

Rectus Sheath Block (RSB) Analgesia Could Enhance Significantly the Patient Satisfaction Following Midline Laparotomy in Benign Disease and in Cancer: A Prospective Study With Special Reference to Nitrosative Stress Marker Nitrotyrosine (NT) Plasma Concentrations

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Abstract. *Background/Aim:* Our hypothesis was that rectus sheath block (RSB) analgesia could enhance satisfaction following midline laparotomy in patients with benign disease and cancer patients. *Patients and Methods:* Initially, 56 patients were randomized into four groups; control group (n=12), single-dose (n=16), repeated-dose (n=12) and continuous infusion (n=16) RSB analgesia groups. The plasma concentrations of the NT marker were measured just before, immediately after and 24 h after operation. Patient satisfaction at 24 h postoperatively was filed on a 11-point numeric rating scale (SFS₂₄; 0=fully unsatisfied; 10=fully satisfied). *Results:* The RSB analgesia significantly enhanced the SFS₂₄ scores in the study groups (p=0.001). The median plasma NT concentrations (pg/ml) following surgery (POPI) were significantly lower in patients with cancer versus patients with benign disease (5.3 vs. 7.6, p=0.008). Jitter plots of the individual SFS₂₄ values versus plasma NT concentrations were significantly correlated in benign and cancer patients (r=-0.284, p=0.028). *Conclusion:* The RSB analgesia could significantly enhance patient satisfaction

following midline laparotomy. Plasma NT concentrations versus patient satisfaction following surgery are significantly correlated in benign disease and cancer.

Today, the benefits of laparoscopic surgery (LS), among which are less postoperative pain, shorter hospital stay and sick leave duration, are undeniable. However, from the patient's point of view, the symptom resolution, quality of life and patient satisfaction are essential. Although the proportion of LS in general surgery was 47-97% in a Swedish register study (1), the proportion of LS in major resection surgery was only between 4-10% including esophago-gastric, liver, colorectal and pancreatic operations (1). Therefore, the midline laparotomy is still needed in cancer and emergency surgery, when the whole peritoneal cavity is necessary to be explored thoroughly. The midline laparotomy patients need proper analgesia peri- and postoperatively and it would be important to predict patients with a higher analgesia requirement.

Our previous article showed that the control group of patients and the rectus sheath block (RSB) groups did not differ in individual pain scores (numeric rating scales, NRS) following surgery (2). Saimanen *et al.* (3) reported a significant correlation between the plasma oxidative stress biomarker catalase (CAT) levels following surgery and the individual NRS pain scores 24 h postoperatively (NRS24) in patients with cholelithiasis. However, a nitrosative stress biomarker nitrotyrosine (NT) plasma concentrations in midline laparotomy patients with benign disease *versus* cancer is unknown. Arsalani-Zadeh *et al.* (4) and Yiannakopoulou *et al.* (5) revised the literature to compare Reactive Oxygen Species (ROS)/Reactive Nitrogen Species (RNS) in open surgery (OS) and LS, and they found

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sixteen clinical trials that investigated the impact of OS and LS on ROS/RNS, however, there were no studies available of plasma NT measurement. Therefore, the present study investigated the NT plasma concentrations in patients with benign disease *versus* cancer following midline laparotomy. The main hypothesis was that RSB analgesia could enhance satisfaction following midline laparotomy in benign and cancer patients. Secondly, our aim was to determine plasma NT levels in patients with benign disease *versus* patients with cancer and determine the association between plasma NT concentrations and patient satisfaction 24 h following surgery (SFS₂₄).

Patients and Methods

The study was approved by the Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (DNRO 120/2011, November 11, 2011) and was registered in the EudraCT database (EudraCT number 2011-005136-25, Consort diagram, Figure 1) and in the ClinicalTrials.gov database (ClinicalTrials.gov Identifier: NCT02869841). It was conducted in accordance with the Declaration of Helsinki. Participants gave written consent after receiving verbal and written information.

Operations were carried out at Kuopio University Hospital, Kuopio, Finland between 2012 and 2015. The CONSORT flowchart of the study is presented in Figure 1. The study design was a prospective, randomised, clinical trial with four parallel groups. The patients with midline laparotomy were randomized into the control group or into one of the three active groups; single-dose, repeated-dose or continuous infusion RSB analgesia groups. The study patients had intravenous oxycodone pumps as the patient-controlled analgesia (PCA). The randomisation list was generated by computer (www.randomization.com), a sealed enveloped method was used for blinding and randomisation was done preoperatively.

