Does the Rectus Sheath Block Analgesia Reduce the Inflammatory Response Biomarkers' IL-1ra, IL-6, IL-8, IL-10 and IL-1β Concentrations Following Surgery? A Randomized Clinical Trial of Patients with Cancer and Benign Disease

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Abstract. *Aim: To evaluate whether the post-surgery placement of the rectus sheath block analgesia (RSB) reduces the inflammatory response following surgery. The main hypothesis of our study was to find any correlation between patients' pain experience, numeric rating scale (NRS) postoperatively and concentrations of inflammatory response biomarkers, such as interleukin-1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, IL-1β, in patients with benign disease and cancer. Patients and Methods: Initially, 46 patients with midline laparotomy were randomized to the placebo group (n=11) and to one of the three active groups; single-dose (n=12), repeated-dose (n=12) and continuous infusion (n=11) RSB analgesia groups. Plasma concentrations of high-sensitivity C-reactive protein (hs-CRP) and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) were measured at three time points; just before, immediately after and 24 h after operation. The primary end-point was to compare plasma concentrations of the hs-CRP and five interleukins in the placebo group and in the three different RSB analgesia groups in patients with benign disease and cancer. Results: The placebo group and three active groups were similar in terms of demographic variables and perioperative data. Of the anti-inflammatory cytokines, patients in the continuous infusion group had significantly higher IL-10 median values postoperatively than the three other study groups (p=0.029). In addition, patients in the three active groups combined had significantly higher IL-10 median values immediately after operation than the placebo group (p=0.028; in all patients with benign disease and cancer). There is a significant correlation between the individual values of NRS and IL-10 values postoperatively in the placebo group and the three active groups separately (r=0.40, p=0.03) and also a significant correlation between the individual values of the NRS scale and IL-1β values postoperatively in the placebo group and the three active groups separately (r=0.38, p=0.04). Conclusion: Placement of RSB analgesia does not significantly reduce the inflammatory response biomarkers' concentrations in patients with benign disease or cancer patients. A new finding in the present work is a significant correlation in the NRS scale versus plasma concentrations of anti-inflammatory cytokine IL-10 and pro-inflammatory cytokine IL-1β postoperatively suggesting that inflammation and pain are related.*

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Acute-phase proteins and cytokines are thought to be early measures of inflammatory stress response induced by surgical trauma. There is also evidence suggesting that inflammation and pain are related (1). Okholm *et al*. (2) reviewed the literature of the inflammatory stress response in laparoscopic (LAP) and open surgery (OS) in gastric cancer. Ten studies published from 1999 to 2013 matched the selection criteria, including three randomized trials and seven retrospective studies, with a number of included patients from 28 to 256. However, it was not possible to perform a meta-analysis due to the diversity of the inflammatory stress markers used and the small number of patients included. The authors concluded that the inflammatory stress response to surgery depends on the degree of trauma and the reduction of surgical trauma by laparoscopy-assisted techniques seems to diminish the

inflammatory stress compared to open surgery (2). The inflammatory stress response after LAP colorectal surgery has been studied by Day *et al*. (3) using two different methods of analgesia in a randomized clinical trial. It was concluded that spinal analgesia reduced early stress responses and decreased morphine use. Crosbie *et al*. (4) studied the effect of single-dose rectus sheath analgesia in 98 consecutive patients with major gynaecological surgery who received either intra-operative local anaesthetic (LA, n=51) to the wound area or the surgical rectus sheath block (RSB, n=47). It was demonstrated that RSB provided a significant postoperative analgesia for patients with major gynaecological surgery and, thus, the investigators suggested that a randomized clinical trial is needed to confirm the efficacy of RSB. In earlier studies, the RSB analgesia for pain management has been investigated mostly using a single-dose block (5). We have previously reported that the inflammatory stress response in patients with minilaparotomy cholecystectomy (MC) *versus* laparoscopic cholecystectomy (LC) was quite similar based on the interleukin (IL)-8, IL-10 and IL-1β values (6). To our knowledge, the effect of post-surgery placement of RSB analgesia to reduce the inflammatory stress response in patients with benign disease and cancer has not been studied. The main hypothesis of our study was to find the correlation between patients' pain experience, numeric rating scale (NRS) postoperatively and the concentrations of inflammatory stress biomarkers interleukin-1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10 and IL-1β in patients with benign disease and cancer.

