

Surgical Stress Reduction in Elderly Patients Undergoing Elective Colorectal Laparoscopic Surgery within an ERAS Protocol

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Rezumat

Reducerea stresului chirurgical în cadrul unui protocol ERAS la pacienții în vârstă supuși chirurgiei electivă colorectale laparoscopice

Protocolul ERAS (Enhanced Recovery After Surgery) de recuperare aplicat chirurgiei colorectale laparoscopice este cunoscut a reduce durata de spitalizare, îmbunătățind rezultatele pe termen scurt și minimizând Răspunsul la Stresul Chirurgical. Totuși, eficacitatea sa în rândul populației de pacienți în vârstă nu a fost încă demonstrată. Scopul primar al acestui studiu este de a compara nivelul markerilor serici imuni și nutriționali pe parcursul etapelor intervenției chirurgicale la pacienții de peste 70 de ani supuși chirurgiei electivă colorectale laparoscopice acompaniate de un protocol ERAS sau conform unui program standard. 83 de pacienți supuși chirurgiei colorectale laparoscopice au fost incluși în studiu și distribuiți în mod randomizat în două grupuri (40 în grupul ERAS și 43 în Grupul Standard), în cadrul unui studiu randomizat efectuat asupra unei populații generale mai ample. Parametrii de stres chirurgical au fost înregistrați preoperator, la una, trei și cinci zile după operație. Parametrii nutriționali au fost înregistrați preoperator, la una, trei și cinci zile după operație. Rezultatele pe termen scurt au fost de asemenea evaluate prospectiv. Nivelurile de IL-6 au fost mai scăzute în

grupul ERAS la una, trei și cinci zile postoperator ($p < 0,05$). Nivelurile de IL-6 au revenit la valorile preoperatorii în grupul ERAS la 3 zile după operație. Nivelul Proteinei C Reactive în grupul ERAS au fost mai scăzute în grupul ERAS la una, trei și cinci zile postoperator ($p < 0,05$). Nu au existat diferențe între grupuri în ceea ce privește nivelurile de cortizol și prolactină. Nivelul seric de prealbumină a fost mai crescut în ziua 5 postoperator ($p < 0,05$) comparativ cu grupul standard. Rezultatele postoperatorii în ceea ce privește motilitatea intestinală normală și durata spitalizării au fost semnificativ mai bune în grupul ERAS. Chirurgia colorectală laparoscopică acompaniată de un protocol ERAS la pacienții în vârstă influențează Răspunsul la Stresul Chirurgical, scăzând nivelurile de IL-6 și PCR postoperator și îmbunătățind sinteza postoperatorie de prealbumină.

Cuvinte cheie: răspunsul la stresul chirurgical, chirurgie colorectală, pacienții vârstnici, program de recuperare îmbunătățit

Abstract

ERAS program applied to colorectal laparoscopic surgery is well known to reduce hospitalization improving short terms outcomes and minimizing the Surgical Stress Response. However its effectiveness in elderly population is yet to be demonstrated. The primary aim of this study is to compare the level of immune and nutritional serum indexes across surgery in patients aged over 70 years old undergoing elective colorectal laparoscopic surgery within an ERAS protocol or according to a Standard

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program. 83 patients undergoing colorectal laparoscopic surgery were enrolled and randomized in two groups (ERAS Group 40, Standard Group 43) within a larger randomized trial on a general population. Surgical stress parameters were collected preoperatively, 1, 3 and 5 days after surgery. Nutritional parameters were collected preoperatively, 1 and 5 days after surgery. Short Term Outcomes were also prospectively assessed. IL-6 levels were lower in the EG on 1, 3, and 5 days post-operatively ($p < 0.05$). IL-6 levels in the Enhanced group returned to pre operative level 3 days after surgery. C-reactive protein level was lower in the Enhanced group on day 1, 3, and 5 ($p < 0.05$). There was no difference in Cortisol and Prolactin levels between groups. Prealbumin serum level was higher on day 5 ($p < 0.05$) compared to standard group. Postoperative outcomes in terms of normal bowel function and length of hospital stay were significantly improved in the ERAS group. Colorectal laparoscopic surgery within an ERAS protocol in elderly patients affects Surgical Stress Response, decreasing IL-6 and CRP levels post-operatively and improving Prealbumin post operative synthesis.

