ENHANCED RECOVERY (ERAS) AFTER LIVER SURGERY: COMPARATIVE STUDY IN A BRAZILIAN TERTIARY CENTER

Recuperação otimizada (ERAS) após cirurgia hepática: Estudo comparativo de um centro terciário brasileiro

Uirá Fernandes TEIXEIRA, Marcos Bertozzi GOLDONI, Fábio Luiz WAECHTER, José Artur SAMPAIO, Florentino Fernandes MENDES, Paulo Roberto Ott FONTES

ABSTRACT – Background: After the publication of the first recommendations of ERAS Society regarding colonic surgery, the proposal of surgical stress reduction, maintenance of physiological functions and optimized recovery was expanded to other surgical specialties, with minimal variations. Aim: To analyze the implementation of ERAS protocols for liver surgery in a tertiary center. Methods: Fifty patients that underwent elective hepatic surgery were retrospectively evaluated, using medical records data, from June 2014 to August 2016. After September 2016, 35 patients were prospectively evaluated and managed in accordance with ERAS protocol. Results: There was no difference in age, type of hepatectomy, laparoscopic surgery and postoperative complications between the groups. In ERAS group, it was observed a reduction in preoperative fasting and in the length of hospital stay by two days (p<0.001). Carbohydrate loading, J-shaped incision, early oral feeding, postoperative prevention of nausea and vomiting and early mobilization were also significantly related to ERAS group. Oral bowel preparation, pre-anesthetic medication, sub-costal incision, prophylactic nasogastric intubation and abdominal drainage were more common in control group. Conclusion: Implementation of ERAS protocol is feasible and beneficial for health institutions and patients, without increasing morbidity and mortality.

INTRODUCTION

Since the publication of the first enhanced recovery after surgery (ERAS) guidelines regarding colonic resections by Gustafsson et al. in 2012, the proposal of reduction of surgical stress, maintenance of physiological functions and optimized recovery quickly gained the attention of the international medical community. On August 2016, ERAS Society published the official recommendations for perioperative care for liver surgery, bringing together some experts from high-volume centers all over the world.

Since then, many papers have shown the feasibility and cost-effectiveness of implementation of enhanced recovery pathways in patients undergoing hepatectomies. In several studies, this multimodal approach was consistently associated with better outcomes, including reduction in the length of hospital stay, postoperative complications and costs.

Hepatic surgery represents one of the surgical specialties that most benefits from multidisciplinarity, but published protocols vary widely between institutions. Despite evidenced-based recommendations available in literature, its application did not follow this progress, mainly due to difficulties in changing paradigms.

Liver surgery still represents a challenging operation. Despite significant
improvements in perioperative management and surgical technique, which led to a reduction in postoperative mortality to less than 5%, major hepatectomies still have a morbidity rate up to 30% in some reports\textsuperscript{5-11}. This way, the implementation of evidenced-based recommendations in order to optimize perioperative recovery can greatly benefit patients and health providers\textsuperscript{1}.

This is a comparative study that aims to analyze the implementation of ERAS protocols for liver surgery in a tertiary center in Brazil.

METHODS

Expertise with implementation of the protocol was initially acquired with colorectal surgery, and it was later expanded to hepatectomies. A database was created with the 23 items proposed by ERAS guidelines, being subsequently filled with the collected data (Table 1).

| TABLE 1 – Guidelines for enhanced recovery after liver surgery |
|---------------------------------------------------------------|
| 1. Preadmission counseling |
| 2. Perioperative nutrition |
| 3. Perioperative oral immunonutrition |
| 4. Preoperative fasting and preoperative carbohydrate loading |
| 5. Oral bowel preparation |
| 6. Pre-anesthetic medication |
| 7. Prophylaxis against thromboembolism |
| 8. Perioperative steroids administration |
| 9. Antimicrobial prophylaxis and skin preparation |
| 10. Incision |
| 11. Minimally invasive approach |
| 12. Nasogastric intubation |
| 13. Drainage of the peritoneal cavity |
| 14. Preventing intraoperative hypothermia |
| 15. Postoperative nutrition and early oral intake |
| 16. Postoperative glycemic control |
| 17. Prevention of delayed gastric emptying |
| 18. Stimulation of bowel movement |
| 19. Early mobilization |
| 20. Analgesia |
| 21. Postoperative nausea and vomiting prophylaxis |
| 22. Fluid management |
| 23. Audit |