Patients and Methods

The study was approved by the Ethics Committee of the Kuopio University Hospital District, Kuopio, Finland (DNRO 120/2011, November 11, 2011), registered in the EudraCT database (EudraCT number 2011-005136-25, Consort diagram, Figure 1) and conducted in accordance with the Declaration of Helsinki. Participants gave written consent after receiving verbal and written information. Operations were carried out in Kuopio University Hospital between 2012 and 2015. The flowchart of the study is presented in Figure 1. The study design was a prospective, randomised, clinical trial with four groups. The patients with midline laparotomy were randomized to the placebo group and to one of the three active groups; single-dose, repeated-dose and continuous infusion RSB analgesia groups. The patients had intravenous oxycodone patient controlled analgesia (PCA) pumps. The randomisation list was generated by computer (www.randomization.com) and a sealed envelope method was used for blinding.

All RSB procedures were performed by an experienced surgeon in the operating room before wound closure. Bilateral RSB catheters were placed with complete aseptic technique to the 'railway-like line' deep in the rectus sheath between the rectus muscle and the posterior rectus sheath. The correct position of catheters was confirmed and a 20-ml bolus of levobupivacaine (Chirocaine; AbbVie, Espoo, Finland) was injected to separate the planes and achieve hydrodissection for placement of the catheters. In the blocks, including the single-dose block, bilateral rectus sheath catheters were used (InfiltraLong Pajunk, Geisingen, Germany). In the single-dose group, the block was performed at the end of operation injecting 20 ml levobupivacaine 1.25 mg/ml for both catheters for a total dose of levobupivacaine of 50mg. In the repeated-dose group, a similar starting injection of 20+20 ml was performed and 10 ml of levobupivacaine 1.25 mg/ml for both catheters for a total dose of two injections 25 mg was repeated every 4 hours for the first 24 h. In the continuous infusion group, the 20+20 ml block was performed as described above and continued with bilateral rectus sheath catheters, *i.e*. infusion of 5 ml/h of levobupivacaine 1.25 mg/ml for each (a total dose of 12.5 mg/h) with ambulatory infusion pumps (Autofuser pumps, Acemedical, Seoul, Korea). The patients in the placebo group had no catheters inserted. However, the patients in the placebo group were blinded using the similar wound dressing as the patients in the active groups.

The exclusion criteria included body mass index (BMI) ≥35 kg/m^2, age under 18 or ≥80 years, pregnancy, reoperations, history of drug or narcotics abuse and earlier allergic reactions to local anaesthetics and contraindications to oxycodone. All study patients were informed by the investigator about different postoperative analgesia methods before they gave a written consent.

For laboratory measurements, EDTA-plasma samples were taken at the pre-specified time points and centrifuged at 1,000 × *g* for 15 min. Plasma was separated and stored frozen at –70˚C until analysed. The plasma interleukins IL-1β, IL-1ra, IL-6, IL-8 and IL-10 assays were performed using ELISA methods from R&D Systems (Minneapolis, MN, USA). The sensitivity of the assays were as follows: hsIL-10: 0.09 pg/ml, IL-8: 0.13 pg/ml, IL-6: 0.70 pg/ml, IL-1ra: 6.3 pg/ml and IL-1β: 0.57 pg/ml. Intra-assay coefficient of variation(CV) % at three concentrations (n=20 for each level) were as follows: 4.6-9.3 % for hsIL-10, 3.7-7.3 % for hsIL-8, 3.3-6.4 % for IL-6, 3.7-7.3 % for IL-1ra and 4.3-10.2 % for hsIL-1β. Plasma high-sensitivity C-reactive protein (hs-CRP) was analysed with a Cobas 6000-analyzer (Hitachi, Tokyo, Japan); the hs-CRP results are partly shown in a previous report from our laboratory (7).

The primary outcome measures were plasma levels of hs-CRP and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) measured at three time points with high-sensitivity assays: before (PRE), immediately after (POP1) and 24 h after operation (POP2) in the placebo *versus* three active groups.

