objective of this retrospective, multicentre, European pilot study was to compare the combined, concomitant treatment of refractory ascites with alfapump® and surgical repair of an hernia to a group of cirrhotic patients with refractory ascites and having undergone repair of a complicated or symptomatic hernia.

Patients and Methods

Population and inclusion criteria

Two groups of patients with cirrhotic refractory ascites were retrospectively studied between January 2008 and February 2017. Patients were attending one of four university or general hospitals in France (Amiens, Clichy, Compiegne, and Saint-Quentin) or two in Switzerland (Geneva and Bern). The first group of patients was the group of patients with a combined treatment (alfapump® and the repair of a symptomatic or complicated umbilical or inguinal hernia in the same surgical session) (i.e Combined Treatment group) (CT group). The second group of patients was the group of patients with a ST (symptomatic or complicated hernia repair without alfapump® insertion during hernia repair procedure) (ST group). In the CT group, all patients were managed in an elective situation. In the ST group, patients were managed in an elective situation (STel group) or in emergency (Stem group).

The non-inclusion criteria were age under 18, a time interval between implantation of the alfapump® and the hernia repair, an asymptomatic hernia, non-refractory ascites, loculated ascites and the use of other techniques for the treatment of refractory ascites (a TIPS, the PleurX device, or a peritoneo-venous shunt).

Endpoints

The endpoints were:

- **short term outcomes:** length of the procedure, requirement of surgical peritoneal drainage; the rate of infectious complications, the rate of local complications related to hernia repair, the in-hospital mortality and the length of stay.

- **long-term outcomes**: hernia recurrence rate, renal status, evaluation of mortality, requirement of paracenteses.

- complications related specifically to the insertion of the pump

A comparison was performed between the overall population of both group and a subgroup analysis was performed to compare the CT group to patients managed electively or in emergency in the ST group.

Diagnosis of cirrhosis

Cirrhosis was diagnosed on the basis of a set of clinical, biochemical, radiographic, endoscopic and histological datasets and/or the results of non-invasive assessments (the Fibroscan or Fibrotest). Refractory ascites was defined as ascites that could not be mobilized by a low-sodium diet or optimal diuretic treatment (400 mg/day spironolactone plus 160 mg/day furosemide) or cases of diuretic-associated complications [24].

Treatment protocols

In the CT group, the implantation of an alfapump® was indicated in cases of refractory ascites for which a TIPS was contra-indicated (i.e. hepatic encephalopathy, heart failure and portal thrombosis). The alfapump® was contra-indicated in cases of (i) poorly controlled spontaneous bacterial peritonitis or systemic infections, (ii) severe portal hypertension with large oesophageal varices, (iii) kidney failure, (iv) severe malnutrition, and (v) bladder or prostate diseases with dysuria. The alfapump® was implanted during an elective, scheduled surgical session as recently published **(figure1)** [25]. On the day before implantation, each patient was admitted to hospital and underwent paracentesis - although the abdominal cavity was not totally emptied and diuretics and any potentially nephrotoxic drugs were withdrawn. Long-term antibiotic prophylaxis (with norfloxacin) was initiated. On the next day, the alfapump® was implanted, by digestive surgeon under general anaesthesia, in the abdominal wall, along with its peritoneal catheter and its tunnelled subcutaneous catheter leading to the bladder. In this same operative time, elective hernia repair was performed. It consisted of reduction of the hernia (after checking for vitality), removal of the herniated sac, and omphalectomy. If the small intestine was trapped in the hernia orifice or the segment was necrotic, segmental resection (and, in some cases, anastomosis) was performed. The surgeon was free to decide mesh associated, and whether or not drainage was required. In the first few days after implantation and hernia repair, each patient was taught how to charge the alfapump® daily. The hepatologist team in each centre was responsible for clinical follow-up and adjustment of the alfapump®'s flow rate.

In the ST group, the paracentesis were performed as needed, at a mean of 2 to 3 times a month. The removal of five or more litres of ascites fluid by paracentesis was compensated by albumin perfusion (8 g per litre removed). A low-sodium diet and diuretics were allowed, depending on the patient's renal status.

Data collection

Data were collected retrospectively. The day of inclusion (D0) was defined as the day of surgery (i.e. combined alfapump® implantation and hernia repair) in the CT group, and the day of hernia repair in the ST group. The follow-up period was 6 months in the two groups. The total length of stay in hospital (in days) for each patient was noted.