First, it was performed a retrospective evaluation of 50 patients that underwent elective hepatic resections (without biliary anastomosis) at Federal University of Health Sciences of Porto Alegre / Santa Casa Hospital of Porto Alegre, from June 2014 to August 2016, through medical records data (group 1). Patients operated on emergency situations were excluded from analysis.

Second phase took place between September 2016 and December 2017, and represents the implementation of the protocol itself. Thirty-five patients, managed by the same hepato-pancreato-biliary team, were prospectively evaluated (group 2).

Nomenclature for liver resections was derived from Brisbane terminology\textsuperscript{12}. Major hepatectomies represents removal of three or more Couinaud segments\textsuperscript{13}. Definitive diagnosis was obtained from analysis of the pathologic specimen. Complications were classified according to Clavien-Dindo Scale\textsuperscript{14}. Preoperative fasting protocol represents light meals ingestion until 6 h before surgery, and no more than 2 h for liquids. Carbohydrate loading with maltodextrin was offered to patients before operation.

The type of incision, as well as the use of prophylactic abdominal drainage, was performed according to surgeon’s discretion. Normothermia during surgery was maintained using circulating water garments and intravenous warmed solutions. Patients that were at mechanical ventilation after the end of the operation received a nasojejunal tube to guarantee enteral feeding on the first postoperative day (POD1). For the remaining, a liquid oral diet was offered on POD1.

Postoperative glycemic control was performed with manual injection of insulin according to a pre-established scale. For postoperative analgesia, thoracic epidural, local anesthesia with ropivacain plus intravenous analgesia or intravenous analgesia alone were used. Postoperative nausea and vomiting prophylaxis was accomplished with at least two of the following drugs: ondansentron, metoclopramide or bromopride. All patients that underwent major hepatectomies received a central line at the beginning of the operation, for central venous pressure mensuration during liver transection. The goal was to maintain central venous pressure below 5 mmHg. When necessary, intermittent hepatic pedicle clamping was held (clamping for 15 min, followed by 5 min of declamping).

Statistical analysis

Groups were tested for normality by Shapiro-Wilk test. Normal distributions were compared using Student’s t test, and non-normal by Mann-Whitney test. Statistical analysis was performed in the SPSS program version 22.0 using the chi-square test of homogeneity, with a level of significance of 5%.

RESULTS

Table 2 summarizes the participating groups. In total, 85 patients were included in the study, 50 that received the standard care and 35 patients the ERAS program. There were no differences between them regarding age, gender or type of major hepatectomy. There were also no significant differences between the groups in overall and major complications, neither in mortality rate nor pathological findings (Table 2).

The overall compliance rate before and after the implementation of ERAS protocol was 20% and 65%, respectively. The median postoperative hospital stay was 5 days (2-15) in ERAS group, and 7 (3-22) in control group (p<0.001). A significant number of patients completed the preoperative fasting protocol in ERAS group (70%), and carbohydrate loading with maltodextrin in 80% of them (p<0.001). Oral bowel preparation was omitted in all patients in group 1, and was performed in 24% of patients in group 2 (p=0.001). Similar outcomes were obtained regarding pre-anesthetic medication (p=0.001). Prophylactic nasogastric intubation was held in 62% in group 2, and in only 11.4% in group 1 (p<0.001). Following the same trend, prophylactic abdominal drainage was less common in ERAS group comparing with control (68.6% and 92%, p=0.012).