The primary outcome measures were the plasma concentrations of Cu/Zn superoxide dismutase (SOD1), catalase (CAT) and NT markers measured at three time points with high-sensitivity assays: before (PRE), immediately after (POP1) and 24 h after surgery (POP2) in the control *versus* the three active groups. The patient satisfaction at 24 h postoperatively were filed on a 11-point numeric rating scale (SFS₂₄; 0=fully unsatisfied; 10=fully satisfied) and the overall pain at rest NRS_r and at 2 kg pressing NRS_p surveyed and filed on a 11-point numeric rating scale at 24 h following surgery (NRS; 0=no pain; 10=worst pain).

All RSB procedures were performed by an experienced surgeon in the operating room before wound closure. The study protocol with the exclusion criteria and informed consent were fully described in our earlier original works (6-9).

EDTA-blood samples were taken at the prespecified timepoints and centrifuged at 1000 g for 15 min. Plasma was separated and stored frozen at -70°C until analyzed. The plasma SOD1 assays were performed using sandwich-type ELISA methods from BioVendor Cu/Zn SOD ELISA Kit (Brno, Czech Republic, www.biovendor.com). The plasma catalase assays were performed using enzyme-linked immunosorbent assay ELISA Kit (Cloud-Clone Corporation, Katy, TX, USA). The plasma NT assays were performed using competitive enzyme immunoassay OxiSelect™ Nitrotyrosine ELISA Kit (STA-305, Cell Biolabs Inc, San Diego, CA, USA). The manufacturer's intra-assay and the inter-assay Cvs were 5.1% and 5.8%, respectively.

The data were entered and analysed with a statistical software program (IBM SPSS Statistics 24.0; IBM, Armonk, NY, USA). Differences in baseline characteristics between groups were tested by Fisher's exact test and in the case of continuous data, the analysis was performed by Kruskal-Wallis *t*-test. Group differences at three time points were tested by the Wilcoxon signed rank test and the Kruskal-Wallis *t*-test. The plasma SOD1, CAT and NT concentrations and the differences in the patients with benign diseases and cancer were tested by the Mann-Whitney *U*-test. The results of the laboratory measurements are presented as median concentrations with interquartile range as distributions were right-skewed. A two-sided *p*-value of less than 0.05 was considered statistically significant. Pearson's method was used to test for correlation of NT values *versus* individual patient satisfaction following surgery (SFS₂₄), and pain at rest and under pressure (NRS_r and NRS_p).

Results

The clinical data of patients with benign disease and cancer were quite similar in the four study groups, although patients' weight and body mass index (BMI) were significantly higher in the single dose and control group than in the two other study groups ($p=0.007$ and $p=0.03$, respectively, Table I). The study group consisted of 15 patients with benign disease, nine patients with gastrointestinal cancer, 17 patients with gynaecological cancer and three patients with other malignancy (Table I). The RSB analgesia enhanced significantly the median SFS₂₄ scores in the following order; control, single dose, repeated dose and continuous dose group (8; 9; 9.5 and 10, respectively, $p=0.001$, Table I).

There were no statistically significant differences detected in the SOD1, CAT and NT values between the control group patients and the three active groups preoperatively and following surgery. Although, the patients in the single dose group had a trend for higher median NT levels preoperatively and immediately after operation (POP1) compared to the control group, repeated dose and continuous dose groups (median plasma concentrations pg/ml, 7.15/7.74 *versus* 5.47/4.03 and 5.28/5.54 and 6.25/5.96, respectively, Table II).