The data were entered and analyzed with the SPSS software package (IBM SPSS Statistics 22.0; IBM, Somers, IL, USA). Baseline characteristics between groups were tested by Fisher's exact test and if variables were continuous then analyses were performed by analysis of variance (ANOVA). The group differences in three time points were tested by the Mann-Whitney *U*-test and Kruskall-Wallis-test. The results of the marker values are presented as median with interquartile range because distributions were right-skewed. A two-sided *p*-value of less than 0.05 was considered statistically significant. The overall satisfaction and an opinion on the success of the analgesia procedure were surveyed and filed on an 11-point NRS (0, fully unsatisfied; 10, fully satisfied). The results of the individual NRS values *versus* the inflammatory marker (IL-1ra, IL-6, IL-8, IL-10, IL-1β) correlations are shown as jitter plots with Spearman's correlation coefficients in Figures 2 and 3.

Results

The placebo group and three active groups were similar in terms of demographic variables and perioperative data (Table

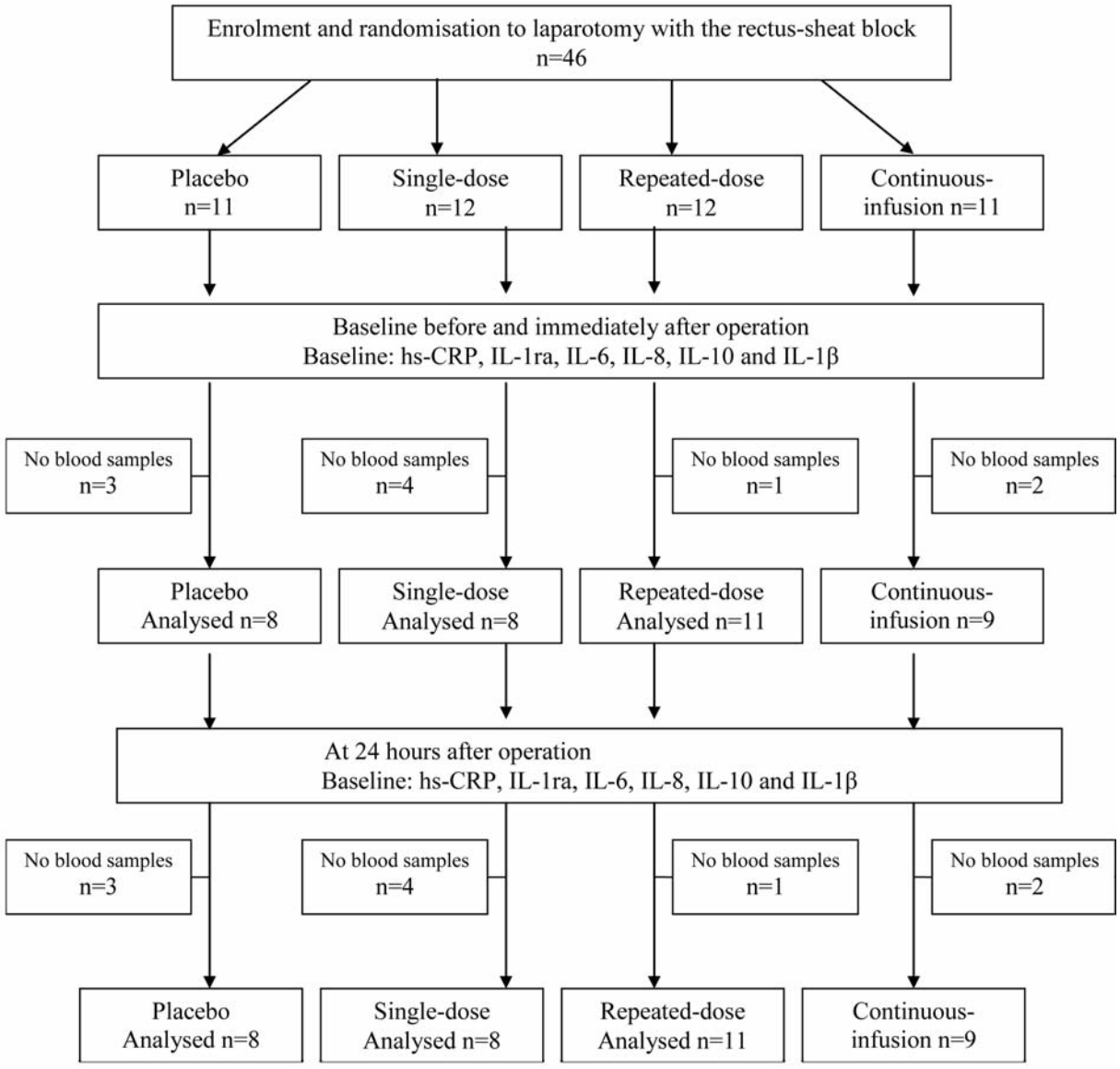

Figure 1. *Flowchart of study's design*.