Regarding the type of incision, the j-shaped one was more prevalent in ERAS group, and bilateral sub-costal in control (29.4% and 69.4% respectively, P<0.001). Thirty-two (91.4%) of patients started enteral feeding on POD1 in ERAS group, being 82% by oral route. This proportion was significant higher than in group 2 (50%, p<0.001). Similarly, 82.9% and 88.6% of patients started postoperative early mobilization and proper postoperative nausea and vomiting prophylaxis in ERAS group (p=0.001). Of note, 100% of patients in ERAS group underwent systematic audit; this data was missing in control group. Table 3 summarizes the main outcomes.

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TABLE 2 - Characteristics of the groups.

|                         | ERAS GROUP (35) | CONTROL GROUP (50) | P   |
|-------------------------|-----------------|--------------------|-----|
| Age (years/max-min)     | 58 (24-78)      | 60 (22-82)         | 0.280 |
| Gender (male/female)    | 16/19           | 22/28              | 0.350 |
| Cirrhosis               | 5 (14.3)        | 9 (18)             | 0.080 |
| Major hepatectomy       | 9 (25.7)        | 14 (28)            | 0.430 |
| Hepatocyte technique    |                 |                    |      |
| Right Hepatectomy       | 3 (8.6)         | 6 (12)             | 0.093 |
| Left Hepatectomy        | 5 (14.3)        | 7 (14)             | 0.530 |
| Trisegmentectomy        | 1 (2.9)         | 1 (2)              | 0.560 |
| Bisegmentectomy         | 15 (42.9)       | 21 (42)            | 0.570 |
| Trisegmentectomy        | 2 (5.7)         | 0                  | 0.130 |
| Atipical Resections     | 9 (25.7)        | 15 (30)            | 0.059 |
| Liver pathology         |                 |                    |      |
| Colorectal Liver Metastases | 13 (37.1)      | 18 (36)            | 0.610 |
| Liver Adenoma           | 5 (14.3)        | 7 (14)             | 0.540 |
| Hepatocellular Carcinoma| 8 (22.9)        | 12 (24)            | 0.645 |
| Gallbladder Neoplasm    | 1 (2.9)         | 3 (6)              | 0.124 |
| Intrahepatic Cholangiocarcinoma | 2 (5.7) | 2 (4)              | 0.510 |
| Other                   | 6 (17.1)        | 8 (16)             | 0.420 |

TABLE 3 - Main outcomes after ERAS implementation.