The postoperative alteration of plasma SOD1, CAT and NT marker concentrations in the groups combined are shown in Table III. There were statistically significant increases in the median plasma concentrations of SOD1 and CAT preoperatively (PRE) and immediately after operation (POP1) ($p=0.007$ and $p<0.001$, respectively, Table III). Then the median plasma concentrations of SOD1 and CAT markers decreased 24 h postoperatively (POP2) and the decrease between the POP1 and POP2 values in the SOD1 and CAT markers were statistically highly significant (43% decrease, $p<0.001$ and 24% decrease, $p=0.001$, respectively, Table III). There was no significant alteration in the median (interquartile range) plasma concentrations of NT preoperatively (PRE) and

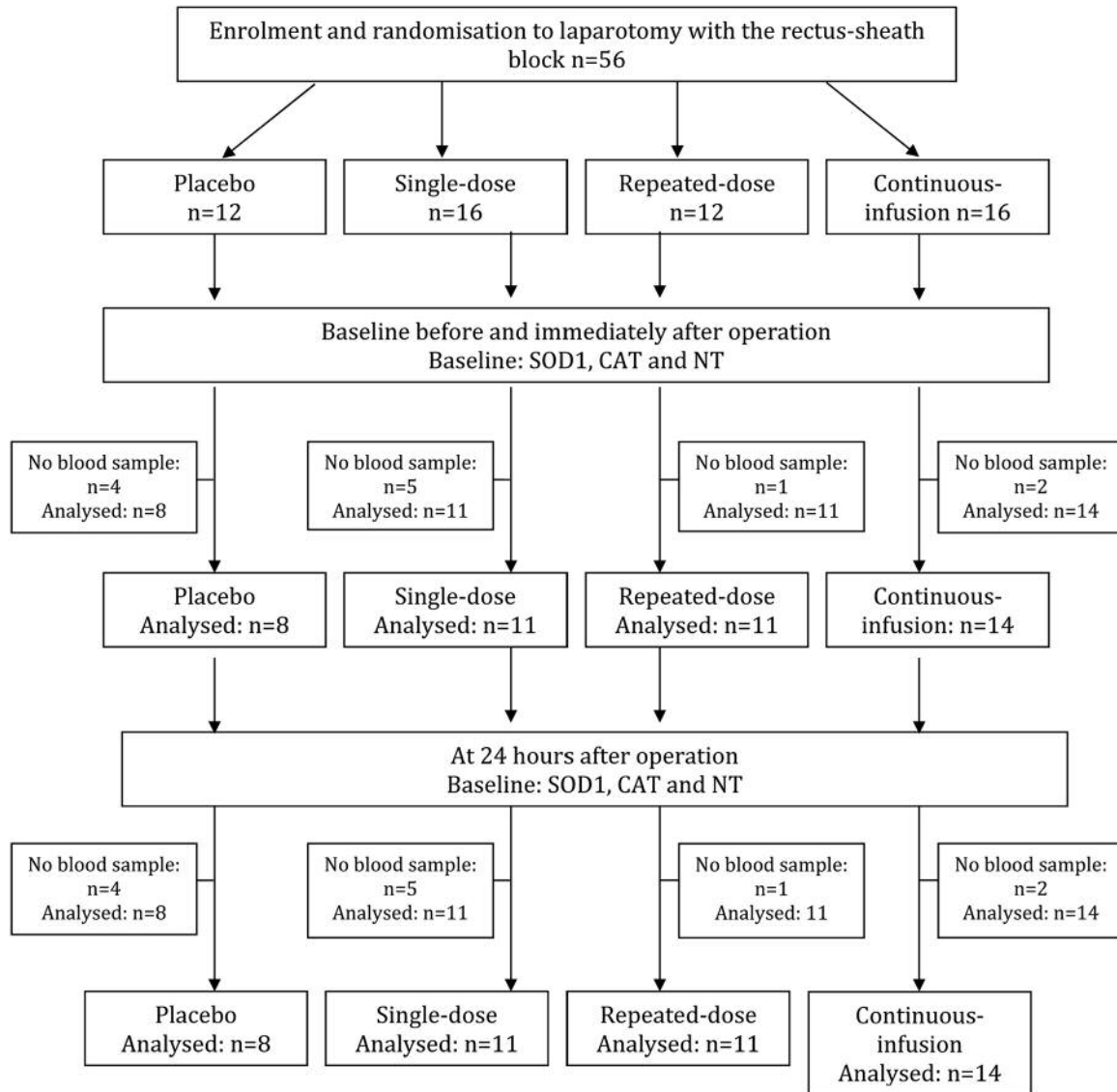


Figure 1. Design of the study as a flowchart.

immediately after operation (POP1) ($p=0.361$, Table III). However, the median plasma concentrations of NT decreased 24 h postoperatively (POP2) and the decrease between the POP1 and POP2 values in the NT were statistically significant (17% decrease, $p=0.041$, Table III).