The clinical parameters collected at inclusion were as follows: age (years), gender, height (cm), weight (kg), body mass index (kg/m^2), alcohol intake (g/L), the aetiology of cirrhosis, the history of ascites (frequency of paracentesis, volume per paracentesis, and use of diuretics), complications of cirrhosis (such as hepatic encephalopathy, hepatocellular carcinoma, portal thrombosis, rupture of oesophageal varices, hydrothorax, spontaneous bacterial peritonitis, previous urinary tract or lung infections, and bacteraemia). The following surgical parameters were recorded: emergency or elective status, the indication for hernia repair (rupture of a strangulated hernia, symptomatic hernia, trophic disorders, etc.), the requirement for intraperitoneal drainage, and the latter's duration (in days) if applicable. The patient's clinical biochemistry parameters prior to surgery and then after surgery (weekly for the first month, and then monthly until the end of the 6-month follow-up period) were recorded: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transferase (GGT), alkaline phosphatases, total bilirubin, conjugated bilirubin, prothrombin time level (PT), the international normalized ratio (INR), the platelet count, albuminaemia, the leukocyte count, haemoglobin, the C-reactive protein and creatinine levels. The severity of cirrhosis was evaluated using the Child-Pugh and Model of End-Stage Liver Disease (MELD) scores.

Complications related to cirrhosis were noted: spontaneous bacterial peritonitis, urinary tract and/or blood infections, hepatic encephalopathy, liver failure, hepatocellular carcinoma, acute kidney injury (AKI). The latter was defined according to the International Club of Ascites's latest criteria; AKI stage 1: an increase in serum creatinine 1.5-1.9 times from baseline within 7 days or ≥ 26.5 µmol/l within 48 hours; AKI stage 2: an increase 2.0-2.9 times from baseline; AKI stage 3: an increase 3.0 times from baseline or ≥ 353.6 µmol/l, or the initiation of renal replacement therapy [26]. Complications related to implantation of the alfapump® (site infection, operating failure, malfunction, blockage, catheter fragmentation, etc.) and complications of hernia repair (surgical site infections, local

hematoma, hernia recurrence, effusion of ascites fluid through the wound, etc.) were also noted. We noted the date of the first paracentesis after surgery or after removal of the peritoneal drainage. Lastly, the date and the cause of death were extracted from deceased patients' medical records.

Statistical analysis

Quantitative variables were expressed as the mean ± standard deviation (SD) or the median (range) and then compared using Student's t-test or a Mann-Whitney test. Qualitative variables were expressed as the number (percentage) and then compared using a chi-squared test or (for small samples) Fisher's exact test. The curves for overall survival and paracentesis-free survival were plotted and compared using a log-rank test. The threshold for statistical significance was set to $p<0.05$. The statistical analysis was performed using the BiostaTGV application in R software (https://marne.u707.jussieu.fr/biostatgv/).

All patients gave their verbal, informed consent for this retrospective study, and patients having received an alfapump® additionally gave their written, informed consent. The study was performed in accordance with the tenets of the Declaration of Helsinki and good clinical practice.

RESULTS

Population

In the CT group there were 12 patients from the investigating centres in Amiens (France; n=2), Bern (Switzerland; n=3), Clichy (France; n=1), and Geneva (Switzerland; n=6). In the ST group there were 26 patients from Amiens (n=13), Geneva (n=1), Compiegne (France; n=11) and Saint-Quentin, France (n=1) (Figure 2).

Baseline characteristics of the study population

The study population's clinical and biochemical characteristics are summarized in Table 1. The proportion of patients with viral cirrhosis was higher in the CT group than in the ST group (p=0.02). The two groups did not differ significantly with regard to age, the Child-Pugh or MELD severity scores, the type of hernia, the paracentesis variables or the length of follow-up.

All the patients in the CT group underwent elective surgery for a symptomatic but non-complicated umbilical or inguinal hernia, whereas 16 patients (61%) in the ST group had undergone emergency surgery (Stem group) ($p<0.05$). The indications in both groups were summarized in **table 1**. In two patients having undergone emergency surgery for a strangulated hernia, small intestine ischemia necessitated a segmental bowel resection.

Endpoints

Short-term outcomes

Requirement of surgical peritoneal drainage

During the post-operative period, none of the patients in the CT group underwent peritoneal drainage for the evacuation of ascites fluid vs 21 patients (80 %) in the ST group ($p<0.0001$). In the ST group, the mean duration of peritoneal drainage was 11.7 ± 7.6 days (median (range): 10 (1-28)).

The rate of infectious complications

The overall incidence of infectious complications was 33% (4 out of 12 patients) in the CT group vs. 57% (15 out of 26 patients) in the ST group (p=0.29). There was no difference between the two groups with regard to the type of infection (Table 2). When comparing the CT group with the STel group (n=10), there was no significant difference in the incidence of infectious complications (33% and 20%, respectively; p=0.6). There were fewer infections in the CT group than in the Stem group (33%, 4 out of 12, and 81%, 13 out of 16, respectively; p=0.01).