| VARIABLES                        | ERAS (n=35) | CONTROL (n=50) | P   |
|----------------------------------|-------------|----------------|-----|
| Length of hospital stay, median  | 5 (2-15)    | 7 (3-22)       | <0.001 |
| (min-max)                        |             |                |     |
| Immune-suppression               | 0 (0.0)     | 1 (2.0)        | 0.928 |
| Carbohydrate loading             | 28 (80)     | 0 (0.0)        | <0.001 |
| Oral bowel preparation           | 0 (0.0)     | 12 (24.0)      | 0.001 |
| Pre-anesthetic medication        | 0 (0.0)     | 12 (24.0)      | 0.001 |
| Anti-thrombotic prophylaxis      | 34 (97.1)   | 48 (96.0)      | >0.999 |
| Perioperative steroid administration | 19 (54.3) | 8 (40.0)       | 0.460 |
| Antimicrobial prophylaxis        | 36 (100.0)  | 48 (96.0)      | 0.510 |
| Incision                         | 0            | 0.001          |     |
| J-shaped                         | 10 (29.4)   | 3 (6.1)        |     |
| Bilateral subcostal              | 10 (29.4)   | 34 (69.4)      |     |
| Laparoscopy                      | 14 (40.0)   | 12 (24.0)      | 0.181 |
| Nasogastric intubation           | 4 (11.4)    | 31 (62.0)      | <0.001 |
| Prophylactic abdominal drainage  | 24 (68.6)   | 46 (92.0)      | 0.012 |
| Preventing intraoperative hypothermia | 33 (94.3) | 36 (94.7)      | >0.999 |
| Postoperative nutrition POD1     | 32 (91.4)   | 25 (50.0)      | <0.001 |
| Postoperative glycemic control   | 24 (68.6)   | 29 (58.0)      | 0.446 |
| Omental flap                     | 2 (5.7)     | 0 (0.0)        | 0.167 |
| Stimulation of bowel movement    | 6 (17.1)    | 6 (12.0)       | 0.540 |
| Early mobilization               | 29 (82.9)   | 19 (38.0)      | <0.001 |
| Analgesia                        |             |                |     |
| Intravenous                      | 17 (48.6)   | 19 (38.0)      | 0.455 |
| Epidural                         | 18 (51.4)   | 31 (62.0)      | 0.455 |
| Local                            | 14 (40.0)   | 11 (22.0)      | 0.121 |
| Postoperative nausea and vomiting prophylaxis | 31 (88.6) | 27 (54.0)      | 0.001 |
| Fluid management                 | 27 (77.1)   | 17 (81.0)      | >0.999 |
| Audit                            | 35 (100.0)  |                |     |
| Overall Complications            | 8 (22.9)    | 12 (24)        | 0.878 |
| Dindo-Clavien ≥ 3               | 4 (11.4)    | 7 (14)         | 0.230 |
| Mortality                        | 0            | 1 (2)          | 0.720 |

**DISCUSSION**

Enhanced recovery programs (ERP), together with the development of minimally invasive approach and strategies to improve liver hypertrophy represent the greatest advances in hepatic surgery in the last decades. ERAS protocols are the most recent of them, bringing the concept of a multimodal pathway to achieve better results.

Probably, the most reproducible outcome in papers comparing ERAS guidelines with traditional care is the length of hospital stay (LOS). Liang et al., evaluating patients that underwent laparoscopic hepatocarcinomas according to ERAS protocols in China, showed a decrease in the median postoperative hospital stay in ERAS group of approximately three days. Similar conclusion was reported in a meta-analysis published by Li et al. in 2017, analyzing 254 patients treated according to ERAS guidelines. They verified that the postoperative recovery time and length of hospital stay were significantly better in this group. These two studies show that the benefit is not only related to laparoscopy itself, but also to the compilation of evidenced-based steps that work together to optimize perioperative recovery. In our work, we reduced the LOS in two days, even with the same rate of laparoscopic hepatocarcinomas in both groups. This result is in line with recent reports.

In our study, a significant number of patients completed the fasting protocol, with light meals intake until 6 h before surgery, and carbohydrate loading with maltodextrin 2 h before operation. These measures not only give comfort and reduce anxiety in preoperative hours, but are also related to a reduction in catabolism and insulin resistance in some papers. Of note, we did not verified and increase in perioperative complications (like aspiration during anesthesia or postoperative pneumonia) following these recommendations. The same line of reasoning can be made for oral bowel preparation, pre-anesthetic medication and prophylactic nasogastric intubation; its omission could be done safely.

Prophylactic abdominal drainage remains an area of uncertainty after liver surgery. Since the first evidenced-based publications regarding the use of prophylactic drains after abdominal operations, the debate about its real benefit in preventing postoperative complications after hepatic resections came to light. A recent study by Brauer et al., analyzing databases of several American institutions, showed that drainage of the surgical site after hepatectomies did not improve the rate of diagnosis of major biliary leaks, in addition to increase the number of interventions, the LOS and 30-day readmissions. On the other hand, Kyoden et al. in 2010, questioned the design of previous studies that disfavored the routine use of drains, as well as its management in the postoperative period. Evaluating the value of prophylactic drainage in 1269 consecutive hepatectomies performed at the University of Tokyo, they concluded that prophylactic drainage was effective in reducing the frequency of subphrenic collections and bilary fistulas in a large number of patients.