The median (interquartile range) plasma concentrations of SOD1 and CAT did not differ significantly between the benign and cancer patients, preoperatively or after operation (Table IV). Patients in the cancer group had a trend for lower median NT levels compared to the benign patients (Table IV). However, there was a statistically significant difference in median NT concentrations between benign and cancer

patients immediately following surgery (POP1) ($p=0.008$, Table IV).

The median (interquartile range) plasma concentrations of SOD1 and CAT did not correlate significantly to NT concentrations in benign and cancer patients (data not shown). Figure 2 shows scatter plots of the plasma NT concentrations *versus* patient satisfaction assessed using a SFS₂₄ at 24 h following surgery in benign and cancer patients ($r=-0.284$, $p=0.028$). There was a statistically significant negative correlation in median plasma concentrations of NT *versus* an increase in patient satisfaction between PRE and POP2 ($r=-0.454$, $p=0.010$) (data not shown).

Table I. The midline laparotomy patients' clinical data in the four study groups. Data are mean (standard deviation) or number of cases.

Variable	RSB group				p-Value
	Control n=8	Single n=11	Repeated n=11	Continuous n=14	
Age, years	62.6 (14.3)	60.8 (12.6)	63.3 (10.8)	58.0 (10.1)	0.74
Gender male/female	4/4	4/7	2/9	2/12	0.22
Height, cm	166.6 (8.6)	168.4 (7.9)	165.7 (7.2)	164.3 (6.6)	0.62
Weight, kg	78.6 (11.8)	83.7 (12.8)	67.8 (13.7)	68.8 (10.6)	0.007
BMI, kg/m ²	28.3 (3.8)	29.6 (4.4)	24.6 (4.3)	25.7 (4.9)	0.03
Time in the operative room, min	229.4 (113.4)	274.9 (148.4)	235.7 (112.0)	279.7 (178.5)	0.85
Operative time, min	209.6 (141.2)	221.8 (156.4)	154.4 (95.0)	253.3 (168.9)	0.55
Perioperative-bleed, ml	696 (741)	822(906)	697 (967)	1340(928)	0.31
ASA 1/2/3/4	0/6/2/0	0/7/3/1	0/5/6/0	2/7/5/0	0.43
NRS _r	2 (1-6)	2 (0-4)	2 (0-3)	1 (0-4)	0.41
NRS _p	5 (3-9)	5 (1-9)	3.5 (1-7)	4 (0-7)	0.42
SFS ₂₄	8 (7-8)	9 (8-10)	9.5 (8-10)	10 (8.3-10)	0.001
Length of the skin incision(s), mm	27.2 (6.6)	24.4 (7.8)	24.2 (7.9)	29.7 (7.3)	0.31
Type of disease					0.32
Benign (n=15)	1	3	5	6	
GI cancer (n=9)	3	2	2	2	
Gyn cancer (n=17)	3	4	4	6	
Other cancer (n=3)	1	2	0	0	

GI: Gastrointestinal tract; Gyn: gynaecological; BMI: body mass index; ASA: American Society of Anesthesiologists physical status score; NRS: 11-point numeric rating scale 24 h after surgery; NRS_r: NRS at rest; NRS_p: NRS under 2 kg pressure to the wound area; SFS₂₄: satisfaction following surgery; RSB: rectal sheath block.

Table II. The plasma superoxide dismutase 1 (SOD1), catalase (CAT) and nitrotyrosine (NT) concentrations in the four study groups. Plasma concentrations were measured before (PRE), immediately after (POP1) and 24 h after (POP2) surgery. Median (interquartile range) concentrations are shown.