The rate of local complications related to hernia repair

None of the patients in the CT group and 8 of the 26 patients (30%) in the ST group presented local complications related to the hernia repair (p=0.03). When comparing the CT group with the Stem (n=16), the incidence of local complications was respectively 0% (0 out of 12) and 37% (6 out of 16; p=0.02). The following complications were observed in the ST group: 2 cases of wound dehiscence (7%), 1 case of leakage of ascites fluid through the wound (3%), 4 cases with a local abscess (15%), and 3 cases with local hematoma (11%).

In-hospital mortality

No patients dying in the CT group. In the ST group, one of the 26 patients (4%) dying. This patient was treated for a strangulated hernia with small intestine resection dying as a result of stomal bleeding.

The length of stay

The mean ± SD length of stay was 12.8 ± 11 days (median (range): 6.5 (3-76)) in the CT group and 20 ± 12 days (median (range): 15.5 (2-114)) in the ST group (p=0.03). In the ST group, the mean length of stay in the subsets of patients having undergone emergency and elective surgery was respectively 27 days (median (range): 21.5 (8-114)) and 8.1 days (median (range): 7 (4-25)) (p=0.03).

Long-term outcomes

Hernia recurrence rate

Hernia recurrence affected one patient (8%) in the CT group and 4 patients (15%) in the ST group (p=1); a ruptured hernia recurred in one of the latter patients.

Renal status

With regard to renal status, 11 of the 12 patients in the CT group (91%) and 23 of the 26 patients in the ST group (88%; p=1) developed AKI (Table 3). For the 11 patients in the CT group with AKI, 2 patients were put on dialysis, and renal function was normalized in 5 patients and stabilized in another 5. Five patients (41%) in the CT group presented with AKI stage III, including 2 with chronic kidney failure prior to implantation of the alfapump®.

Requirement for paracenteses

At 6 months, In the CT group, 8 patients (66%) had undergone paracentesis at least once whereas in the ST group all 26 patients (100%) had undergone paracentesis at least once (p=0.006; odds ratio [95% confidence interval] = Inf [1.68-Inf]). Paracentesis-free survival was significantly better (p=0.0003) in the CT group than in the ST group (Figure 3).

Evaluation of mortality

The survival curves for the two groups of patients did not differ significantly at 6 months (Figure 4), p=0.1. There was no significant difference between the CT and ST treatments groups with regard to in-hospital mortality (0 out of 12 (0%) vs. 5 out of 26 (19%), respectively; p=0.15) or mortality at 1 month (0 out of 12 (0%) vs. 4 out of 26 (15%), respectively; p=0.2), 3 months (0 out of 12 (0%) vs. 4 out of 26 (15%), respectively; p=0.2) and 6 months (1 out of 12 (8%) vs. 9 out of 26 (34%), respectively; p=0.12). When comparing the CT group (n=12) with the subset of patients in the ST group having undergone emergency surgery (n=16), the mortality rate was 1 out of 12 (8%) and 8 out of 16 (50%), respectively (p=0.03) (Table 4).

The causes of death in the ST group were rupture of oesophageal varices in one case (11%), acute-on-chronic liver failure in 3 cases (33%), intracerebral haemorrhage in 1 case (11%), stomal bleeding in 1 case (11%), and acute kidney failure in 1 case (11%). The cause could not be determined in 2 cases (22%). In the CT group, the cause of death was rupture of oesophageal varices.

Complications during the follow-up period related to the pump insertion

The complications related specifically to implantation of the alfapump® included 2 cases of infection of the device associated with concomitant bacterial peritonitis, 6 cases of malfunction or intermittent blockage (i.e. the alfapump was obstructed by debris or the omentum), and 1 case in which the device had to be replaced. Three alfapump® devices (25%) were removed as a result of a liver transplant (in two cases) or an antibiotic-refractory infection of the device (in one case). In a fourth patient, the alfapump® failed and had to be replaced. Three patients (25%) reported abdominal pain (due to infection of the alfapump® in two cases and spontaneous bacterial peritonitis in the other case).

DISCUSSION

This is the first series that reported a combined treatment of refractory ascites and hernia repair showing the feasibility of this procedure.

Indeed, in the present study, we found that the need for evacuation of ascites fluid was significantly lower in the CT group than in the ST group (80% vs 0%, p<0.0001), this was not associated with a difference of risk of infectious complications but led to a significant reduction of long-term paracentesis and thus a better paracentesis-free survival in the CT group.

The mean prevalence of hernia in cirrhotic patients is 20% but it may be as high as 40% in patients with refractory ascites [6]. Indeed, refractory ascites is a real challenge for the surgical treatment of abdominal wall defects in cirrhotic patients. Inadequate ascites control increases the post-operative complication rate and the hernia recurrence rate, which may be as high as 73% [6, 27]. After surgery, poorly controlled ascites is an independent risk factor for hernia recurrence; an OR [95%CI] of 8.51 [2.69-26.9] was determined in a meta-analysis [10].