Enhanced recovery pathways, in general, discourage the routine use of drains, as there is some evidence that a no-drain policy is safe and feasible after uncomplicated hepatectomies. In our cohort, there was a significance reduction in the placement of abdominal drains in ERAS group, without increasing complications like infected collections, hemorrhage, percutaneous drainage or reoperations.

Minimally invasive liver surgery (MILS) still represents a challenge operation even for experienced surgeons. However, after the publication of two consensus giving recommendations about laparoscopic liver resections, its use has grown and spread throughout the world, mainly because of the benefits related to the method, as less wound complications and postoperative pain, early mobilization and a decrease in LOS. Despite this, it requires specific material for its adequate fulfillment, which is not available in the Brazilian public health system. Thus, in our series, even with and increase in MILS in ERAS group, the 40% report rate is far behind from our expectations, especially when we have 68% of patients that underwent bisegmentectomies or atypical resections.

Therefore, many hepatic resections in our series were...
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REFERENCES

1. Amico EC, Alves JR, Joao SA, Guimarães PL, Medeiros JA, Barreto EJ. Immediate complications after 80 hepatectomies - Brazilian consecutive series. Arq Bras Cir Dig. 2016;29(3):180-184.
2. Aguilar-Nascimento JEC, Bicudo-Salomoa A, Caporossi C, Silva RM, Cardoso EA, Santos TP. Enhancing surgical recovery in Central-West Brazil: The ACERTO protocol results. e-SFEN, Eur J Clin Nutr. 2006;32:e78-e83.
3. Aguilar-Nascimento JEC, Bicudo SA, Waizberg DL, Nascimento DB, Correa MI, Campos ACL, et al. ACERTO guidelines of perioperative nutritional interventions in elective general surgery. Rev. Col. Bras. Cir. 2017; 44(6):633-648.
4. Belghiti J, Clavien PA, Gadzijev. The Brisbane 2010 terminology of liver anatomy and resections. HPB 2000;2:333–9.
5. Belghiti J, Kabbe J, Sauvanet A, Vilgrain V, Panis Y, Fekete F. Drainage after elective hepatectomy. Randomized trial. Ann.Surg.1993;218(6):748-53.
6. Bond-Smith G, Belgaumkar AP, Davidson BR, Gurusamy KS. Enhanced recovery protocols for patients undergoing upper gastrointestinal surgery. Cochrane Database Syst Rev. 2016;2:CD011382.
7. Brauer DG, Nywening TM, Jaques DP. Operative Site Drainage after Hepatectomy: A Propensity Score Matched Analysis Using the American College of Surgeons NSQIP-Targeted Hepatectomy Database. J Am Coll Surg. 2016;223(6):774-783.
8. Buefl JF, Cherqui D, Geller DA, O’Rourke N, Iannitti D, Daghir J, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg. 2009;250:825–830.
9. Chang SB, Palavecino M, Wray CJ, Kishi Y, Pisters PW, Vauthey JN. Modified Makuuchi incision for foregut procedures. Arch Surg. 2010;145(3):281-4.
10. D’Angelica M, Maddennini S, Fong Y, Martin RCG, Cohen MS, Ben-Porta L, et al. Optimal abdominal incision for partial hepatectomy: increased late complications with Mercedes-type incisions compared to extended right subcostal incisions. World J Surg. 2006;30(3):410-8.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.
12. Fortner JG, Blumgart LH. A historic perspective of liver surgery for tumors at the end of the millennium. J Am Coll Surg 2001; 193:210–222.
13. Ichida H, Ihamura H, Yoshimoto J, Sugo H, Ishizaki Y, Kawaiaki S. Randomized Controlled Trial for Evaluation of the Routine Use of NasogastricTube Decompression After Elective Liver Surgery. J Gastrointest Surg. 2016;20(7):1324-30.
14. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012;6:CD000259.
15. Koiden Y, Imamura H, Sano K, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg. 2009;250:825–830.
16. Lee J, Kwon CH, Kim JM, Shin M, Joh JW. Effect of early enteral nutrition after hepatectomy in hepatocellular carcinoma patients. Korean J Hepatobiliary Pancreat Surg. 2012;16(4):129-33.
17. Li L, Chen J, Liu Z, Li Q, Shi Y. Enhanced recovery program versus traditionalcare after hepatectomy: A meta-analysis. Medicine (Baltimore). 2017;96(36):e8052.
24. Liang X, Ying H, Wang H, Xu H, Yu H, Cai L. Enhanced Recovery Program Versus Traditional Care in Laparoscopic Hepatectomy. Medicine (Baltimore). 2016;95(8):e2835.

