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Addition of Molecular Adsorbent Recirculating System (MARS®) Albumin Dialysis for the Preoperative Management of Jaundiced Patients with Hilar Cholangiocarcinoma

Jean-Marc Regimbeau[a, e] David Fuks[a] Emilie Chapuis-Roux[a]
Thierry Yzet[b] Cyril Cosse[a, f] Eric Bartoli[c] Eric N'Guyen-Khac[c]
Brice Robert[b] Eric Lobjoie[d]

Departments of [a]Digestive Surgery, [b]Radiology and [c]Gastroenterology and [d]Intensive Care Unit, Amiens University Hospital, and [e]EA4294 and [f]INSERM U1088, Jules Verne University of Picardy, Amiens, France

Key Words
Hilar cholangiocarcinoma · Albumin dialysis · MARS® · Serum bilirubin level

Abstract
The preoperative management of hilar cholangiocarcinoma (HC) with jaundice focuses on decreasing the total serum bilirubin level (SBL) by performing preoperative biliary drainage (PBD). However, it takes about 6–8 weeks for the SBL to fall at a sufficient extent. The objective of this preliminary study was to evaluate the impact of Molecular Adsorbent Recirculating System (MARS®) dialysis (in association with PBD) on SBL decrease. From January 2010 to January 2011, we prospectively selected all jaundiced patients admitted to our university hospital for resectable HC and requiring PBD prior to major hepatectomy. The PBD was followed by 3 sessions of MARS dialysis over a period of 72 h. A total of 10 patients with HC were screened and two of them were included (Bismuth-Corlette stage IIIa, gender ratio 1, median age 68 years). The initial SBL in the two patients was 328 and 242 µmol/l, respectively. After three MARS dialysis sessions, the SBL had fallen by 30 and 52%, respectively. After the end of each session, there was a SBL rebound of about 10 µmol/l. The MARS decreased the serum creatinine level, the platelet count and the prothrombin index, but did not modify the serum albumin level. Pruritus disappeared after one and two sessions, respectively. MARS-related morbidity included hypotension (n = 1), tachycardia (n = 1), thrombocy-

Prof. J.-M. Regimbeau
Department of Digestive Surgery, CHU Nord Amiens and University of Picardy
Place Victor Pauchet, FR–80054 Amiens Cedex 01 (France)
E-Mail regimbeau.jean-marc@chu-amiens.fr

topenia (n = 2) and anaemia (n = 1). When combined with PBD, MARS dialysis appears to accelerate the decrease in SBL and thus may enable earlier surgery. This hypothesis must be validated in a larger study.

Introduction

Hilar cholangiocarcinoma (HC) accounts for less than 3% of all digestive cancers and has an incidence of about 2,000 new cases per year in France [1]. However, its incidence may well have increased over the last 30 years in Western countries [2, 3]. Jaundice is the most common symptom and results from obstruction of the upper biliary convergence by the tumour [1]. It has long been accepted that surgical resection with complete removal of all cancerous tissue is the only way to provide patients with a chance of cure or long-term survival [1, 2, 4]. This radical treatment requires extended hepatectomy (with combined caudate lobectomy and bile duct resection) and lymphadenectomy [4]. Most of these complicated procedures are performed in patients with cholestatic livers and are thus associated with a high risk of postoperative mortality and morbidity. To reduce the risk of postoperative liver failure in jaundiced patients, preoperative biliary drainage (PBD) and portal vein embolization (PVE) can be used before hepatectomy [4–6] to decrease hyperbilirubinaemia and increase the residual liver volume, if necessary. However, there is no consensus on how long before hepatectomy PBD should be initiated; some researchers suggest a few days or several weeks, whereas others consider that hepatectomy should only be performed once the serum bilirubin level (SBL) has fallen to normative values [7, 8]. Indeed, we recently highlighted the fact that <60% of drained patients had a normal SBL at the time of surgery [9]. Given that the time required for the SBL decrease depends on the initial bilirubin value, the duration of the jaundice and the patient's renal status, preoperative PVE is generally carried out after 3–4 weeks of PBD [6]. Liver resection is then performed if the forecast residual liver volume has increased after 2–4 weeks of PBD. Therefore, this preoperative management must be initiated 6–8 weeks prior to hepatectomy [7] and is associated with specific morbidity and mortality [8].