Key words: surgical stress response, colorectal surgery, elderly patients, enhanced recovery program

Introduction

ERAS (Enhanced Recovery After Surgery) is a multidisciplinary approach aimed to enhance recovery and preserve immune function. (1,2,3)

Its effectiveness in reducing hospital stay is well described in literature above all in colorectal surgery (4).

No mechanical bowel preparation, no preoperative fasting, early postoperative feeding, avoidance of opiates, avoidance of fluid overload, reduced use of surgical devices such as nasogastric tube and drains are only some of ERAS items (5).

Hospitalization and surgery are known to affect the normal homeostasis. This process is called Surgical Stress Response and involves both immune and neuro-endocrine systems (6,7,8). ERAS aims at protecting the organism from an excessive surgical stress. However, to date there is only an initial knowledge about the measurable reduction of Surgical Stress Response that ERAS allows and about the mechanisms involved in such reduction (9,10,11).

C-Reactive protein (CRP) and cytokines (IL-1, IL-6) above all are known to be related to the extent of inflamed and traumatized tissue involved (10,11).

ERAS applied to elective colorectal laparoscopic surgery has been initially associated to a reduction in SSR when compared to the standard of care. This seems to be true for a general population. However ERAS capability of reducing SSR in an elderly population to our knowledge has not been proven yet (12). This study is a sub-analysis of elderly patients within a larger randomized trial aiming to compare the levels of immune and nutritional serum markers before and after surgery in patients undergoing elective colorectal laparoscopic procedures within an ERAS protocol or according to the Standard of care.

Table 1. Patient characteristics. EG: ERAS Group; SG: Standard Group; ASA: American Society of Anesthesiologists Score; B.M.I: Body Mass Index

TOT	GC	ERAS	TOT	
N°	83	43	40	n.s.
Age	76 (70 - 87)	76,5 (70 - 85)	77,1 (70 - 87)	n.s.
Male	41	19	22	n.s.
Female	42	24	18	n.s.
B.M.I.	25.9 (± 4.6)	25.7 (± 3.3)	26.9 (± 4.2)	n.s.
A.S.A. I	14	9	5	n.s.
A.S.A. II	53	25	28	n.s.
A.S.A. III	16	9	7	n.s.
Stage I	22	12	10	n.s.
Stage II	23	13	10	n.s.
Stage III	32	14	18	n.s.
Stage IV	6	4	2	n.s.
Right hemicolectomy	38	18	20	n.s.
Left hemicolectomy	32	19	13	n.s.
Rectal Resection	13	6	7	n.s.

Materials and Methods

Patients 70 years old and above randomized in the ERAS Group (EG) and in the Standard of Care Group (SG) are described in Table 1. To be enrolled in either group they had to be autonomous for mobilization and walking, eligible for laparoscopic technique, with an American Society of Anaesthesiologists score I through III, with an indication for major colo-rectal surgery. EG followed ERAS guidelines as suggested by Gustafsson with a 90% accordance (5). SG differed from EG in delaying oral feeding and mobilization on day 1, in keeping nasogastric tube until day 1 and in giving opioid based analgesia on day 0 and 1 (up to 30 mg in 24 h). Peripheral blood and serum were collected pre-operatively (baseline), 1, 3 and 5 days after surgery for stress parameters, pre-operatively, 1 and 5 five days after surgery for nutritional parameters. Pre-operative samples were collected within 4 days before surgery.

QOL was investigated with the Gastrointestinal Quality of Life Indicator (GIQLI) developed to indicate QOL in patients undergoing major gastrointestinal surgery 19, 20 and recorded 30 days post-operatively for all patients. BARTHEL index (meant to measure performance in daily living activities) was assessed for all patients at the admission and at 1 month post-operatively.