25. Maurice-Szamburski A, Auquier P, Viarre-Oreal V. Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. JAMA. 2015;313(9):916-25.

26. Melloul E, Hubner M, Scott M, Snowden C, Prents J, Dejong CH, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg 2016;40:2425–2440.

27. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2007;18(3):CD004929.

28. Pais-Costa SR, Araújo SLM, Lima OAT, Martins SJ. Critical evaluation of long-term results of malignant hepatic tumors treated by means curative laparoscopic hepatectomy. Arq Bras Cir Dig. 2017;30(3):205-210.

29. Pessaux P, Regimbeau JM, Dondéro F, Plasse M, Mantz J, Belghiti J. Randomized clinical trial evaluating the need for routine nasogastric decompression after elective hepatic resection. Br J Surg. 2007;94(3):297-303.

30. Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. Ann Surg. 2004;240(6):1074-84.

31. Reddy SK, Marroquin CE, Kuo PC, Pappas TN, Clary BM. Extended hepatic resection for gallbladder cancer. Am J Surg. 2007;194(3):355-61.

32. Rodrigues TFDC, Silveira B, Tavares FP, et al. Open, laparoscopic, and robotic-assisted hepatectomy in resection of liver tumors: an non-systematic review. Arq Bras Cir Dig. 2017;30(2):155-160.

33. Sánchez-Urdazpal González L, Salido Fernández S, Alday Muñoz E, Gómez Martín-Tesorero L, Molina Baena B. Implementation of an ERAS program in liver surgery. Nutr Hosp. 2015;31 Suppl 5:16-29.

34. Savikko J, Ilmakunnas M, Mäkisalo H, Nordin A, Isoniemi H. Enhanced recovery protocol after liver resection. Br J Surg. 2015;102(12):1526-32.

35. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255:405–414.

36. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Moriga. Ann Surg. 2015;261:619–629.

37. Wang C, Zheng G, Zhang W, Zhang F, Lv S, Wang A, et al. Enhanced Recovery after Surgery after Liver Resection: a Meta-analysis. J Gastrointest Surg. 2017;21(3):472-486.

38. Wilmore D. From Cuthbertson to Fast-Track Surgery: 70 Years of Progress in Reducing Stress in Surgical Patients. Ann Surg. 2002;236(5):643-8.

39. Wong-Lun-Hing EM, van Woerden V, Lodewick TM, Bemelmans MHA, Olde Damink SWM, Dejong CHC. Abandoning Prophylactic Abdominal Drainage after Hepatic Surgery: 10 Years of No-Drain Policy in an Enhanced Recovery after Surgery Environment. Dig Surg. 2017;34(5):411-420.

40. Yan X, Zhou FX, Lan T, Xu H, Yang XX, ChieCH, et al. Optimal postoperative nutrition support for patients with gastrointestinal malignancy: A systematic review and meta-analysis. Clin Nutr. 2017;36(3):710-721.

41. Yip VS, Dunne DF, Samuels S, Tan CY, Lacasia C, Tang J, et al. Adherence to early mobilisation: Key for successful enhanced recovery after liver resection. Eur J Surg Oncol. 2016;42(10):1561-7.