

69354_Auto_Edited - check.docx

Name of Journal: *World Journal of Transplantation*

Manuscript NO: 69354

Manuscript Type: SYSTEMATIC REVIEWS

Enhanced recovery after surgery in liver transplantation: Challenges and feasibility

Katsanos G *et al.* ERAS in liver transplantation

Georgios Katsanos, Konstantina-Eleni Karakasi, Nikolaos Antoniadis, Stella Vasileiadou, Athanasios Kofinas, Antonios Morsi-Yeroyannis, Evangelia Michailidou, Ioannis Goulis, Emmanouil Sinakos, Olga Giouleme, Ilias-Marios Oikonomou, George Evlavis, Georgios Tsakiris, Eleni Massa, Eleni Mouloudi, Georgios Tsoulfas

Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) started a revolution that changed age-old surgical stereotypical practices regarding the overall management of the surgical patient. In the last decade, ERAS has gained significant acceptance in the general Surgery community, in addition to several other surgical specialties, as the evidence of its superiority continues to grow. One of the last remaining fields, given its significant complexity and intricate nature, is Liver Transplantation.

AIM

To investigate the existing efforts at implementing ERAS in liver transplantation.

METHODS

We conducted a systematic review of the existing studies that evaluate ERAS in Orthotopic LT, with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stays.

RESULTS

All studies demonstrate a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocol applied in the postoperative course.

CONCLUSIONS

ERAS is a well validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT.

Key Words: Enhanced recovery; Enhanced recovery after surgery; Recovery; Liver transplantation; Liver

Katsanos G, Karakasi KE, Antoniadis N, Vasileiadou S, Kofinas A, Morsi-Yeroyannis A, Michailidou E, Goulis I, Sinakos E, Giouleme O, Oikonomou IM, Evlavis G, Tsakiris G, Massa E, Mouloudi E, Tsoulfas G. Enhanced recovery after surgery in liver transplantation: Challenges and feasibility. *World J Transplant* 2021; In press

Core Tip: ² Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. The benefits of ERAS in liver transplantation seem promising and further studies should be conducted in order to validate its application in properly selected patients.

INTRODUCTION

3 Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery^[1]. Since its introduction in 1997 by Kehlet *et al*^[2], initially destined for and subsequently established in Colorectal surgery, the concept of ERAS was validated and has since evolved and spread to a multitude of surgical disciplines^[3], including solid organ transplantation^[4].

Although the concept of enhanced recovery was explored in liver transplantation (LT) before its official introduction by Kehlet *et al*^[2] as early as 1990 in the form of early extubation yielding encouraging results^[5], it was done so without the classic multimodal approach, focusing and highlighting on the importance of anesthesia management in these patients^[6]. Over the years, independent studies validated the significance and efficiency of other classic ERAS parameters, such as preoperative nutrition, early mobilization, early feeding and optimal analgesia of patients undergoing LT, but the medical literature is scarce in studies that combine all of the above parameters in a classic large scale ERAS approach specific for LT. This narrative review paper will investigate the existing efforts at implementing ERAS in LT, as well as try to identify the existing challenges and the future potential developments in the field.

Although the concept of enhanced recovery was explored in LT before its official introduction by Kehlet *et al*^[2], as early as 1990, in the form of early extubation, yielding encouraging results^[5], it was done so without the classic multimodal approach, focusing and highlighting on the importance of anesthesia management in these patients^[6]. Over the years, independent studies validated the significance and efficiency of other classic ERAS parameters, such as preoperative nutrition, early mobilization, early feeding and optimal analgesia of patients undergoing LT, but the medical literature is scarce in studies that combine all of the above parameters in a classic large scale ERAS approach specific for LT. This review paper will investigate the existing efforts at implementing ERAS in LT, as well as try to identify the existing challenges and the future potential developments in the field.

MATERIALS AND METHODS

Our goal was to identify the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stays. Medline, Embase, OVID and the Cochrane library were searched with the language restricted to English, and using the search terms [ERAS OR “Enhanced recovery” OR “fast track” AND “Liver Transplantation”] from years 1990 to 2021 and after independent assessment from 3 reviewers, 3 articles were selected. PRISMA flow chart is presented in Figure 1.

RESULTS

There was a small number of studies identified, which were limited scale non-randomized single center observational studies, with the exception of the work of Rao *et al*^[7], who presented a prospective single-blinded randomized study including 128 patients divided in 2 groups, ERAS ($n = 54$) and control ($n = 74$). The ERAS group was analyzed by a logistic stepwise regression analysis and displayed a decreased ICU and hospital stay, without significant difference in the postoperative complication rate between the two groups and no readmissions or postoperative mortality during the follow-up period. Brustia *et al*^[8] conducted a small scale feasibility study with 10 patients treated prospectively with an ERAS protocol that were compared with 20 matched patients treated by the same team the previous years. They designed an elaborate 26 point ERAS protocol and ⁵observed a 47% reduction of the total length of stay compared to the control arm. There were no readmissions or postoperative mortality during the follow-up period.

