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CHAPTER 9

Surgical stress response and post-operative immune function after laparoscopy or open surgery with fast track or standard perioperative care: A randomized trial

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Abstract

Purpose

To evaluate the effect of laparoscopic or open colectomy with fast track or standard perioperative care on patient's immune status and stress response following surgery.

Methods

Patients with non metastasized colon cancer were randomized to laparoscopic or open colectomy with fast track or standard care, resulting in four different treatment groups. Blood samples were taken preoperatively (baseline), 1 hour, 2 hours, 24 hours and 72 hours following surgery. Systemic HLA-DR expression on monocytes, C-reactive protein, Interleukin-6, growth hormone, prolactin and cortisol were analyzed.

Results

Nineteen patients were randomized for laparoscopy and fast track care (LFT), 23 for laparoscopy and standard care (LS), 17 for open surgery and fast track care (OFT) and 20 for open surgery and standard care (OS). Patient characteristics in terms of age, gender, ASA classification, localization of the tumor and type of resection were comparable for all groups. HLA-DR expression on monocytes was best preserved in the LFT group 2 hours (P=0.002) and 24 hours (P=0.003) postoperatively. Interleukin-6 was significantly increased in the OS group 24 hours (P=0.048) and 72 hours (P=0.05) postoperatively. C-reactive protein was significantly increased in the OS group 1 hour (P=0.002), 2 hours (P=0.011), 24 hours (P=0.048) and 72 hours (P=0.009) postoperatively. No differences between the groups were seen regarding growth hormone, prolactin, or cortisol levels. No differences in (infectious)complication rates were observed between the groups.

Conclusion

This randomized trial showed that immune function is best preserved in patients having laparoscopic colectomy within a fast track program. Patients treated by open surgery in combination with standard care do worst. There are no differences between the groups concerning the hormonal response to surgery. These results support the accelerated recovery of patients treated laparoscopically within a fast track program.

Introduction

The first minimally invasive colon resection was described in 1991 by Jacobs et al.[1] The short term advantages of minimally invasive colon resection have been well established in several randomized trials.[2-5] However, major surgery still remains associated with postoperative morbidity and undesirable side effects such as pain, cardiopulmonary, infective, and thromboembolic complications. A major factor in the development of morbidity is the surgical stress response with subsequent increased demand on the patient's reserves and immune competence. Increased demands in organ functions are thought to be mediated by trauma induced endocrine and metabolic changes.

HLA-DR expression on monocytes is a measure for immune competence and is associated with adequate presentation of antigen and specific immune response in humans. Levels of C-reactive protein and cytokines are closely related with the inflammatory response and the extent of the inflamed tissue involved, as well with the activity of the immune reaction. Interleukin-6 levels are associated with postoperative complication rates and are a predictor of morbidity following surgical intervention.

Previously, Harmon et al.[6] and Wu et al.[7] have described lower interleukin-6 levels following laparoscopic colectomy in smaller trials. Schwenk et al.[8] reported lower concentrations of both interleukin-6 and C-reactive protein following laparoscopic colectomy.

Following the introduction of minimally invasive techniques, in 2001 Kehlet introduced the second major advancement in modern elective colorectal surgery; the implementation of the 'fast track' perioperative care.[9-11] The fast track recovery program comprises a multidisciplinary approach aiming to reduce surgical stress response, enhance immune function, and thereby reduce organ dysfunction and allow for a faster recovery following surgery.[9]

Up to date there is little evidence for a better preserved immune status, which is in line with the observed lower morbidity and faster recovery of minimally invasive colectomy. In addition, no previous studies have investigated immune status and stress response following fast track recovery programs. Hence, the aim of this study was to evaluate the effect of laparoscopic or open colectomy with fast track or standard perioperative care on patient's immune status and stress response following surgery.