Stress status

Cortisol concentrations in serum were measured by competitive immunoassay. Its range of normality (r.n.) is between 2.3-19.4 mcg/L. Prolactin concentrations in serum were measured by immunometric assay (r.n. 4.05-23.3 ng/mL). IL-6 concentrations in serum were measured using ELISA test kits (r.n. 0-10 pg/mL). C-Reactive Protein levels were measured by immunoturbidimetric method (r.n. 0-5 mg/L). Procalcitonin levels were measured with immunoluminometric assay (r.n. 0-0.5 ng/mL). White Blood Cell Count was also performed (r.n. 4000-10000/mm³).

Nutritional status

Transferrin serum levels were measured with immunonefelo-metric test (r.n. 174-331 mg/dL). Prealbumin serum levels were measured by immunoturbidimetric method (r.n. 10-40 mg/dL). Albumin (r.n. 3.8-5.3 g/dL) and Triglyceride (r.n. 24-152 mg/dl) serum levels were measured by colorimetric analysis.

Statistical analysis was performed using the SPSS software package (SPSS 16.0 for Windows; SPSS, Chicago, IL). Chi-square Test, T test, Fisher Exact Test, and analysis of variance (ANOVA) Tests were applied for group comparison when appropriate. An intention-to-treat principle was applied, therefore, conversions were still analyzed. Significance was set at $p < 0.05$.

The trial was approved by the local ethical committee.

Results

Patient characteristics in terms of age, body mass index, sex, American Society of Anaesthesiologists classification and surgical procedure were comparable for all groups and are described in Table 1. 100% (43/43) of samples were collected and analyzed in the SG, 95% (38/40) of samples were collected in the EG.

Stress status

All values for Stress Status are described in Table 2. There was no statistically significant difference in the pre-operative Stress Status for all parameters in the two groups. IL-6 increased significantly after surgery in both groups. However IL-6 levels were lower in the EG on 1, 3, and 5 days p.o. ($p < 0.05$) compared to SG. IL-6 levels in the EG, returned to pre operative level 3 days after surgery (Fig. 1). C-Reactive Protein level as well increased significantly after surgery in both groups. PCR was lower in the EG on 1, 3 and 5 days p.o. ($p < 0.05$). We did not appreciate return to pre-operative levels in both groups (Fig. 2). There were no significant differences between groups for White Blood Cell Count, Cortisol and Prolactin before and after surgery.

IL-6

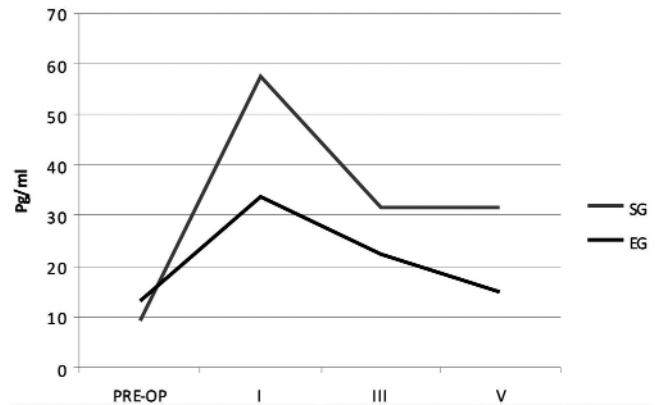


Figure 1. IL-6 trend shows significance on day I,III and V for EG compared to SG. IL-6 values for EG returned to pre-op. levels on day III.

*: Statically significant difference between groups ($p < 0.05$).

IL-6: Interleukin-6; PRE-OP: Pre-operative; I,III,V: Post-operative day.