The Molecular Adsorbent Recirculating System (MARS®) (Gambro Lundia AB, Lund, Sweden) is an extracorporeal liver support system [10]. It is based on a hollow-fibre dialysis module in which the patient's blood is dialyzed across an albumin-impregnated membrane while a constant flow of albumin-rich (20%) dialysate is maintained in the extracapillary compartment. The albumin molecule subserves important transport and detoxification functions by offering a large number of binding sites. The indications for MARS currently include acute liver failure, decompensated cirrhosis, liver failure after liver resection or liver transplantation and refractory pruritus. The latter indication prompted the present work. The aim of the present study was to assess the value of MARS (when combined with PBD) in reducing the SBL in jaundiced HC patients.

Patients and Methods

This was a phase II, prospective study approved by the local independent ethics committee (CPP Nord Ouest II: reference 2008-47 dated 18/12/2008) and the French health authorities (AFSSAPS: #2008-A01474-51 dated 17/12/2008; insurance: SHAM #123440 from 01/09/2009 to 31/12/2009). Written informed consent was provided by all patients at enrolment.

Patient Selection

The study was performed between January 2010 and January 2011 (inclusive) at the Department of Digestive Surgery and the Intensive Care Unit at Amiens University Hospital, Amiens, France. All jaundiced HC patients in whom curative surgical resection was scheduled and who met the criteria for preoperative PBD (cholangitis, malnutrition and hyperbilirubinaemia >200 μmol/l) were invited to participate in the study.

During the study period, a total of 10 jaundiced patients were treated at our department for resectable HC. Two patients declined to participate in the present study, three had left-sided HC and/or did not undergo preoperative PBD, one had severe cholangitis following PBD and two had intraoperative contraindications to curative resection revealed during laparoscopic assessment (carcinomatosis and contralateral subcapsular metastasis). However, the remaining two patients (referred to as patients 1 and 2) were eligible and agreed to participate in the present study. They constituted the study treatment group (fig. 1).

Control Group

The control group comprised four patients in all: two patients who underwent MARS sessions for postoperative liver failure after major hepatectomy (constituting the liver failure subgroup) and two other non-drained patients who underwent palliative MARS sessions for non-resectable HC with refractory pruritus.

Extracorporeal Liver Support and MARS Sessions

All patients were admitted to the Intensive Care Unit and underwent three MARS sessions (each lasting 6–8 h) over a 3-day period. Vascular access was obtained via a double-lumen haemodialysis catheter (preferably placed in a femoral vein with ultrasound guidance). Unfractionated heparin was used for anticoagulation: a priming dose of 10,000 IU in the haemodialysis machine's blood circuit was followed by a maintenance infusion, with the dose then being adjusted to maintain the activated clotting time at between 140 and 200 s. Citrate anticoagulation was used in patients with signs of active or recent bleeding. The blood flow rates were 40–230 ml/min. Ultrafiltration rates were set according to the patient's fluid balance requirements. The MARS monitor (MARS Gambro Lundia AB, reference 800 424) was primed with 600 ml of 20% human albumin, run according to the manufacturer's instructions and then attached to a standard haemodialysis machine. The albumin flow rate was 200 ml/min, and the albumin circuit was dialyzed against a standard dialyzing solution (multiBIC from Fresenius Medical Care, Bad Homburg, Germany) with flow rates of 200–3,000 ml/h (mean 1,900 ml/h).