I). However, the patients in the placebo group and in the single-dose group had significantly higher BMI than the patients in the other two study groups. No differences were detected in the type and number of surgeries between the placebo group and the three active groups separately (p=0.32, Table I).

There was no statistical significant difference in the hs-CRP median values between the placebo group and the three active groups pre- and postoperatively (Table II). However, the patients in the three active groups combined (RSB combined, Table III) showed lower elevation of the hs-CRP median values 24 h postoperatively than the placebo group and the repeated-dose group (Table II).

Plasma levels of pro-inflammatory markers were all raised postoperatively (POP1 and POP2). There was no statistical significant difference in the IL-6 and IL-8 median values between the placebo group and the three active groups separately (Table II) or the three active groups combined (Table III).

No differences were detected in the anti-inflammatory IL-1ra values between the placebo and the three active groups preoperatively and immediately after operation. However, the patients in the placebo group had slightly higher elevation of the IL-1ra level immediately after operation (POP1) than the three other active groups separately (Table

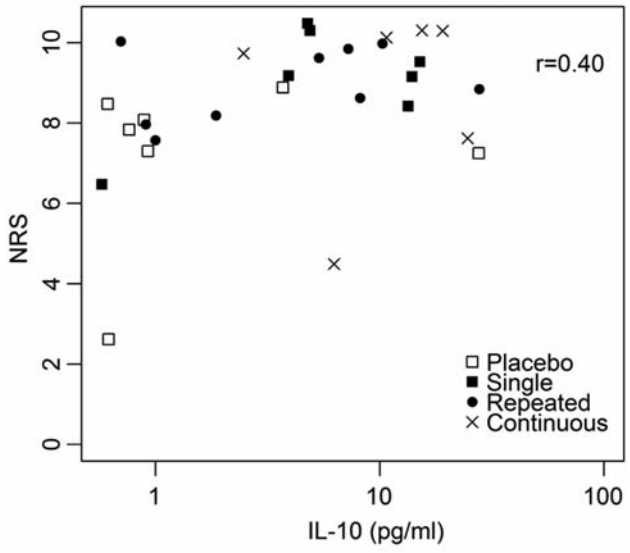

Figure 2. *Jitter plots of the individual NRS values versus IL-10 values for the placebo group and three study groups (r=0.4, p=0.03).*

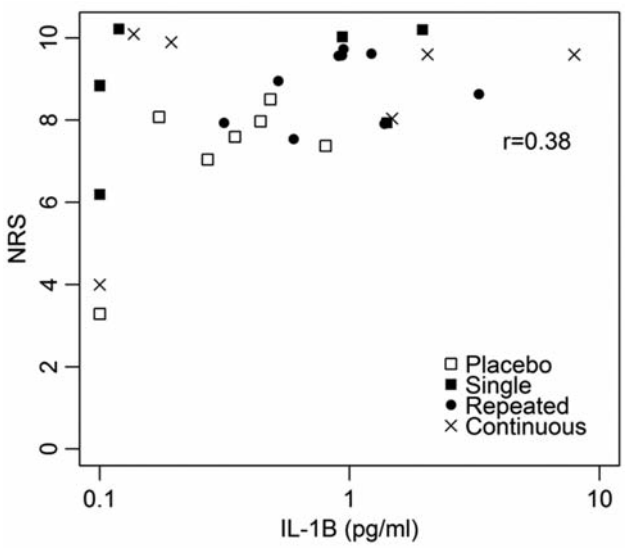

Figure 3. *Jitter plots of the individual NRS values versus IL-1β values for the placebo group and three study groups (r=0.38, p=0.04).*

Table I. *Baseline demographic characteristics and surgical data for the placebo group and the three active groups; single-dose, repeated-dose and continuous infusion RSB analgesia groups. Values are mean (standard deviation) or number of cases*.*

Variable	Placebo n=11	Single n=12	Repeated n=12	Continuous n=11	*p*-Value
Age (years)	62.6 (14.3)	60.8 (12.6)	63.3 (10.8)	58.0 (10.1)	0.74
Sex (male/female)*	1/10	3/9	3/9	4/7	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 operation 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*	1/8/2/0	0/7/4/1	1/5/6/0	2/6/3/0	0.43
Length of the scin incision(s) (mm)	27.2 (6.6)	24.4 (7.8)	24.2 (7.9)	29.7 (7.3)	0.31
Type of surgery* (Benign/GI-cancer/Gyn-cancer/ other malignancy)#	1/3/6/1	3/3/4/2	5/2/4/1	3/2/6/0	0.32

BMI, Body mass index; ASA, American Society of Anesthesiologists physical status score. #Benign disease, n=12/gastrointestinal tract cancer, n=10/gynecological cancer, n=20/other malignancy, n=4.