PCR

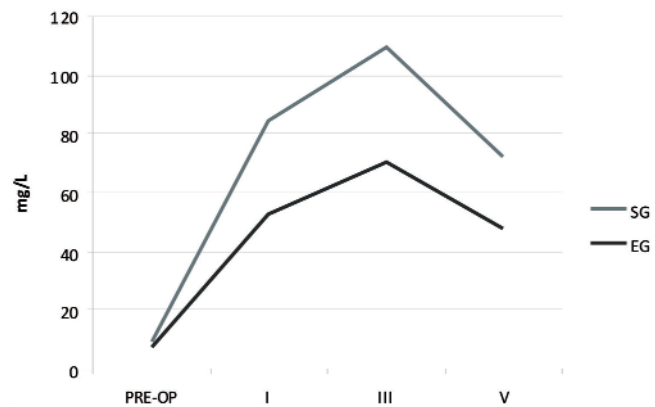


Figure 2. CRP levels shows significance on day I, III and V for EG vlaues compared to SG. CRP: C Reactive Protein; PRE-OP: Pre-operative; I,III,V: Post-operative day.

*: Statically significant difference between groups ($p < 0.05$).

Table 2. Stress status values

Stress markes		PRE-OP.	I	III	V
CRP (mg/L)	EG	7.9 (±10.8)	*52.9 (±29.9)	*70.8 (±69.2)	*47.8 (±53.7)
	SG	9.7 (±28.9)	84.2 (±67.9)	109.3 (±76.4)	72.1 (±54.5)
PRL (ng/dl)	EG	17.5 (±10.6)	25.4 (±14.6)	20.2 (±13.46)	18.1 (±10.9)
	SG	11.6 (±5.8)	17.9 (±15.2)	16.5 (±13)	17.16 (±11.7)
WBC (/mm³)	EG	6345 (±2065)	9295 (±2587)	7905 (±2444)	6260 (±1825)
	SG	6428 (±1596)	10132 (±2929)	9600 (±2984)	7880 (±2262)
IL-6 (pg/ml)	EG	13.1 (±36.5)	*33.5 (±24.2)	*22.3 (±17.2)	*14.8 (±24.1)
	SG	9.2 (±11.8)	57.4 (±19.1)	31.6 (±21.1)	31.5 (±27.3)
CORTISOL (mcg/dl)	EG	16.4 (±6.6)	11.7 (±8.1)	18.8 (±9.7)	16.2 (±8.1)
	SG	18.1 (±3.6)	17.4 (±11.1)	22.1 (±8.1)	22.8 (±10.9)

EG: Eras Group; SG: Standard Group. *Lower significantly $p < 0.05$. CRP: C Reactive Protein; PRL: Prolactin; WBC: White Blood Cells; IL-6: Interleukin-6.

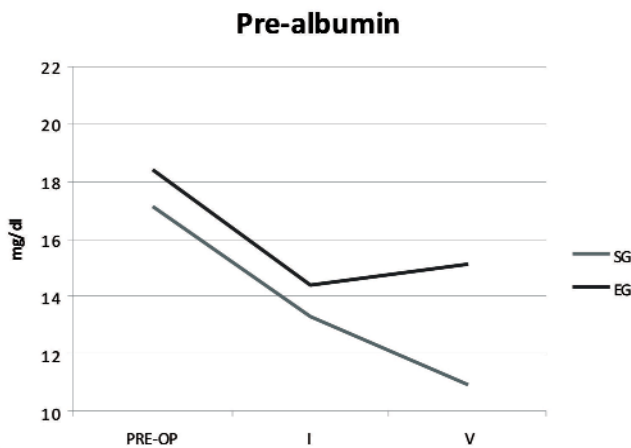


Figure 3. Pre-Albumin levels shows significance on day V for EG compared to SG. PRE-OP: Pre-operative; I,III,V: Post-operative day.

*: Statically significant difference between groups ($p < 0,05$).

Nutritional Status

All values for Nutritional Status are described in Table 3. Prealbumin serum level was higher in EG on day 5 ($p < 0.05$) compared to SG (Fig. 3). There was no return to pre operative levels for both groups. There where no significant differences for Albumin, Triglyceride and Transferrin levels between groups before and after surgery.

Operative data and short term outcomes

There was no difference in length of surgery between groups. 1 patients in the SG and 2 in the EG received laparotomic conversion due to peritoneal adhesions in 2 cases (1 SG/1EG), due to bulky tumor in 1 case (1SG). 1 patients in the EG and 1 in the SG developed an anastomotic fistula. 1 patient in the EG and 1 patient in the SG required re-intervention.