Study Criteria

Clinical parameters included age, gender, diagnosis on admission, presence or absence of pruritus and outcome. Laboratory data (including SBL, serum creatinine level, prothrombin time, serum albumin level, blood cell counts and platelet count), daily health scores, any requirement for norepinephrine before and/or after each MARS session and any requirement for the transfusion of packed red blood cells, fresh frozen plasma or platelets during a session were also recorded. Technical problems related to the MARS were recorded as well. Each patient (other than the two with postoperative liver failure) filled out a quality of life questionnaire immediately before and after the MARS treatment period. The questionnaire notably probed appetite, general condition and the time to alleviation of itching.

Role of the Funding Source

The trial was funded by the French government's 'Programme Hospitalier de Recherche Clinique' programme (PHRC 2008 RCB: #2008-A01474-51). The funding body did not have access to outcome data during the trial and did not participate in data analyses or the preparation of the manuscript. Devices were provided by the Head Office of Gambro Inc. (Toronto, Ont., Canada).

Results

Study Treatment Group

The study treatment group comprised a 72-year-old female and a 64-year-old male. Both patients were jaundiced, suffered from pruritus and had a right-side Bismuth-Corlette type III HC [11]. The initial SBL exceeded 250 μmol/l in both patients. Only patient 2 had kidney failure (defined as a serum creatinine level >120 μmol/l. Both patients underwent left-side PBD 2 and 4 days before the first MARS session, respectively. The demographic data and initial laboratory test results are summarized in table 1. Patients 1 and 2 each underwent three 6-hour sessions over a median 3-day period. The time interval between sessions was 24 h. After each MARS session, patient 1 developed anaemia and required blood transfusion. Technical problems included replacement of the femoral vascular access in two patients and partial coagulation in the device. We did not observe any impact of MARS on diuresis and body temperature. Both patients had thrombocytopenia (defined as a platelet count <150,000/mm^3).

Control Group

The control group included three women and one man (median age 67 years, range 49–78). The two patients with postoperative liver failure (patients 3 and 4) had right-side type III HC (n = 1) and type IV HC, respectively, whereas the two patients receiving palliative MARS treatment (patients 5 and 6) had type IV HC. Although all four patients had jaundice before the MARS sessions, only the two patients receiving palliative MARS presented refractory pruritus. As detailed in table 1, the initial SBL exceeded 150 μmol/l in all cases and 300 μmol/l in three of them. None of the patients had thrombocytopenia prior to MARS sessions and all had kidney failure. A total of eight MARS sessions were performed in the control group (1–4 per patient). Six of the sessions lasted more than 5 h. None of the patients required fresh frozen plasma transfusion. Two patients developed hypotension requiring fluid perfusion.

Results of MARS Treatment

SBL. For the two patients in the study treatment group, the mean decrease in SBL after each session was 37 and 24%, respectively. After three MARS sessions, the median decrease in SBL was 41%. A 10–20 μmol/l rebound in SBL was observed after each MARS session (table 2). Despite the absence of PBD in patients 5 and 6, we did not observe any significant differences in SBL decrease when comparing the study and the control group.

Other Variations in Laboratory Test Data. The median decrease in serum creatinine level was 11% (range –5 to 19%) with no difference between the study and the control group. The median decrease in the prothrombin time was 18% (range –45 to 44%) and the median decrease in platelet count was 36% (range –71 to 175%). The haemoglobin decreased by 2.2 percentage points (range 0–3.1). The serum albumin levels after MARS treatment in the study and control groups did not differ significantly (3 vs. 5%, p = 0.62).

Quality of Life. Pruritus disappeared after the first session in two patients and after the second session in the two other patients. According to the questionnaire filled out by patients 1, 2, 5 and 6, we did not observe any difference in quality of life ratings between the study treatment and the control group. In particular, MARS did not have a significant impact on appetite or general health status.