Materials and methods

Eligible patients were those with a histologically confirmed malignancy or adenoma planned for an elective, segmental, curative colectomy. Patients had to be between 40 and 80 years of age with an American Society of Anaesthesiologists (ASA) grade I through III. Patients with a previous midline laparotomy, emergency surgery, a planned stoma or immune depressant disease or medication were excluded from this study. Once informed consent was obtained, patients included in the VU University Medical Center and Academic Medical Center were randomized. This was done as a substudy of the LAFA trial, a randomized trial of a 2 x 2 balanced factorial design.[12]

Randomization was achieved by means of an internet module. Patients were randomized to 4 different treatment groups; laparoscopic colectomy with fast track care (LFT), laparoscopic colectomy with standard care (LS), open colectomy with fast track care (OFT), and open colectomy with standard care (OS). The study was conducted in accordance with the principles of the Declaration of Helsinki and the present protocol was approved by the local medical ethics review boards (protocol NTR222).[12]

Peripheral blood and serum (BD Vacutainer Systems, Plymouth, UK) were collected preoperatively (baseline), 1 hour, 2 hours, 24 hours, and 72 hours after surgery. All samples had to be collected within 10 minutes of the exact preset postoperative times. Transportation of the serum to the laboratory had to be accomplished within 10 minutes. Serum interleukin-6, C-reactive protein, prolactin, cortisol, and growth hormone samples were obtained by centrifugation for 10 minutes at 3 000 rpm at 4 degrees Celsius. All samples were stored in aliquots at -80 degrees Celsius until tested in a one block fashion. HLA-DR expression on monocytes were analysed directly on full blood samples.

Immune status

HLA-DR expression on monocytes

Numbers and phenotype of white blood cells and monocytes were determined in fresh (<2 hrs) heparinised venous blood. Phenotyping was performed by using CD14-PE and HLA-DR-FITC moAbs (Becton Dickinson), subsequent lysis of erythrocytes and fixation with paraformaldyde. Monocyte HLA-DR expression was evaluated by FACS analysis (FACS Calibur, Becton Dickinson, San Jose, CA, USA) quantified by using calibration beads (Quantum-TM 26, Flow Cytometry Standards Corp, Bangs Laboratories, Inc, Fisher IN) and expressed as ratio of the mean fluorescence intensity post/pre surgery.

Interleukin-6 (IL-6)

IL-6 concentrations in serum were measured using commercially available enzyme-linked immunosorbent assay kits (Pelikine compact human ELISA kits, Sanquin, Amsterdam, the Netherlands).

C-reactive protein (CRP)

Plasma CRP levels were measured by immunoturbidimetric method, using the BM/Hitachi 705 (Boeingher, Mannheim, Germany).

Stress response

Cortisol

Cortisol concentrations in serum were measured by competitive immunoassay (Bayer Diagnostics, Mijdrecht, The Netherlands).

Prolactin

Prolactin concentrations in serum were measured by immunometric assay (DPC, Los Angeles, USA).

Growth hormone

Growth hormone concentrations in serum were measured by immunometric assay (Bayer Diagnostics, Mijdrecht, The Netherlands).

Statistical analysis

Statistical analysis was performed using the SPSS software package (SPSS 16.0 for Windows; SPSS, Chicago, IL, USA). Medians, means, ranges, and inter-quartile ranges were calculated and subsequently depicted when appropriate. The Mann Whitney U test, Chi-squared test, Fisher's exact test, independent samples T-test or ANOVA test were applied when appropriate for group comparisons. An intention to treat principle was applied. Significance was set at $p<0.05$.

Results

Patients

A total of 79 patients were randomized. Nineteen patients were randomized for laparoscopic surgery with fast track care (LFT), 23 for laparoscopic surgery with standard care (LS), 17 for open surgery with fast track care (OFT) and 20 for open surgery with standard care. Patient characteristics in terms of age, body mass index (BMI), gender, ASA classification or operative procedure were comparable for all groups and are depicted in Table 1. Of all blood sample accrual times described by protocol, 94.9% of samples were collected and analysed on time as described by study protocol.

Immune Status

All exact values for immune competence are depicted in Table 2. Monocyte HLA-DR expression was used as a parameter for surgery induced attenuated immune competence. Two hours and 24 hours following surgery HLA-DR expression on monocytes was significantly better preserved in the LFT group (P=0.002 and P=0.003, respectively). After 72 hours a trend was observed for better preservation of immune competence in the LFT group (P=0.07, Figure 1).

IL-6 levels did not significantly differ between the groups 1 hour and 2 hours following surgery. After 24 hours and 72 hours a significant increase in IL-6 levels was observed for the OS group (P=0.048 and P=0.05, respectively, Figure 2).

CRP levels were significantly increased for the OS group at 1 hour, 2 hours, 24 hours and 72 hours following surgery (P=0.002, P=0.011, P=0.048 and P=0.009, respectively, Figure 3).