In the postoperative period, EG patients returned faster to a normal bowel function. Passage of flatus and return to a solid meal happened statistically earlier in the EG. First flatus occurred on day 1.5 ± 0.6 in the EG versus 2.4 ± 0.9 in the SG ($p < 0.05$). However there was no difference between groups for passage of stool. Solid meal was tolerated at day 1.2

± 0.8 in the EG versus 2.9 ± 0.3 in the SG ($p < 0.05$). EG patients could walk at least 100 meters on day 1.6 ± 0.8 versus $2,9 \pm 0.9$ in the SG ($p < 0.05$). Day of discharge was 4.7 ± 1.2 in the EG versus 6 ± 1.6 in the SG ($p < 0.05$). (Table 4)

Discussion

In elderly patients the homeostatic balance is more easily alterable by exogenous stimuli. That’s why functional recovery after surgery can be more complex compared to non-elderly patients. It is therefore extremely important to affect as little as possible a balance already compromised by age itself. From this point of view early discharge as well, in the elderly is an important goal to achieve. Returning home is physically and mentally restorative for people used to spend most of the time indoors. Long hospitalization in fact can easily worsen mental perception in the elderly. The application of the ERAS protocol to elderly patients has been well described and tested with encouraging results. This study tries to go further, improving the understanding on the physio-pathological mechanisms whereby ERAS attenuates surgical stress response in such a population. To a certain extent an adequate stress response is advantageous for patients. Excessive and prolonged stress consequent to invasive surgery, can nevertheless leadto a pathological state, above all in fragile patients.

The data collected in the first place denote that an elderly population of patients, such as the one described in our study, is able to field a significant inflammatory response both innate and cell-mediated.

The reduced expression of IL-6 and CPR in the EG as compared tothe SG confirms the information given by other studies in the literature by extending this result also to an elderly sub-population (10,11).

Pre-albumin level was significantly higher in the EG on day 5. Pre albumin levels reflect the inflammatory status and the hepaticsynthesis in patients undergoing surgery. Both these aspects seem to be positively affected by the ERAS protocol resulting in a possible earlier end of the catabolic phase induced by surgery.

The short terms outcomes that we report confirm the available data about ERAS applied to colorectal laparoscopic surgery in a normal age range population (1). Recently two studies reported the feasibility of ERAS programs applied to

Table 3. Nutritional status values

Nutritional markers		PRE-OP	I	V
TRF (mg/dl)	EG	243 (± 43.2)	202 (± 42.2)	197 (± 49.8)
	SG	234 (± 37.8)	178 (± 34.5)	174 (± 39.3)
PRE-ALB (mg/dl)	EG	18.4 (± 5.1)	14.4 (± 5)	*15.1 (± 3.4)
	SG	17.1 (± 6.6)	13.3 (± 4.4)	10.9 (± 4.1)
ALB (g/dl)	EG	3.59 (± 0.35)	3.12 (± 0.3)	3.13 (± 0.35)
	SG	3.59 (± 0.38)	3.09 (± 0.36)	3.16 (± 0.41)
TRGL (mg/dl)	EG	102.8 (± 53)	69.55 (± 36.2)	95.8 (± 34)
	SG	97.3 (± 30.9)	63.28 (± 17.6)	90.92 (± 28.5)

EG: Eras Group; SD Standard Group. * Higher significantly ($p < 0,05$). TRF: Transferrin; PRE-ALB: Pre-Albumin; ALB: Albumin; TRGL: Triglycerides.

elderly patients undergoing open and laparoscopic colorectal surgery (13,14). This study enforces these initial clinical findings being the first one to focus on the SSR.

The main bias of this study is that it was not designed to specifically inquire an elderly population. Statistical analysis could therefore be underpowered. However the described data provide precious and reliable informations on SSR in elderly patients. A larger study with a pre-fashioned sample size calculation is advisable.

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