Editorial

Enhanced recovery for liver resection—early recovery pathway for hepatectomy: data-driven liver resection care and recovery

Benjamin Morrison, Leigh Kelliher, Chris Jones

Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

Correspondence to: Chris Jones. Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK. Email: drchrisnjones@yahoo.co.uk.

Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Warner SG, Jutric Z, Nisimova L, *et al.* Early recovery pathway for hepatectomy: data-driven liver resection care and recovery. Hepatobiliary Surg Nutr 2017;6:297-311.

Submitted Feb 22, 2018. Accepted for publication Mar 13, 2018.
doi: 10.21037/hbsn.2018.03.13
View this article at: http://dx.doi.org/10.21037/hbsn.2018.03.13

First described as a model for perioperative care in the early 1990's, the success of the enhanced recovery after surgery (ERAS) approach in colorectal surgery has given rise to pathways being developed for an ever-increasing range of surgical specialities/procedures. The fundamental principles of comprehensive patient optimisation combined with minimising the surgical stress response remain at the heart of ERAS and, as evidence for the benefit of this approach continues to emerge, the drive to conduct further research in this area and continue the development of new guidelines grows. Despite this, challenges to achieving a wide-spread uptake of ERAS remain, prominent amongst these being the currently low grade of evidence available for some individual ERAS elements e.g., the use of oral nutritional supplements and early post-operative mobilisation (1). However, the volume and quality of evidence continues to grow with a number of randomised controlled trials (RCTs) and meta-analyses showing favourable results for the use of ERAS programmes in a wide variety of settings. Fewer postoperative complications, reduced hospital length of stay (LoS) and costs, lower readmission rates and improved short and longer-term mortality have all been reported.

In recent years, ERAS programmes have been developed for use in both open and minimally invasive liver resection surgery with several RCTs demonstrating significantly improved outcomes including reduced hospital LoS, fewer complications and increased patient quality of life (QoL) (2-9). Previous systematic reviews, including one meta-analysis, have also concluded that ERAS programmes conferred improved mortality alongside a reduction in hospital LoS and postoperative complication rates (10) [which in turn are an independent determinant of long term survival (11)]. Longer-term benefits for patients and the health economic advantages of ERAS are also beginning to emerge as established ERAS programmes begin to produce 5- and 10-year follow-up data (7,12). In cancer surgery, by facilitating a more rapid recovery and return to baseline function, ERAS programmes may permit earlier treatment with adjuvant cancer therapies—potentially conferring an improvement in oncological outcomes and survival (13).

The historically high rate of post-operative morbidity and mortality makes liver resection surgery an important area of research (14,15). In their article Warner *et al.* (16) have reviewed the evidence behind the components of existing ERAS programmes for liver surgery and then used this information to develop their own comprehensive programme. They conclude by publishing their recommended ERAS pathways for use in major open, minor open and minimally invasive/robotic liver resection surgery. The original article was accepted for publication shortly before the ERAS Society published their own consensus guidelines for perioperative care in liver surgery (17). Whilst there is much concurrence between the recommendations of Warner *et al.* and those of the

ERAS group, there are some notable exceptions. One such is the issue of perioperative steroid administration, recommended by ERAS (albeit weakly) but not addressed in the Warner publication. As detailed in the ERAS guidelines, the evidence-base for this is weak but has since been strengthened by a study of fast-track perioperative care in 121 hepatectomy patients which included the use of high-dose steroid administration pre-operatively. It demonstrated a reduction in hospital LoS without detriment to morbidity, mortality or readmission rates. Although this could not be directly attributed to the introduction of high-dose steroid supplementation the authors postulate that steroid therapy may have positive pathophysiological effects, particularly with regard to liver resection surgery, and reinforce the importance of further research in this area (18).