The timing of hernia repair in the cirrhotic patient (elective repair vs. emergency repair), the use of Mesh and the laparoscopic approach have all been widely debated over the last few years. The “wait and see” attitude (with an underlying increase in morbidity and mortality due to refractory ascites [6]) must be weighed against more recent data showing that elective abdominal wall surgery in the cirrhotic patient with ascites can indeed be performed before the hernia becomes complicated [28]. However, most literature studies of hernia repair in cirrhotic patients are retrospective and have small sample sizes; this is why guidelines with a high supporting level of evidence are very limited [10].

Conventional management of cirrhotic refractory ascites is based on repeated paracentesis, TIPS placement or liver transplant. More recently, the PleurX [29] and alfapump® devices have been developed [30]. In a context of hernia repair in patients with refractory ascites, ascites can be better controlled by the implementation of peritoneal drainage after surgery [31], the use of peritoneo-venous shunting, or the pre or post-operative implantation of a TIPS [32], however, there is no consensus on the optimal approach. The alfapump® is a programmable, rechargeable, implantable device for low-flow drainage of ascites fluid from the peritoneal cavity to the urinary bladder. It was specifically developed for the management of refractory ascites. The feasibility, efficacy and safety results of a pilot clinical study of 40 patients were published [30]. It has also been described an implantation by interventional radiologists with neither general anaesthesia nor surgery [33]. Complications such as catheter blockage and infections of the ascites fluid, the urinary tract or the device itself were initially reported. However, these complications became less frequent after the systematic implementation of long-term antibiotic prophylaxis. The recent data from the

multicentre, randomized controlled trial confirmed that the alfapump® was associate with a significant reduction in the requirement for paracentesis, better paracentesis-free survival, and better quality of life but also a greater incidence of at least one serious adverse events especially acute kidney failure and nervous system disorders [23, 34]. These adverse events must be known by the clinician. The information must be given to the patient and balanced with the outcomes of other techniques. In this randomised control trial, no patients had a hernia repair during the same procedure than alfapump® implantation.

The objective of the present multicentre, retrospective pilot study was to evaluate the putative benefit of combining elective abdominal hernia repair with refractory ascites control via alfapump® implantation during the same surgical session. We constituted a CT group and a ST group, which were similar with regard to the proportion of patients with alcoholic cirrhosis, age, and severity of cirrhosis. However, the groups were not balanced with regard to the indication for surgery (elective for 100% of the patients in the CT group but for 38% of those in the ST group). Although we built the control (standard treatment) group by using data bases screening technique, we found relatively few refractory ascites patients having undergone elective hernia repair. This is related to the reluctance of anaesthetists and surgeons to operate on patients with severe cirrhosis (with a score of MELD ≥14 and a Child C score [35]) and poorly controlled ascites[10]. However it is a major bias in the analysis of the results as morbidity cannot be strictly compared between groups.

The mean length of stay in the CT group (12.8 days) was significantly shorter than in the ST group (20 days, with medians of 6.5 and 15.5 days, respectively). This difference can be explained by the absence of post-operative peritoneal drainage, fewer infectious complications, fewer hernia-related post-operative complications and no emergency procedures in the CT group. We observed a greater difference between the mean and median lengths of stay in the CT group, suggesting the presence of greater heterogeneity than in the standard treatment. The mean length of stay in the two groups was similar to the literature data. In a study of ten refractory ascites patient having received an alfapump®, the mean length of stay was 11 days [36]. The median length of stay of the cirrhotic patients with elective hernia repair varied from 3 to 5 days [13, 35], whereas the patients having undergone emergency surgery were hospitalized for longer (between 5 and 14 days)[15, 28].

Our study results revealed a statistically significant advantage for the alfapump® with regard to the requirement (or not) for paracentesis in 6 months after surgery. Thirty-three percent of the patients in the CT group no longer required paracenteses, whereas all the patients in the ST group underwent at least one paracentesis. In the preliminary study of 40 patients with an implanted alfapump®, 40% of the patients no longer required paracenteses. Furthermore, the number of paracenteses per

month fell from 3.4 before alfapump® implantation to 0.24 paracenteses after implantation [30]. A second study confirmed this result, and showed a fall in the number of paracenteses per month from 3.36 paracenteses before alfapump® implantation to 0.45 after the implantation[36]. Lastly, in the randomized trial, the mean number of paracenteses over 6 months was 1.1 for patients with an implanted alfapump® and 8.6 in a group of patients without an alfapump® [23]. The same results are reported in a post marketing registry [37]. Lastly, it is important to note the absence of a requirement for immediate post-operative peritoneal drainage in the CT group studied here in the period, which thereby eliminates the risk of secondary infections and haematoma.