Marker	RSB group				p-Value*
	Control	Single	Repeated	Continuous	
SOD1 (pg/ml)					
PRE	150 (101-288)	146 (96-287)	171 (113-216)	168 (128-199)	0.922
POP1	281 (144-522)	160 (101-305)	184 (123-275)	243 (151-292)	0.392
POP2	119 (93-202)	87 (59-105)	116 (88-171)	167 (94-217)	0.138
CAT (pg/ml)					
PRE	0.95 (0.67-2.36)	0.74 (0.45-1.58)	0.61 (0.41-1.09)	0.61 (0.43-1.17)	0.407
POP1	1.36 (0.89-3.71)	1.89 (0.78-2.93)	1.53 (0.78-2.17)	1.39 (0.84-2.03)	0.907
POP2	1.17 (0.58-1.65)	0.86 (0.60-1.73)	1.15 (0.77-1.50)	1.06 (0.83-1.92)	0.891
NT (pg/ml)					
PRE	5.47 (3.03-6.01)	7.15 (5.84-8.81)	5.28 (4.00-8.74)	6.25 (5.09-8.78)	0.128
POP1	4.03 (2.98-5.93)	7.74 (5.96-9.16)	5.54 (3.21-7.21)	5.96 (4.30-8.43)	0.127
POP2	4.39 (3.24-7.55)	4.58 (3.41-5.87)	4.70 (4.15-5.51)	6.37 (4.55-7.31)	0.277

*The Kruskal-Wallis test.

Discussion

The NT plasma concentrations *versus* patient satisfaction 24 h following surgery (SFS₂₄) in midline laparotomy patients with RSB analgesia is unknown. The original study hypothesis was that RSB analgesia could lower postoperative pain

following surgery and enhance satisfaction in benign and cancer patients. Interestingly, in the present study, patients in the continuous infusion group had a trend for lower pain score at rest (NRS_r) compared to other groups. However, no statistically significant differences were detected in the pain scores; NRS pain at rest and under pressure (NRS_r and NRS_p)

Table III. The postoperative alteration of plasma superoxide dismutase 1 (SOD1), catalase (CAT) and nitrotyrosine (NT) concentrations in all groups combined (all patients). Plasma concentrations were measured before (PRE), immediately after (POP1) and 24 h after (POP2) surgery. Median (interquartile range) concentrations are shown.

Marker	All patients	Alteration	p-Value*
SOD1 (pg/ml)			
PRE	164.0 (114-213)		
POP1	185.0 (137-301)	PRE vs. POP1	0.007
POP2	105.0 (86-176)	POP1 vs. POP2	<0.001
CAT (pg/ml)			
PRE	0.66 (0.48-1.17)		
POP1	1.39 (0.84-2.43)	PRE vs. POP1	<0.001
POP2	1.03 (0.70-1.57)	POP1 vs. POP2	0.001
NT (pg/ml)			
PRE	6.02 (4.78-8.16)		
POP1	5.96 (4.14-8.03)	PRE vs. POP1	0.361
POP2	4.96 (4.12-6.53)	POP1 vs. POP2	0.041

*Wilcoxon signed-rank test.

Table IV. The plasma superoxide dismutase 1 (SOD1), catalase (CAT) and nitrotyrosine (NT) concentrations in patients with benign diseases (n=15) and those with cancer (n=29). Plasma concentrations were measured before (PRE), immediately after (POP1) and 24 h after (POP2) surgery. Median (interquartile range) concentrations are shown.

Marker	Benign	Cancer	p-Value*
SOD1 (pg/ml)			
PRE	167 (132-216)	160 (107-211)	0.647
POP1	182 (135-286)	202 (136-338)	0.989
POP2	105 (76-171)	112 (86-196)	0.610
CAT (pg/ml)			
PRE	0.62 (0.41-1.17)	0.73 (0.48-1.30)	0.407
POP1	1.09 (0.78-2.50)	1.46 (1.13-2.36)	0.304
POP2	0.83 (0.75-1.65)	1.12 (0.68-1.50)	0.593
NT (pg/ml)			
PRE	6.83 (5.05-8.32)	5.67 (4.10-8.10)	0.250
POP1	7.58 (5.96-9.71)	5.28 (3.41-6.44)	0.008
POP2	5.75 (4.35-6.73)	4.69 (4.09-6.27)	0.308

*Mann-Whitney U-test.

between the control group and three RSB study groups showing that our main hypothesis is not fully realized. In contrary, statistically significant differences were detected in the patient satisfaction 24 h following surgery (SFS₂₄) between the control group and three RSB study groups supporting our main hypothesis. Our results are in line with an earlier study assessing patient satisfaction after various surgical procedures, which indicated that even though 62% of patients experienced severe postoperative pain, 87% of them were satisfied with pain treatment (10). Owen *et al.* 1990 (11) and Svensson *et al.* 2001 (12) have also reported this finding of patient satisfaction.