Stress response

All values regarding stress response are depicted in Table 2. Growth hormone, prolactin and

cortisol levels did not differ during the postoperative follow-up between the 4 groups at any time-interval.

Operative and hospital data

Duration of the operative procedure was significantly longer for laparoscopy, whereas blood loss was significantly lower. In-hospital morbidity for the first 72 hours was similar for all groups. One patient in the LS group required a conversion due to a bulky tumor with minor ingrowth in the abdominal wall. The results of this patient were analyzed in an intention to treat principle (Table 3).

Table 1 Patient and tumour characteristics

	LFT (n=19)	**LS (n=23)**	**OFT (n=17)**	**OS (n=20)**	**P**
Gender, n (%)					
- Male	10 (53)	19 (82)	9 (53)	14 (70)	0.12
- Female	9 (47)	4 (18)	8 (47)	6 (30)	
Age, years	65 (46-80)	68 (42-80)	65 (40-80)	68 (42-80)	0.77
BMI, kg/m^2	27 (22-36)	24 (20-32)	27 (19-39)	25 (21-31)	0.14
ASA, n (%)					
- 1	7 (37)	7 (30)	3 (18)	6 (30)	0.34
- 2	11 (58)	13 (57)	13 (76)	8 (40)	
- 3	1 (5)	3 (13)	1 (6)	6 (30)	
Operation, n (%)					
- Left-sided	14 (74)	10 (44)	9 (53)	7 (35)	0.09
- Right-sided	5 (26)	13 (56)	8 (47)	13 (65)	

Values are mean (range) / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard / BMI = Body Mass Index / ASA = American Society of Anaesthesiologists

Table 2 Postoperative immune and stress response

Variable	Groups	1 hour	2 hours	24 hours	72 hours
HLA-DR	- LFT		87 (42-89)	59 (24-89)	73 (19-118)
	- LS		80 (44-171)	55 (20-99)	65 (16-147)
	- OFT		58 (6-137)	41 (15-67)	61 (13-132)
	- OS		47 (10-92)	33 (11-62)	42 (5-102)
P-value			**0.002**	**0.003**	**0.07**
IL-6	- LFT	2548 (97-12063)	3672 (92-20475)	2091 (200-5515)	821 (31-3140)
	- LS	2447 (68-16500)	6278 (100-74525)	2344 (202-15607)	770 (33-9508)
	- OFT	6342 (553-50429)	9702 (351-73571)	2227 (330-5650)	809 (174-2486)
	- OS	8196 (112-58478)	22850 (578-213913)	11151 (159-90659)	2357 (396-10412)
P-value		**0.277**	**0.168**	**0.048**	**0.051**
CRP	- LFT	101 (89-115)	96 (72-174)	2752 (133-7292)	2302 (94-5581)
	- LS	82 (53-130)	94 (48-149)	2302 (80-8184)	2916 (55-23912)
	- OFT	93 (64-112)	96 (62-119)	3493 (512-6976)	2888 (481-6760)
	- OS	279 (72-910)	434 (77-2186)	9724 (391-71053)	11160 (366-68579)
P-value		**0.002**	**0.011**	**0.048**	**0.009**
Growth hormone	- LFT	188 (12-1443)	204 (3-1102)	159 (8-1148)	107 (3-620)
	- LS	479 (15-3100)	450 (21-1800)	626 (2-3500)	272 (8-1848)
	- OFT	383 (12-2800)	445 (8-2040)	312 (6-1250)	386 (2-2744)
	- OS	265 (14-714)	634 (6-3200)	248 (6-850)	393 (6-2013)
P-value		**0.6**	**0.229**	**0.55**	**0.298**
Prolactin	- LFT	229 (53-1144)	167 (31-839)	74 (6-317)	74 (5-278)
	- LS	243 (21-972)	226 (14-938)	71 (11-155)	105 (6-426)
	- OFT	199 (50-640)	379 (12-4329)	93 (5-315)	73 (8-314)
	- OS	279 (41-911)	201 (10-678)	105 (5-332)	85 (7-211)
P-value		**0.854**	**0.65**	**0.53**	**0.544**
Cortisol	- LFT	175 (36-383)	170 (16-660)	112 (20-328)	102 (19-380)
	- LS	155 (26-334)	166 (46-441)	116 (18-265)	138 (16-343)
	- OFT	162 (17-286)	163 (15-327)	142 (4-306)	128 (4-395)
	- OS	136 (33-323)	180 (48-608)	184 (16-580)	141 (48-326)
P-value		**0.669**	**0.978**	**0.124**	**0.525**