Xu *et al*^[9] report a cohort of 93 patients, 40 in the ERAS group and 53 in the control group; they reported a significant reduction of postoperative hospital stay in favor of the ERAS group (14.5 vs 16 d, $P < 0.001$). No difference in the postoperative complication rate between the two groups and no readmissions or postoperative mortality was noted.

Common inclusion criteria used in the aforementioned studies are presented in Table 1. As expected, patient MELD score is low in all four studies, as they reflect patient status^[10]. All studies included patients with a MELD score well below 25. Patients with no previous history of LT were also selected for the ERAS group in all 3 studies. A considerable number of patients for ERAS LT had a hepatocellular carcinoma (HCC) related indication in all 3 studies (Brustia 90%, Xu 42.5%, Rao 33.3%).

Given the lack of a standardized ERAS protocol, each team designed its own protocols, based on previous experience from existing literature on other surgical fields. Table 2 depicts a comparison of the preoperative, intraoperative and post-operative characteristics between the 3 studies. All the studies applied multimodal measures in the 3 distinct phases of classic ERAS protocols, namely preoperative, intraoperative and postoperative phase. In Table 3, measures applied by all 3 authors are depicted in capital letters. Of the 26 points proposed by Brustia *et al*^[8], 11 (42.3%) were observed by all 3 authors.

All 3 studies demonstrate a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocol applied in the postoperative course (Table 2). From the above mentioned publications, we meta-analyzed the primary endpoint, postoperative hospital stay.

The variable was continuous, and the results were summarized using median and 25%-75% values (because the data were skewed). The sample mean and standard deviations were calculated using the formula of Wan *et al*^[11]. The random-effects model was applied for the meta-analysis as high heterogeneity was expected among the studies with regard to study populations and diagnostic procedures. The presence of between-study heterogeneity was quantitatively reflected with the I^2 index, considering I^2 of more than fifty percent ($I^2 > 50\%$) indicative of statistically significant heterogeneity. R studio version 4.0.2 software was used to perform all the statistical analyses, employing the packages “meta” and “metafor”. The comparison of the total hospital stay showed a statistically significant difference in both groups ($n = 251$; MD-5.79; 95% confidence interval (CI), 10.89 to 0.69; $I^2 = 89\%$; $P < 0.01$). Nevertheless, a great

heterogeneity was observed between the samples (Figure 2). A similar meta-analysis of the MELD score showed that there was no statistically significant difference in both groups. ($n = 251$; MD-0.25; 95%CI, -1.36 to 0.85; $I^2 0\%$; $P = 0.62$) (Figure 3). As mentioned above, all patients were low MELD patients with a mean MELD well below 20.

DISCUSSION

The scarcity of strong evidence in the widespread application of ERAS programs in LT may reflect the reluctance of teams to implicate such protocols in a cohort of patients that are generally perceived as a frail, high risk group, undergoing a major surgical procedure of a life-threatening nature. The evolution of LT on the other hand, is a successful story, evolving from an experimental and innovative procedure to a more “standard” one over the last several decades, and especially when performed in high volume centers with experienced multidisciplinary teams. Throughout the years, LT has proved its life saving nature as an operation and the morbidity and mortality plummeted, offering patients excellent survival and quality of life^[12]. The major incentives in applying ERAS in LT came from the successful application of Enhanced Recovery Programs in Liver Surgery^[13] and the subsequent publication of suggested guidelines for ERAS in Liver Surgery^[14]. Although ERAS with its multimodal approach pattern did not appear in the literature until recently, the concept of multimodal clinical pathways in LT is raised as early as 2011 by Pavlakis *et al* of the Beth Israel Deaconess Medical Center team^[15], characterizing the transplantation domain as an “*ideal forum for successful implementation of clinical pathways*” and highlighting their importance and potential in reducing length of stay, morbidity, costs, as well as improving patient satisfaction. Piñero *et al*^[16] introduced in 2015 the concept of the early discharge from hospital following liver transplantation (ERDALT) focusing on healthcare costs and proposed an early discharge prediction model based on MELD points (exception MELD points were deemed a favorable prognostic factor), length of surgery (time < 4 h), transfusion of less than 5 units of packed red blood cells and early respirator weaning. The author concluded that early discharge from hospital following LT is feasible,

without a negative impact on patient or graft survival, nor did it increase short-term re-hospitalization. The recent publication of Brustia *et al*^[18] and the Pitié-Salpêtrière team in Paris reinforced the basis for further developing ERAS in LT. Although it is a small scale single center observational study, the authors report a 47% reduction of length of hospital stay with no safety issues in a small but well-designed protocol. This conclusion is corroborated by all 3 publications mentioned above, demonstrating that ERAS in LT could be possible in a larger scale and should be further studied. Rodríguez-Laiz *et al*^[17] presented a cohort of 236 patients that were treated with a comprehensive multi step ERAS protocol that is the product of lessons and experiences emanating from Liver Surgery and other disciplines and evaluate its value as a proof-of-concept. In this study, the authors identified 133 patients that were discharged early and they retrospectively defined them as the ERAS group. However, their study, with extremely short lengths of stay, is inherently flawed, as the authors point out, by a lack of a traditional control group and for this reason their article was not included in our final selection. In 2021 Brustia *et al*^[18] drafted the “*Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations*”, after a systematic review by a wide international panel of experts and the application of the Delphi method. The Authors of the manuscript recognize the lack of current strong evidence in ERAS in LT, but laid a solid foundation and a precious scaffold which can serve as the base for large studies in the definitive validation of ERAS in LT.