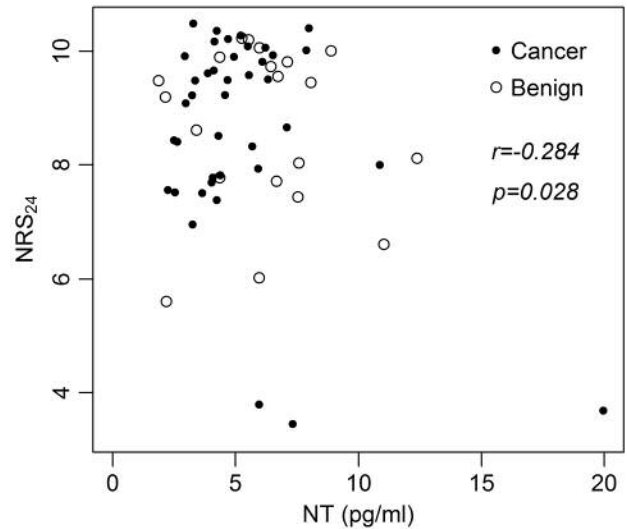


Figure 2. Scatter plots of the plasma nitrotyrosine (NT) concentrations versus patient satisfaction assessed using a 11-point rating scale (SFS₂₄; 0=fully unsatisfied; 10=fully satisfied) at 24 h following surgery in benign and cancer patients (r=-0.284, p=0.028).

NT is a fingerprint of peroxynitrite-mediated nitration, and the presence of NT has been identified in *H. pylori* gastritis (13), and several human cancers as lung carcinoma (14), cholangiocarcinoma (15), pancreatic carcinoma (16), esophageal carcinoma (17) and melanoma (18). It is very difficult to directly measure the peroxynitrite concentration in plasma, therefore NT is an available biomarker for indirect detection of peroxynitrite concentration. In earlier studies NT was detected in plasma, urine and bronco-alveolar fluid. In the present study the patients in the cancer group had a trend for lower median NT levels compared to the benign patients and there was statistically significant difference in median NT concentrations between benign and cancer patients immediately following surgery (POP1). In addition, patients in the single dose group had a trend for higher plasma NT concentrations preoperatively (PRE) and immediately following surgery (POP1) compared to other study groups. We have reported earlier that midline laparotomy with RSB significantly enhances the concentration of the oxidative stress markers SOD1 and CAT immediately after operation, but both marker concentrations drop back 24 h following surgery (2, 9). RSB analgesia could be effective in midline laparotomy, where RSB is suggested as a part of a multimodal postoperative analgesia (19).

Also, we recently reported that cholecystectomy patients with enhanced concentrations of SOD1 and CAT appeared to have significantly lower analgesia requirement during the first 24 h postoperatively (3, 20). In this study, the most important finding is the significant correlation between plasma NT concentrations and SFS₂₄ following surgery in benign and

cancer patients. In contrary, plasma NT concentrations decreased significantly 24 h following surgery (POP2).

The blinding of the different RSB analgesia groups was challenging. We decided not to use an invasive placebo, which meant that the control group was without RSB catheterization, however the patients in the control group had no local anaesthetic used and they were blinded using similar wound dressing to that of the patients in the active study groups. The blinding between the control group and RSB study groups could have been done with normal saline infiltrations, however invasive placebo with normal saline could have affected ROS/NRS mediators as well as pain scores.

In conclusion, it is important to develop ROS/RNS biomarkers in combination with clinical variables used as predictors of patient satisfaction and pain following surgery (21, 22). In earlier studies, the most promising clinical role of nitric oxide and NT as clinical biomarkers has been in neurodegenerative (23) and neuropsychiatric disorders (24), brain aging (23) and the understanding of the mechanisms of inflammation-associated colorectal cancer (25). The most important finding of the present study is that NRS analgesia could significantly enhance the patient satisfaction following midline laparotomy. In addition, it seems that plasma NT concentration is significantly correlated with patient satisfaction following surgery in benign disease and cancer.

Conflicts of Interest

The Authors report no conflicts of interest or financial ties to disclose. The authors alone are responsible for the content and writing of this article.

Authors' Contributions

All Authors have met all of the following four criteria: 1. Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, 2. Drafting the work or revising it critically for important intellectual content, 3. Final approval of the version to be published, 4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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