In the three literature studies, kidney failure after implantation of alfapump® occurred in 27.5%, 50% and 51% of cases [23, 30, 36]. A study by Solà et al. specifically assessing renal function after alfapump insertion in ten patients also found that treatment with alfapump system was associated with impairment of renal function [38]. In the present study, we have observed higher but similar frequencies of kidney failure (91% and 88% in the CT and ST groups respectively). In the CT group, 16% of the patients with AKI were dialysed, renal function was stabilized in 16% and normalized in 66% after albumin perfusion and volume expansion. It should be noted that the evaluation of renal complications included selection bias because some centres implanted an alfapump® in patients with pre-existing chronic kidney failure. Lastly, we used the International Club of Ascites' criteria for AKI, which are more sensitive for the detection of kidney failure in cirrhotic patients (relative to a creatinine threshold of 133 µmol/l [26]).

Local/regional post-operative complications related to hernia repair were significantly more frequent in the ST group (30%) than in the CT group (0%). Controlling ascites through continuous drainage by the alfapump® promoted good skin healing and helped to avoid leakage of ascites through the wound, early dehiscence, and long-term recurrence. However, this advantage was not significant for patients in the ST group having undergone elective surgery. The alfapump®'s impact on local/regional complications may be similar to that of a TIPS. In a cohort of 21 patients having undergone surgery for a complicated hernia (including 8 cases with prior or subsequent TIPS implantation), the incidence of wound healing complications was 17% in the TIPS group and 27% in the non-TIPS group. Hence, TIPS placement did not influence the mid- or long-term mortality but appeared to decrease the occurrence of wound healing complications [32]. However, a TIPS is not applicable in all patients - heart failure, severe hepatocellular insufficiency, portal thrombosis and hepatocellular carcinoma are contraindications - and the surgical procedure is performed separately from hernia repair (i.e. two sessions of general anaesthesia, compared with just one for alfapump® implantation in the CT protocol). The infectious complication rates were similar in both groups

studied here, although the rate was lower in the CT group than in the subset of patients in the ST group having undergone emergency surgery.

Complications related to implantation or operation of the alfapump® (infections, malfunction or blockage) affected 58% of the patients in our CT group (vs. 52% in the randomized trial [23]). CT does not appear to increase the frequency of alfapump®-related complications. Three alfapumps® (25%) had to be removed due to liver transplant (in 2 cases) and infection of the device (1 case). In the original study, 13 of the 40 alfapumps® (32%) were removed due to non-controlled infections (7 cases), catheter disconnection (3 cases), wound dehiscence (1 case), and withdrawal of consent (2 cases)[30]. In another study of 10 patients, five alfapump® (50%) were removed, due to death (3 patients), liver transplant (1 patient) and device failure (1 patient) [36]. Lastly, in the randomized trial, 3 alfapumps® (11%) were removed due to non-controlled infections (2 cases) and dehiscence (1 case) [23]. Even though a case of sclerosing peritonitis has been reported [30], alfapump® implantation is not a contraindication for liver transplant. Recently, complications and outcomes after alfapump® implantation have been shown to decrease after technical modifications (especially concerning catheter) [39].

The 6-month mortality rate was higher in the ST group than in the CT group (34% vs. 8%, respectively), although the difference was not statistically significant. In fact, the difference was statistically significant only when patients having undergone emergency surgery were considered. This result is not surprising because it has already been shown that patients having undergone emergency surgery have higher mortality and post-operative complication rates than electively operated patients. A literature review of 16 retrospective studies in cirrhotic patients with refractory ascites and an hernia reported a mortality rate of 2.7% and a morbidity rate of 21% [10]. This encouraging result must be interpreted with caution because the numbers of patients having undergoing emergency vs. elective surgery were not reported. Hence, we cannot conclude that alfapump® implantation influenced the mortality or morbidity rates and the adverses events at implantation are pitfalls that should be address by a radnomised control trial comparing hernia repair with or without alfapump. In the same study, the hernia recurrence rate was 44% for non-controlled ascites and 4% for controlled ascites, as assessed over a follow-up period ranging from 6 to 24 months [10]. In the present study, a hernia recurred in only one of the 12 patients (8%) in the CT group (vs. 4 patients (15%) in the ST group), after median follow-up periods of 5 and 4 months, respectively.

Our study had several limitations. It was a non-randomized, retrospective study, with a small sample size and a lack of statistical power - particularly for patients in the ST group having undergone

elective hernia repair. A study comparing the alfapump® with repeated paracentesis or a TIPS in electively operated patients is required.

In conclusion, the present pilot study established the feasibility of simultaneous treatment of the cirrhotic refractory ascites with an alfapump®, enabling the elective hernia repair. This combination is associated with a shorter mean length of stay, and provides effective ascites control. It is associated with fewer local/regional complications, fewer infections, and better survival, relative to ST(i.e. repeated paracentesis and emergency surgery). However, the advantages over ST with elective hernia repair have yet to be established. The value of this combination treatment (particularly with regard to both elective hernia repair and a TIPS) should now be investigated in a randomized trial.