ERAS is a well validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT. The majority of the studies analyzing ERAS in liver transplantation use a cohort of low MELD highly selected patients that might not represent the majority of patients that benefit from LT and this is an issue that will have to be addressed. The overall majority of patients in the 3 studies analyzed were low MELD HCC patients and this type of selection might harbor an inherent bias in evaluating ERAS in LT. However it is a first step and understandably first steps must be careful. The encouraging results presented, along

with the observed benefit of a well-designed ERAS protocol in these patients mandates further exploration and expansion of inclusion criteria in these types of protocols. After all, an earlier discharge might be the result of a better overall patient management in all aspects of their journey through the hospital and not necessarily the primary endpoint.

One of the key factors in implementing ERAS protocols is the understanding of the philosophy behind ERAS by both patients and caregivers and although this might seem simple or a given, studies indicate that it might not be the case^[19,20]. As ERAS is new to the field of LT, similar issues are expected to occur. In the first years of the implementation of ERAS in colorectal surgery, many issues arose concerning patient and physician capability of correctly implementing and accepting what proved to be a validated protocol for better patient recovery^[21,22] including the complexity of these multimodal pathways^[23], the need for teamwork along with the difficulty of eradicating old surgical stereotypes of traditional care. Agrafiotis *et al*^[24], along with the first author of the present review, have explored in 2013 the efficacy of a “soft”, non-strict fast-track protocol in a cohort of 92 patients undergoing colorectal surgery. The conclusion was that even without a strict ERAS protocol, enhanced recovery and accelerated safe patient discharge is possible, pointing out among others^[25] that *“length of stay should not be an aim in itself within an enhanced recovery protocol. The main object of these programs ought to be the enhancement of patient recovery and not earlier discharge”*. This statement is endorsed by our team, in the Transplantation Department of a public Medical School part of a public health system with significant financial and other challenges, who tried to evaluate the implementation of a non-strict ERAS protocol in selected LT patients in a small cohort of patients trying to replicate the results of Brustia *et al*. In a small feasibility and safety study we observed a 56% decrease in hospital stay in the ERAS group without any safety issues (unpublished data). These encouraging results might indicate that ERAS, when implemented in the right way, can be beneficial to patients even in small volume transplant centers and their implementation should be encouraged. We also noted the lack of estimation of the importance of every point in the proposed ERAS protocols towards the final endpoint, which hinders the simplification of these

protocols, as we do not currently know which one of the steps – if any – could be omitted without a significant compromise in the outcome.

Henric Kehlet has pointed out the delay of the development of ERAS: *“there is an urgent need for better implementation of the current established scientific evidence for ERAS practices in order to fill the still very present gap between knowing and doing”* and has been advocating for many years the concept of “stress free, pain free” operations^[26], which might seem an impossible task for operations of the magnitude of a LT. However, as the term “fast-track” was gradually replaced by the more correct term “Enhanced Recovery”, the concept of *“first better, then faster”* had to be reappraised^[27,28].

CONCLUSION

Enhanced recovery means better recovery and its value should be further exploited for Liver Transplant patients. After all, ERAS is not about the type of operation; ERAS is about the patient.

ORIGINALITY REPORT

4%

SIMILARITY INDEX

PRIMARY SOURCES

- | | | |
|----------|--|----------------------|
| 1 | www.ncbi.nlm.nih.gov
<small>Internet</small> | 41 words — 2% |
| <hr/> | | |
| 2 | journals.lww.com
<small>Internet</small> | 23 words — 1% |
| <hr/> | | |
| 3 | jtd.amegroups.com
<small>Internet</small> | 22 words — 1% |
| <hr/> | | |
| 4 | Federico Piñero, Martín Fauda, Rodolfo Quiros, Manuel Mendizabal et al. "Predicting early discharge from hospital after liver transplantation (ERDALT) at a single center: a new model", Annals of Hepatology, 2015
<small>Crossref</small> | 15 words — 1% |
| <hr/> | | |
| 5 | Raffaele Brustia, Antoine Monsel, Filomena Conti, Eric Savier et al. "Enhanced Recovery in Liver Transplantation: A Feasibility Study", World Journal of Surgery, 2018
<small>Crossref</small> | 15 words — 1% |

EXCLUDE QUOTES ☒ ON

EXCLUDE BIBLIOGRAPHY ☒ ON

EXCLUDE SOURCES

< 12 WORDS

EXCLUDE MATCHES

< 12 WORDS