Warner *et al.*'s review includes details of their own research into the use of perioperative blood phosphate concentrations as a marker of clinical recovery following hepatectomy. As such the authors have taken the opportunity to promote phosphate supplementation as part of an ERAS programme for liver resection surgery. They cite several studies linking postoperative complications to hypophosphataemia, specifically in relation to liver resection surgery, one of which suggested phosphate supplementation could actually reduce postoperative complications (19). This review includes the author's own retrospective analysis of 125 patients undergoing liver resection surgery looking into perioperative phosphate levels and supplementation. They identified two nadir points at 2 and 44 hours postoperatively and a period between postoperative days 1.5 to 3 during which patients were most likely to be hypophosphatemic regardless of the extent of surgery. With supplementation patients largely avoided severe hypophosphataemia (defined as <1.0 mg/dL). Their study findings correlated with previous work in demonstrating an increased risk of complications for patients with hypophosphataemia with a further increase in risk if the hypophosphataemia persisted beyond 2 days. Conversely, they also demonstrated that over-supplementation and subsequent hyperphosphataemia was a risk factor for postoperative complications. They conclude by recommending phosphate supplementation as part of an ERAS programme for liver resection surgery with the proviso that phosphate levels are closely monitored to avoid hyperphosphataemia. This marks a major disparity between the work of Warner *et al.* and ERAS society, who no mention of phosphate supplementation in their guidelines.

An area addressed by Warner *et al.*'s analysis but not highlighted in the ERAS society paper is that of liver surgery technique—i.e., the use of specific surgical techniques/equipment, the duration of surgery and blood loss/transfusion requirements. Surgical technique/equipment may be particularly pertinent to liver resection surgery where copious blood loss and the requirement for blood transfusion is historically prevalent, unless obviated by measures which threaten the integrity of the remaining liver segments post-operatively, such as the "Pringle" manoeuvre. The authors of this article make particular reference to low central venous pressure (CVP) anaesthetic techniques facilitating reduced blood loss but acknowledge that such techniques can have consequences on optimal physiology for the rest of the body. They explain that shorter operating times allow earlier fluid resuscitation to improve organ perfusion and thus reducing the risk of, amongst others, renal dysfunction, hypothermia and bacterial translocation. The ERAS Society guideline also explores, and indeed advocates, the use of a low CVP technique as a means of reducing intraoperative blood loss. They go on to mention a recent Cochrane review which showed reduced blood loss with low CVP techniques but no difference in red cell transfusion requirements, intraoperative morbidity or long-term survival benefits (20).

With regard to outcome measures the authors quite rightly state that much emphasis is put upon hospital LoS as being a marker of the success of an ERAS programme. Some studies point out the difference between readiness for discharge and actual LoS and the same factors which keep patients in hospital beyond the predefined point of readiness would be shared between ERAS and control groups. These factors, such as social infrastructure or low patient confidence, in themselves may be elements which could be addressed in future ERAS programmes as they appear readily identifiable. Other outcome measures include in-hospital/30-day mortality but as more time passes from when the original trials in ERAS commenced a clearer understanding of the impact upon longer-term mortality will begin to emerge. Follow-up data from one study in this setting, which showed significantly reduced complications and LoS with ERAS in its initial results, has demonstrated reduced mortality with ERAS at 2 years postoperatively. Interestingly this reduction is not present at 5 years (12). This disagrees with previous work showing a negative correlation between postoperative complications and long-term survival which suggests this effect should be sustained (11). This disparity may be a simple reflection of the underlying natural history of the disease which

necessitated surgery in the first place. Certainly, with a long enough time frame, all survival curves converge. Nevertheless, this is an encouraging signal.