Values are depicted as percentage with the preoperative value set at 100% / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard / IL-6 = interleukine 6 / CRP = C-reactive protein

Figure 1 HLA-DR expression on monocytes in percentage with baseline set at 100%

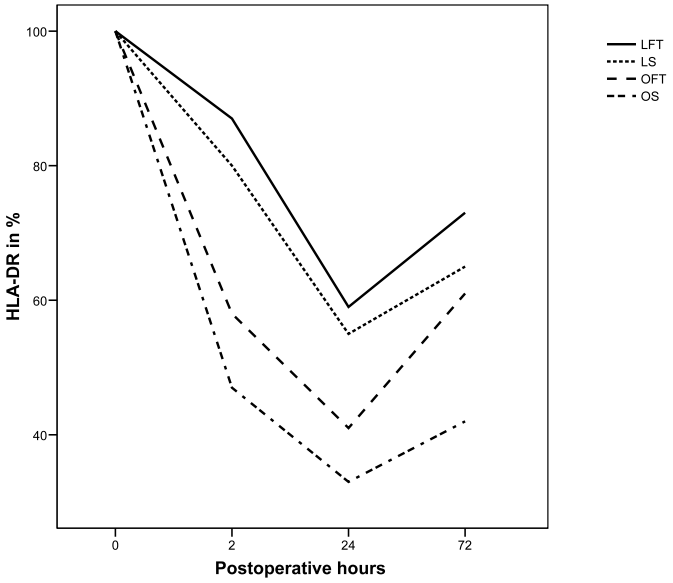

Figure 2 Interleukine-6 levels in percentage with baseline set at 100%

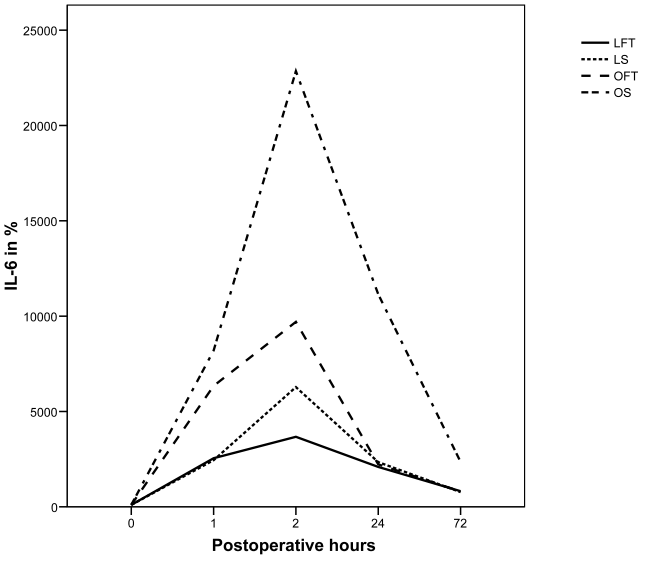

Figure 3 C-reactive protein in percentage with baseline set at 100%

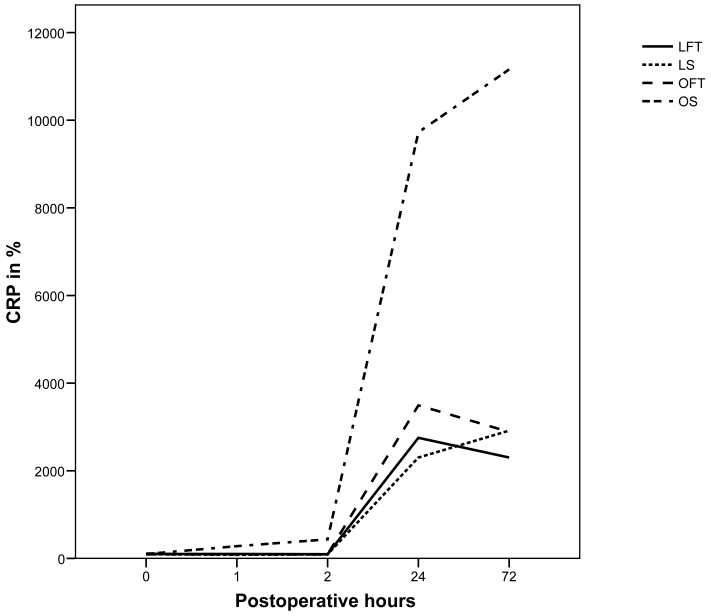

Table 3 Operative and morbidity data

	LFT (n=19)	LS (n=23)	OFT (n=17)	OS (n=20)	P
Operation					
- Time, minute	201 (130-300)	185 (120-280)	130 (60-258)	138 (60-213)	0.001
- Blood loss, ml	93 (0-1000)	68 (0-600)	228 (0-500)	313 (0-1200)	0.012
Complications, n (%)	2 (11)	7 (30)	5 (29)	5 (25)	0.273
Total No. of complications					
- Wound infection	1	1	2	1	
- Ileus	1	1	1	1	
- Anastomotic leakage	0	3	2	1	
- Pneumonia	0	2	0	2	

Values are mean (range) / LFT = laparoscopic/fast track / LS = laparoscopic/standard / OFT = open/fast track / OS = open/standard

Discussion

This randomized trial showed that patients undergoing laparoscopic colectomy combined with perioperative fast track care have a significantly better preserved immune competence (HLA-DR presentation on monocytes) until 3 days after surgery. Laparoscopic surgery with standard care seemed marginally superior to open colectomy with fast track care, followed by open colectomy with standard care. Inflammatory parameters such as IL-6 and CRP were significantly increased in patients undergoing open colectomy with standard care. Differences in the other 3 groups were marginal, therefore a clear order could not be discriminated.

These results might reflect a biological substrate to the longstanding question as to why patients undergoing minimally invasive techniques with fast track perioperative care have been described to have an accelerated recovery.[9,15] In addition, a better preserved immune competence, including specific HLA-DR immune response, may protect against potential consequences of seeding free tumor cells and thus distant metastases.[13] As described by Wind et al.[14] this is most important during surgery, as circulating tumor cells are highest directly after the onset of surgery. It will therefore be interesting to investigate whether patients in the laparoscopic group with fast track perioperative care will have a lower cancer recurrence rate during long-term follow-up.

