Extracorporeal Liver Support Therapy [Using MARS]

2020. 8.

NECA 한국보건의료연구원
National Evidence-based Healthcare Collaborating Agency

Summary

□ Background

Extracorporeal liver support therapy [using MARS] is a molecular absorbents recirculating system (MARS)-based technology used to improve or maintain the patient status in case of a liver failure until liver functioning naturally recovers or the patients can receive liver transplant.

The said technology had not been covered by the national health insurance (Jo-842), but since July 1, 2019, a preliminary coverage of 90% (Ja-729) has been applied to the technology, given that the clinical evidence is insufficient, and severe patients have a burden of high treatment costs. Hence, the needs for the assessment and management of the safety and effectiveness of extracorporeal liver support therapy [using MARS] arose, and the National Health Insurance Review & Assessment Service (HIRA) requested the Korea National Evidence-based Healthcare Collaborating Agency (NECA) to reassess the health technology (August 14, 2019). Accordingly, the NECA assessed the safety and effectiveness of extracorporeal liver support therapy [using MARS] as part of the Health Technology Reassessment Program,

□ Committee operation

A subcommittee of 7 members held a total of 4 meetings over 7 months between December 10, 2019, and June 15, 2020, to assess the safety and effectiveness of the technology based on evidence in the literature. During the 7th Health Technology Reassessment Committee meeting (July 10, 2020), a final review was performed on the results of the safety and effectiveness assessment by the subcommittee.

□ Purposes and Methods

A systematic review was performed to assess the safety and effectiveness of extracorporeal liver support therapy [using MARS] for liver failure patients (acute liver failure, and acute liver failure in patients with chronic liver disease). A final decision on all specific methods of assessment was made through a review by the "Extracorporeal Liver Support Therapy [Using MARS] Subcommittee" (hereafter, the subcommittee).

For the systematic review, using 5 domestic and 3 foreign databases were searched for literature relevant to the core question. Three reviewers independently selected the articles based on the inclusion and exclusion criteria; they resolved any disagreements through discussion. Three reviewers independently evaluated the risk for bias in the finally selected articles using the Cochrane risk-of-bias tool. All disagreements were resolved by discussion among all subcommittee members. Both qualitative and quantitative analyses of data were conducted. Based on the results of the systematic review, the level of evidence was evaluated using GRADE, and the grade of recommendation was determined based on the assessment results.

□ Results

Six articles were finally selected for systematic review, all of which were randomized controlled clinical trials that compared intervention (MARS treatment) and comparison (standard medical treatment, SMT) groups. The total number of subjects for all the articles was 405. Five articles focused on acute-on-chronic liver failure (ACLF), which is an acute exacerbation of the chronic underlying liver disease, and 1 article focused on acute liver failure (ALF). A summary of safety and effectiveness outcomes is presented below.

The safety of extracorporeal liver support therapy [using MARS] was assessed by examining the procedure-related adverse events and complications. It was not possible to perform quantitative synthesis because the classification of safety indices and the reporting format varied across the articles. Hence, the findings presented in each of the articles were qualitatively reviewed.

A total of 4 articles reported procedure-related adverse events and complications. Two of them reported a statistically significant difference between the total and severe adverse effects in the MARS and SMT groups, but the inter-group difference was not significant for any of the safety indices (Banares et al., 2013; Saliba et al., 2013). The other 2 articles (Hassanein et al., 2007; Heemann et al., 2002) did not indicate whether there was statistical significance. Based on a review of the results regarding MARS-related adverse events, however, the subcommittee determined that they were at an acceptable level.

The effectiveness of extracorporeal liver support therapy [Using MARS] was assessed by evaluating mortality (short- and long-term), transplantation-free survival, bridging to liver transplantation, and hepatic encephalopathy.

Four articles reported the short-term mortality rate; all were ACLF cases. A meta-analysis showed that the short-term mortality rate did not differ significantly in the MARS and SMT groups (RR 0.85; 95% CI 0.62, 1.16; I^2=15%).

Five articles reported the long-term mortality rate. Four of them focused on ACLF patients, and 1 focused on ALF patients. In the meta-analysis of long-term mortality, the difference between the MARS and SMT groups was not statistically significant (RR 0.89; 95% CI 0.74, 1.08; I^2=0%).

Transplantation-free survival was reported in 2 articles: one focused on ACLF patients and another focused on ALF patients. According to the meta-analysis of transplantation-free survival, the difference between the MARS and SMT groups was not statistically significant (RR 1.10; 95% CI 0.92, 1.32; I^2=0%).

None of the articles reported the outcomes of bridging to liver transplantation.

Four articles reported hepatic encephalopathy, and all the patients had ACLF. Hepatic encephalopathy in ALF patients was not reported in any of the articles. The meta-analysis on hepatic encephalopathy showed that the grade of hepatic encephalopathy improved significantly in more patients in the MARS group than in the SMP group (RR 0.60; 95% CI 0.41, 0.86). The heterogeneity of the articles included in the meta-analysis was low (I^2=0%).

□ Conclusion and Suggestions

Based on the evidence currently available in the literature, the subcommittee presented the following results for the safety and effectiveness assessment of extracorporeal liver support therapy [using MARS] in liver failure patients.

The safety of Extracorporeal liver support therapy [using MARS] is determined to be acceptable. Regarding effectiveness, extracorporeal liver support therapy [using MARS] is not different from SMT based on mortality (short- and long-term) or transplantation-free survival, but it is significantly more effective in improving hepatic encephalopathy.

Currently, liver transplantation is the only treatment available for liver failure patients. Despite the remarkable advancement in liver transplant technology, however, several patients die of liver failure because of the lack of donors and the limited time

window for patients to receive the transplant due to rapid disease progression. Accordingly, the subcommittee expressed that extracorporeal liver support therapy [using MAS], a technology used to replace liver function, should be available as an option for physicians to use in treating liver failure patients since there is no alternative in practice. In addition, they stated that it is difficult to conduct a randomized controlled clinical trial of liver failure, because it is a severe disease that occurs less frequently compared with other liver diseases and additional evidence cannot be obtained over a short period.

Accordingly, the subcommittee made the following assessments. Although current evidence in the literature on the safety and effectiveness of extracorporeal liver support therapy [using MARS] is not sufficient, the technology has clinical significance in that it provides liver failure patients with a treatment option. As a procedure utilized until liver functioning naturally recovers or the patient's condition is improved or maintained so that liver transplantation can be performed, the technology's safety is acceptable. In reducing mortality, the effectiveness of the technology is not different from that of SMD, but it can improve hepatic encephalopathy.

Based on the subcommittee's review, the Health Technology Reassessment Committee assessed the "Extracorporeal Liver Support Therapy [Using MARS]," as follows (July 10, 2020).

The safety of extracorporeal liver support therapy [using MARS] is acceptable. The effectiveness of the technology is not different from that of SMT in reducing mortality, but it is somewhat effective in improving hepatic encephalopathy. Although there is insufficient evidence in the literature on its safety and effectiveness, the technology has clinical significance in that it provides a treatment option to liver failure patients.

Accordingly, the Health Technology Reassessment Committee recommends extracorporeal liver support therapy [using MARS] because it is confirmed to be somewhat effective in improving hepatic encephalopathy in liver failure patients (Grade of recommendation: I-b).

Keywords

extracorporeal liver support therapy, bioartificial liver, acute liver failure, acute-on-chronic liver failure, liver transplantation