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Table 1: Baseline characteristics of the participants in each of the two study groups

	Combined treatment group (alfapump® plus surgery) (n=12)	**Standard treatment group (paracentesis plus surgery)** (n=26)	p
Female sex, n (%)	5 (41%)	3 (11%)	0.08
Age (years) mean (range)	56 (44-68)	58 (34-84)	0.4
Body mass index (kg/m^2)	24.4 ± 3.7	24 ± 3	0.9
Aetiology of cirrhosis			
Alcohol, n (%)	8 (66%)	22 (84%)	0.2
NASH, n (%)	0 (0%)	3 (11%)	0.5
Viral infection, n (%)	3 (25%)	0 (0%)	0.02
Autoimmune hepatitis, n (%)	1 (8%)	1 (3%)	0.5
Severity scores			
Prothrombin time (%) PT, mean ± SD	63 ± 10	60 ± 12	0.09
Creatinine (µmol/L), mean ± SD	88 ± 42	89 ± 55	0.9
Total bilirubin (µmol/L), mean ± SD	47 ± 45	36 ± 25	0.4
Kidney failure, n (%)	3 (25%)	7 (26%)	1
Child-Pugh score, mean ± SD	9 ± 1.02	9 ± 1.6	0.3
Child-Pugh A/B/C, n	0/9/3	0/18/8	1
MELD score, mean ± SD	14 ± 4.3	13 ± 6.1	0.7
Hepatocarcinoma, n (%)	2 (16%)	6 (23%)	1
Oesophageal varices, n (%)	12 (100%)	23 (88%)	0.5
Variceal ligation, n (%)	6 (50%)	5 (19%)	0.06
Portal vein thrombosis, n (%)	1 (8%)	4 (15%)	1
Infections before surgery n (%)			
Urinary tract, n (%)	2 (16%)	1 (3%)	0.2
Spontaneous bacterial peritonitis, n (%)	6 (50%)	6 (23%)	0.1
Bacteraemia, n (%)	0 (0%)	1 (3%)	1
History of paracentesis			
Paracenteses per month, (n) mean ± SD	2.9 ± 1.5	2.19 ± 0.9	0.14
Duration of repeated paracentesis (years), mean ± SD	1.25 ± 0.5	1.35 ± 0.8	0.6
Ascites volume per paracentesis (L), mean ± SD	6.08 ± 2.3	6.26 ± 2.3	0.8
Type of hernia			
Umbilical, n (%)	10 (83%)	25 (96%)	0.2
Inguinal, n (%)	2 (16%)	1 (3%)	0.2
Nature of the intervention			
Emergency, n (%)	0 (0%)	16 (61%)	0.0002
Elective (scheduled), n (%)	12 (100%)	10 (38%)	0.0002
Indications for surgery (hernia repair)			
Trophic skin changes, n (%)	2 (16%)	10 (38%)	0.2
Symptomatic hernia, n (%)	10 (83%)	1 (3%)	0.0001
Ruptured umbilical hernia, n (%)	0 (0%)	10 (38%)	0.01
Strangulated umbilical hernia, n (%)	0 (0%)	5 (19%)	0.1
Mean length of follow-up (months), mean ± SD	5.04 ± 1.2	4.6 ± 1.6	0.5
Length of the procedure (min)	75 ± 5	55 ± 3	0.04

Table 2: Follow-up of infectious complications in both groups

	Combined treatment group (alfapump® plus surgery) (n=12)	**Standard treatment group (paracentesis plus surgery) (n=26)**	**P**
All infections, n (%)	4 (33%)	15 (57%)	0.29
Urinary tract infection	0 (0%)	2 (7%)	1
Spontaneous bacterial peritonitis	4 (33%)	12 (46%)	0.5
Local infection (abscess)	0 (0%)	4 (15%)	0.2
Bacteraemia	2 (16%)	4 (15%)	1
Fever	1 (8%)	3 (11%)	1

Table 3: Acute kidney injury (AKI) during follow-up in both groups

Acute kidney injury stage, n (%)	**Combined treatment group (alfapump® plus surgery)** (n=12)	**Standard treatment group (paracentesis plus surgery)** (n=26)	p
AKI ≥ I	11 (91%)	23 (88%)	1
AKI I	3 (25%)	15 (57%)	0.08
AKI II	3 (25%)	5 (19%)	0.6
AKI III	5 (41%)	3 (11%)	0.08
Hepatorenal syndrome	0	2 (7%)	1
Renal replacement therapy	2 (16%)	0 (0%)	0.09