The complex interaction between inflammatory cytokines and the hypothalamic-pituito-adrenal axis is still difficult to assess. In this study, stress response in terms of growth hormone, cortisol, and prolactin were not different between the groups. Therefore the 'fast track theory' including a reduced stress response due to epidural anaesthesia could not be demonstrated.[10,11] However, cortisol, growth hormone, and prolactin are anterior pituitary hormones and secretion is stimulated by hypothalamic releasing factors.[15,16] Therefore, the standard epidural in fast track recovery programs may not have had any effect on these hormones. It would be interesting to evaluate the secretion of catecholamines and/or its metabolized products in future studies as the epidural would have been more likely to have had an effect on these adrenal gland stress hormones.

Morbidity within 72 hours was lower in the laparoscopic group with fast track perioperative care, but did not reach a statistical difference between the 4 groups. It is however unlikely that the clear differences in immune response are simply based on morbidity percentages. The hypothesis that laparoscopic surgery in combination with fast track perioperative care reduces demand on the patient's immune reserves is supported by the results of the present study. Other authors have described lower morbidity following fast track postoperative care.[17]

In the present study, 94.9% of all samples were obtained and analysed according to study protocol. All obtained samples were analysed in a one block analysis, therefore the presented differences could not have been due to altered analyzing techniques or modified analyzing apparatus.

Smaller trials investigating immune response following laparoscopic and open colectomy have previously been presented. Harmon et al.[6] were the first to describe differences in postop-

erative IL-6 levels when laparoscopic colectomy was compared to open techniques in favor of laparoscopic surgery. Wu et al.[7] measured cytokine levels both in serum and peritoneal drain fluid and found significantly lower levels of IL-6 after laparoscopic surgery confirming the previous studies. A randomized study by Schwenk et al.[8] showed significantly lower peak concentrations of IL-6 and CRP two days after laparoscopic colon surgery. To our knowledge no previous randomized studies have presented advantages for laparoscopic colectomy in HLA-DR presentation on monocytes. In addition, no previous studies have investigated the effect op fast track perioperative care on patient's postoperative immune status.

In conclusion, this randomized trial showed that immune function is best preserved in patients having laparoscopic colectomy within a fast track program. Patients treated by open surgery in combination with standard care do worst. These results support the accelerated recovery which can be observed when patients are treated laparoscopically within a fast track program.

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