Outcomes after the MARS Sessions in the Study Treatment Group

Patients 1 and 2 underwent preoperative PVE 8 and 10 days after the last MARS session, respectively. They underwent surgery (right trisectionectomy with hepaticojejunostomy) 10 and 50 days after PBD, respectively. Patient 1 had a pT3N1 tumour with microscopic invasion of the surgical margins. The patient developed postoperative cholangitis that required antibiotics. The postoperative length of stay was 28 days. The patient underwent 6 cycles of adjuvant gemcitabine chemotherapy. The patient suffered a recurrence 18 months after surgery and died 7 months later. Patient 2 had a pT3N0 tumour with clear surgical margins. He did not develop any complications and the postoperative length of stay was 15 days. He received 6 cycles of adjuvant gemcitabine plus cisplatin chemotherapy. Thirty-three months later, the patient was alive and recurrence-free.

Discussion

HC is generally revealed by obstructive jaundice [12]. Extensive hepatectomy is usually required if the patient is to have a chance of long-term survival [13, 14]. However, liver resections in jaundiced patients carry a very high risk of postoperative mortality and morbidity [15]. PBD has been the rule in most centres, since the direct experimental and indirect clinical justification is that this procedure reverses cholestasis-associated hepatic and systemic toxicity [16] and impaired hepatic regeneration [17, 18].

MARS is an extracorporeal liver assist device used worldwide. Most of the studies having demonstrated the system's utility and safety have focused on biochemical markers and the influence on hepatic encephalopathy and hepatorenal syndrome. Despite widespread usage of the MARS, a meta-analysis of prospectively designed randomized controlled trials (with a total of 67 patients) failed to demonstrate a survival benefit [19]. To the best of our knowledge, the present study is the first to assess the MARS as part of the preoperative management of cholestatic HC patients scheduled to undergo extended liver resection.

Here, we evaluated two HC patients treated with a combination of MARS albumin dialysis and PBD prior to curative-intent resection. On the basis of clinical and laboratory test data, we found that the MARS sessions were relatively well tolerated. The study and control groups did not differ in terms of the requirement for hemodynamic support or transfusion, which suggests that safety was similar. We observed a significant decrease in serum creatinine and bilirubin levels in all six patients treated with MARS. The decrease in SBL after each session of nearly 30% enabled a significant overall decrease (measured 72 h after the initiation of MARS use). Lai et al. [20] and Sorkine et al. [21] focused on changes in biochemical variables during MARS treatment of patients with acute liver failure. They observed significant changes in ammonia, lactate, urea, creatinine and haemoglobin levels, platelet count, international normalized ratio and total and direct bilirubin levels.

We found that the decrease in SBL did not differ significantly when comparing two patients with resectable HC, two patients with liver failure and two other patients with unresectable HC. Moreover, our findings raise the question of whether MARS could be an

alternative to PBD (given the specific complications of drainage), although this requires validation in a larger series.

Interestingly, we observed a 10–20 μmol/l rebound in SBL after each MARS session and in all groups of patients. This rebound may correspond to (i) the transfer of bilirubin from the extravascular compartment to the intravascular compartment when there is a concentration difference between the two, and (ii) interference caused by the use of citrate anticoagulation in some patients.

Admittedly, this study has several limitations. The major limitation of our single-centre study was the very small sample size. Our patient population is heterogeneous and opportunities for inclusion were limited by the low prevalence of the disease and the high proportion of non-resectable patients at diagnosis.