Table 4: Mortality in both groups

Mortality	**Combined treatment group (alfapump® plus surgery)** (n=12)	**Standard treatment group (paracentesis plus surgery)** (n=26)	p
1 month	0/12	4/26 (15%)	0.2
3 months	0/12	4/26 (15%)	0.2
6 months	1/12 (8%)	9/26 (34%)	0.12
In-hospital	0/12	5/26 (19%)	0.15
	(alfapump® plus surgery) (n=12)	**(paracentesis plus surgery)** (emergency surgery, n=16)	
1 month	0/12	4/16 (25%)	0.1
3 months	0/12	4/16 (25%)	0.1
6 months	1/12 (8%)	8/16 (50%)	0.03
In-hospital	0/12	5/16 (31%)	0.05

Legend of the figures

Figure 1: Peroperative vues for pump insertion : upper line (from left to right) bladder catheter and peritoneal catheter insertion, pump pocket creation. Lower line : before and after hernia repair.

Figure 2: Flow chart

Figure 3: 6-months paracentesis-free survival in the combined treatment group and the standard treatment group

Figure 4: 6-month survival in the combined treatment group and the standard treatment group

Figure 1:

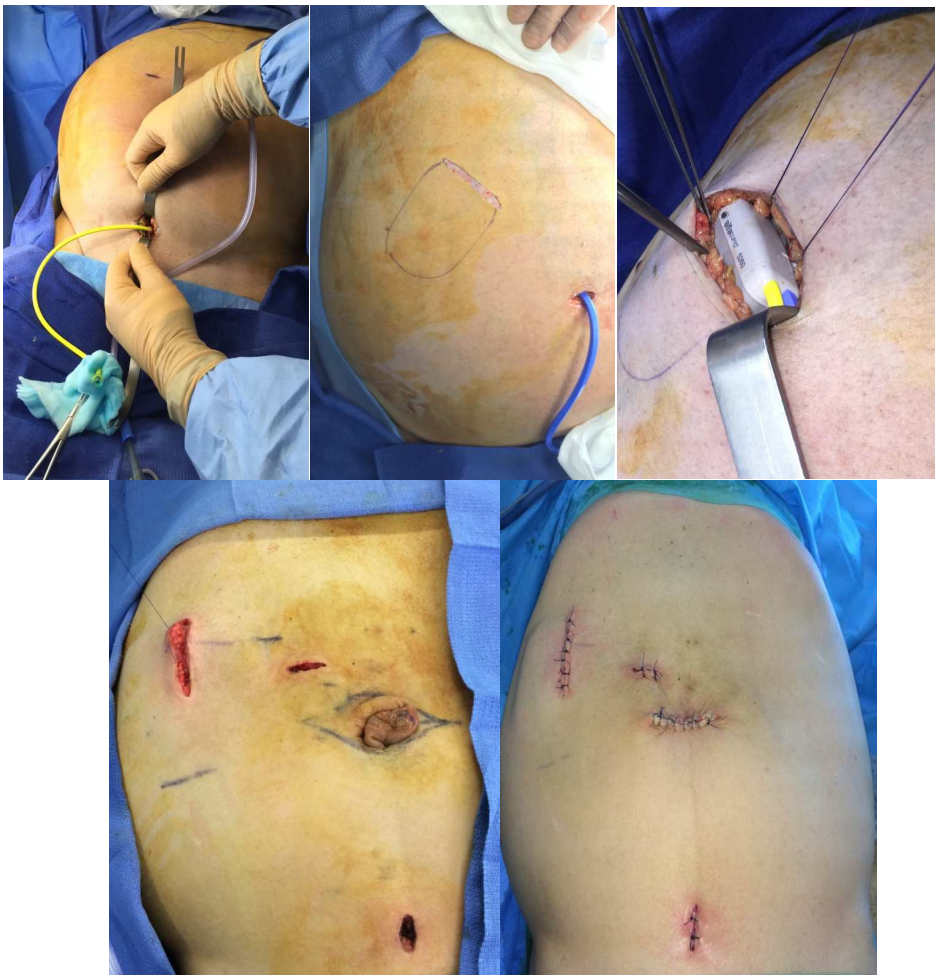

Figure 2: Flow chart

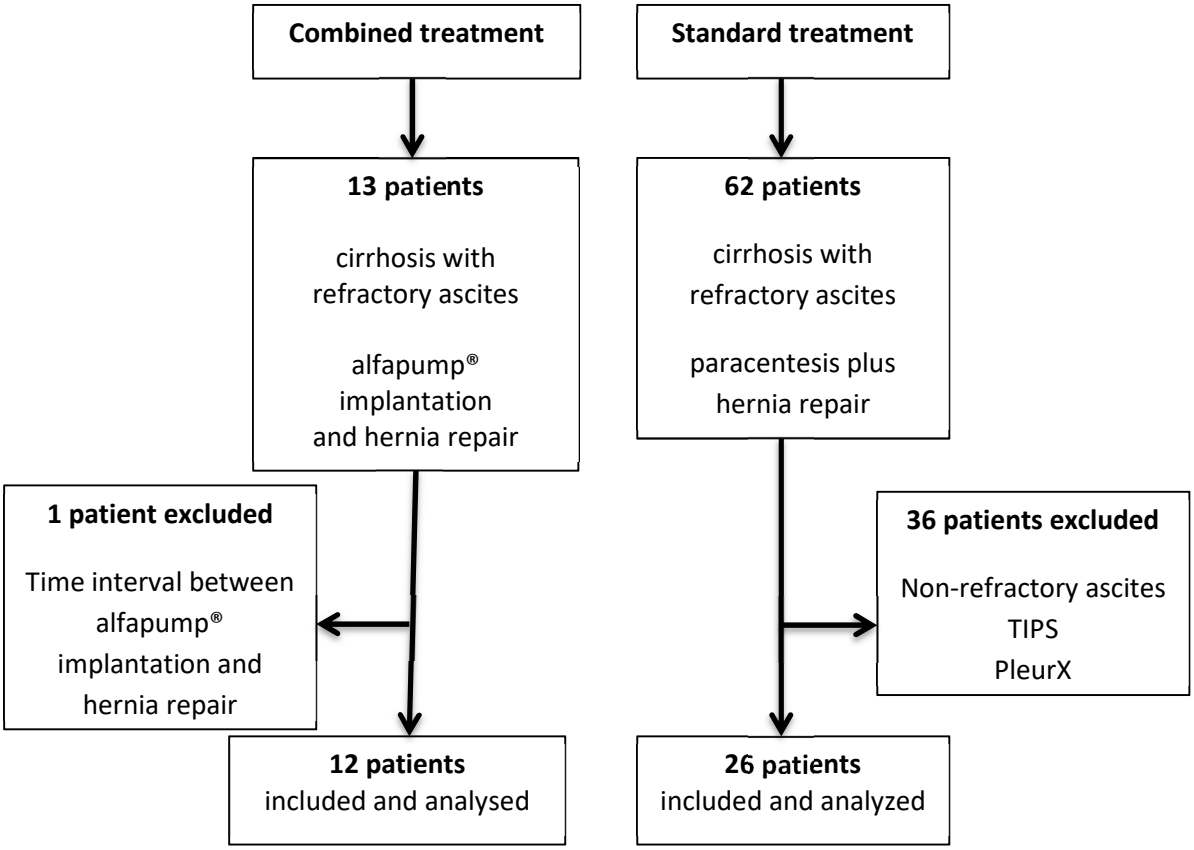

Figure 3: 6-months paracentesis-free survival in the combined treatment group and the standard treatment group

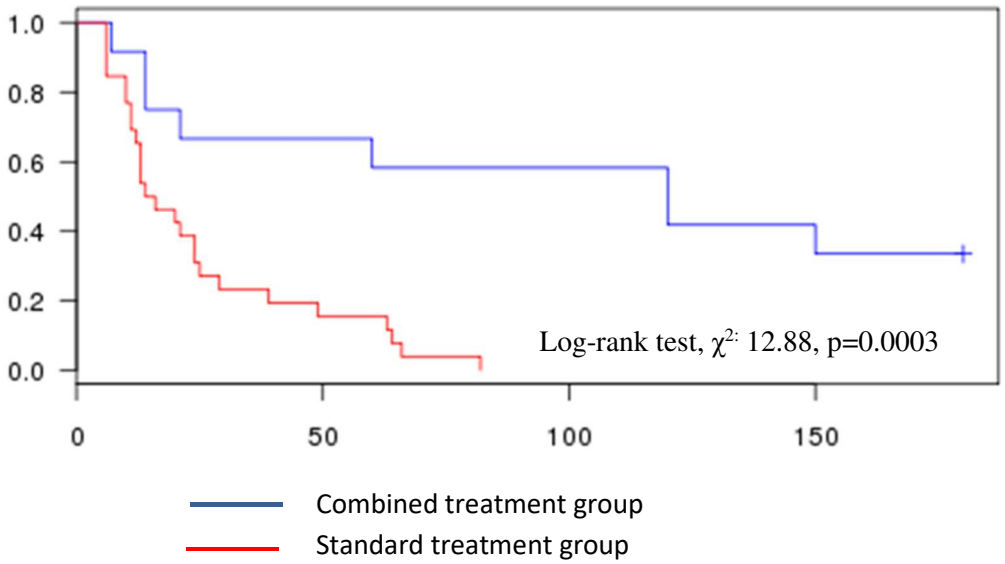

Figure 4: 6-month survival in the combined treatment group and the standard treatment group