Finally, the authors discuss future areas of research and discussion. One suggestion made is to study more closely the of ERAS effect upon patients' QoL. This is not an unexplored area of research with at least one RCT showing higher QoL scores in patients following an ERAS programme (2). The data in this trial is limited to the first 30 days post-op and as longer-term mortality data emerges the psychological and socio-economic effects should be looked into in greater depth with new trials. With health economics a key driver for change and the development of new treatment pathways, robust evidence demonstrating the economic benefit of ERAS would be welcome. A trial from Alberta, Canada showed significant economic benefit with ERAS—illustrated by a return of $3.8 for every $1 invested with the authors concluding that protocolization of liver resection surgery across all centres should be a future aim (7). Whilst in reality further research and stronger evidence will be required before wide-scale adoption of ERAS is feasible, the case for developing and using ERAS protocols across specialties—from a clinical, economic and patient experience standpoint—is gaining momentum all the time and excitingly we are beginning to see the principles and approach being applied to areas beyond elective surgery such as emergency surgery, obstetrics and even medical specialties. Will the benefits be replicated? Time will tell.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr 2012;31:783-800.
2. Jones C, Kelliher L, Dickinson M, et al. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. Br J Surg 2013;100:1015-24.
3. Koea JB, Young Y, Gunn K. Fast track liver resection: the effect of a comprehensive care package and analgesia with single dose intrathecal morphine with gabapentin or continuous epidural analgesia. HPB Surg 2009;2009:271986.
4. Lin DX, Li X, Ye QW, et al. Implementation of a fast-track clinical pathway decreases postoperative length of stay and hospital charges for liver resection. Cell Biochem Biophys 2011;61:413-9.
5. Page AJ, Gani F, Crowley KT, et al. Patient outcomes and provider perceptions following implementation of a standardized perioperative care pathway for open liver resection. Br J Surg 2016;103:564-71.
6. Stoot JH, van Dam RM, Busch OR, et al. The effect of a multimodal fast-track programme on outcomes in laparoscopic liver surgery: a multicentre pilot study. HPB (Oxford) 2009;11:140-4.
7. Thanh NX, Chuck AW, Wasylak T, et al. An economic evaluation of the Enhanced Recovery After Surgery (ERAS) multisite implementation program for colorectal surgery in Alberta. Can J Surg 2016;59:415-21.
8. Ni TG, Yang HT, Zhang H, et al. Enhanced recovery after surgery programs in patients undergoing hepatectomy: A meta-analysis. World J Gastroenterol 2015;21:9209-16.
9. van Dam RM, Hendry PO, Coolsen MM, et al. Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. Br J Surg 2008;95:969-75.
10. Hughes MJ, McNally S, Wigmore SJ. Enhanced recovery following liver surgery: a systematic review and meta-analysis. HPB (Oxford) 2014;16:699-706.
11. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326-41; discussion 341-3.
12. Morrison B, Jones C, Kelliher L, et al. ERAS for open liver resection surgery improves two year survival but not five year survival. Clinical Nutrition ESPEN 2017;19:78.
13. Day RW, Cleeland CS, Wang XS, et al. Patient-Reported Outcomes Accurately Measure the Value of an Enhanced Recovery Program in Liver Surgery. J Am Coll Surg 2015;221:1023-30.e1-2.
14. Benzoni E, Molaro R, Cedolini C, et al. Liver resection for HCC: analysis of causes and risk factors linked to postoperative complications. Hepatogastroenterology 2007;54:186-9.
15. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of

1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406; discussion 406-7.
16. Warner SG, Jutric Z, Nisimova L, et al. Early recovery pathway for hepatectomy: data-driven liver resection care and recovery. Hepatobiliary Surg Nutr 2017;6:297-311.
17. Melloul E, Hübner M, Scott M, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg 2016;40:2425-40.
18. Schultz NA, Larsen PN, Klarskov B, et al. Second Generation of a Fast-track Liver Resection Programme. World J Surg. 2018;42:1860-66.
19. Pomposelli JJ, Pomfret EA, Burns DL, et al. Life-threatening hypophosphatemia after right hepatic lobectomy for live donor adult liver transplantation. Liver Transpl 2001;7:637-42.
20. Gurusamy KS, Li J, Sharma D, et al. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database Syst Rev 2009;4:CD007338.

Cite this article as: Morrison B, Kelliher L, Jones C. Enhanced recovery for liver resection—early recovery pathway for hepatectomy: data-driven liver resection care and recovery. HepatoBiliary Surg Nutr 2018;7(3):217-220. doi: 10.21037/hbsn.2018.03.13