In conclusion, we suggest that MARS may be used safely in the preoperative management of patients with HC. Prospective clinical studies are needed to support our findings.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Table 1. Demographic data and initial laboratory test results

	Study treatment group (n = 2)		Postoperative MARS (n = 2)		Palliative MARS (n = 2)	
	patient 1	patient 2	patient 3	patient 4	patient 5	patient 6
Demographic data						
Age, years	72	64	65	70	49	78
Gender	female	male	female	female	male	female
ASA status	2	2	3	4	1	2
Bismuth-Corlette classification	III right	III right	IV	III right	IV	IV
Initial laboratory test results						
Total serum bilirubin, μmol/l	328	252	317	168	360	550
Indirect serum bilirubin, μmol/l	76	75	75	31	54	74
Serum creatinine, μmol/l	58	126	140	169	122	226
Prothrombin time, %	92	86	59	45	88	84
Platelet count, /mm^3	268,000	285,000	252,000	213,000	208,000	322,000
MARS						
Number of sessions	3	3	1	4	2	1
Duration, h	6	7	5	6	4	7
MARS-related complications	anaemia, thrombocytopenia, mobilization of the vascular access	hypotension, thrombocytopenia, partial coagulation in the device	hypotension	thrombo-cytopenia	mobilization of the vascular access	hypotension, septic shock

Table 2. SBL change over time in the six patients

	Study treatment group (n = 2)		Postoperative MARS (n = 2)		Palliative MARS (n = 2)	
	patient 1	patient 2	patient 3	patient 4	patient 5	patient 6
Number of sessions	3	3	1	4	2	1
Serum bilirubin, μmol/l	328	242	317	168	360	550
Overall decrease (measured 72 h after the initiation of MARS)	52%	30%	28%	40%	49%	27%
Decrease per session	24%	13%	–	28%	28%	–

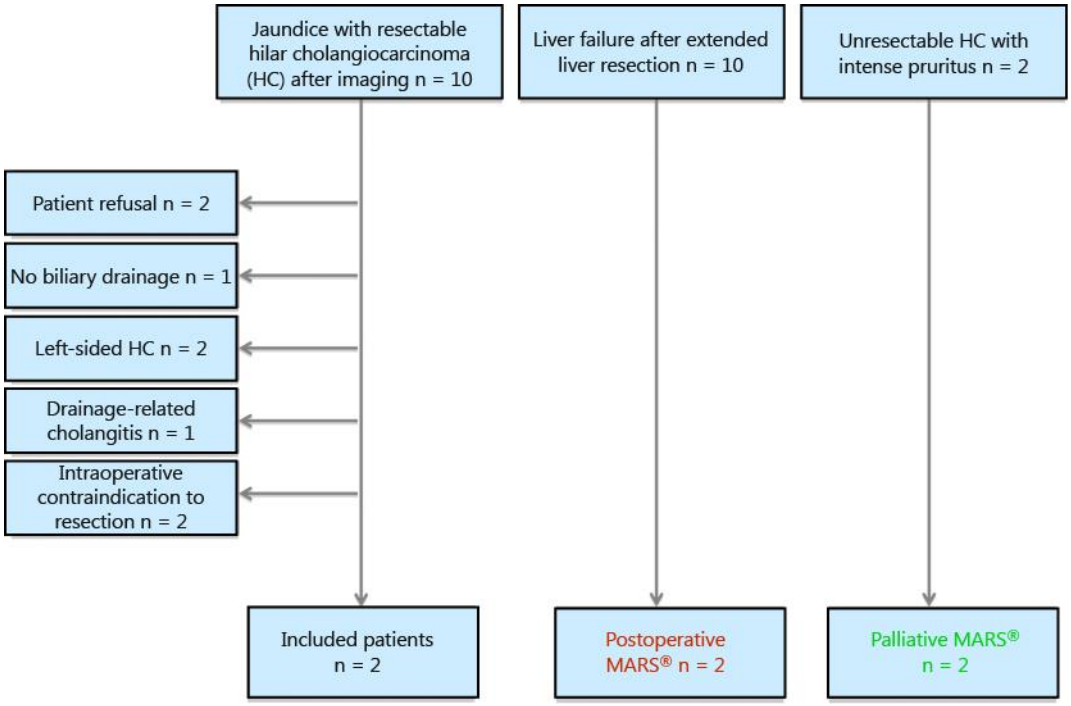

Fig. 1. Flowchart of patient selection.