II) or the three active groups combined (Table III). In addition, the patients in the continuous infusion group had higher elevation of the IL-1ra median values at 24 h than the three other study groups (Table II).

The patients in the continuous infusion group had significantly higher anti-inflammatory IL-10 median values postoperatively (POP1) than the three other study groups (p=0.029, Table II). In addition, the patients in the three active groups combined had significantly higher IL-10 median values immediately after operation (POP1) than the placebo group (p=0.028, Table III).

Figure 2 shows the jitter plots of the individual values of the NRS scale *versus* IL-10 values postoperatively (POP1) in the placebo group and the three active groups separately. The individual values of the NRS scale *versus* anti-inflammatory cytokine IL-10 values correlated significantly

Table II. *The inflammatory marker levels for the placebo group and the three active groups; single-dose, repeated-dose and continuous infusion RSB analgesia groups. Data are median and interquartile range.*

Marker	Placebo	Single	Repeated	Continuous	*p*-Value
hs-CRP (mg/l)					
PRE	3.48 (1.21-13.05)	4.65 (0.89-48.23)	1.20 (0.59-4.00)	9.60 (1.46-73.96)	0.455
POP1	6.60 (1.01-13.24)	9.18 (2.90-83.25)	2.30 (0.59-5.13)	25.87 (1.04-231.81)	0.289
POP2	246.11 (82.25-469.10)	189.55 (96.15-348.97)	206.50 (81.50-284.42)	159.00 (79.33-478.93)	0.875
IL-1ra (pg/ml)					
PRE	220.31 (185.85-315.85)	346.19 (236.82-828.82)	258.79 (207.48-309.66)	294.02 (230.60-658.17)	0.177
POP1	1,671.25 (350.53-2000)	943.56 (595.11-2057.68)	946.24 (569.5-13828.63)	2,000 (702.55-15500)	0.787
POP2	701.17 (495.77-902.33)	565.17 (410.23-1449.52)	661.33 (317.52-753.20)	616.70 (398.28-957.22)	0.895
IL-6 (pg/ml)					
PRE	3.34 (3.11-4.32)	7.04 (3.31-19.96)	3.11 (3.11-4.50)	6.20 (3.74-22.45)	0.051
POP1	85.16 (37.67-165.45)	87.61 (63.98-170.64)	112.00 (68.95-300.00)	218.09 (62.60-744.58)	0.564
POP2	66.69 (50.54-128.71)	82.59 (43.66-176.05)	55.29 (27.48-110.59)	57.06 (49.55-147.02)	0.716
IL-8 (pg/ml)					
PRE	6.96 (4.84-12.40)	9.52 (5.66-24.35)	5.99 (4.83-8.78)	8.78 (6.66-20.03)	0.620
POP1	26.00 (7.94-42.04)	11.82 (8.10-40.77)	17.23 (8.49-54.65)	31.38 (7.65-64.00)	0.889
POP2	11.36 (7.45-23.50)	12.79 (6.99-26.98)	14.46 (6.96-21.61)	26.07 (12.77-51.66)	0.316
IL-10 (pg/ml)					
PRE	0.77 (0.77-0.77)	0.77 (0.77-1.14)	0.77 (0.77-0.77)	0.94 (0.77-1.85)	0.010
POP1	0.77 (0.77-3.50)	4.80 (2.00-13.89)	3.68 (0.77-8.83)	13.02 (5.38-23.20)	0.029
POP2	0.78 (0.77-3.23)	0.77 (0.77-1.40)	0.77 (0.77-0.90)	1.23 (0.77-3.72)	0.371
IL-1β (pg/ml)					
PRE	0.15 (0.12-0.37)	0.32 (0.12-2.45)	0.28 (0.12-0.92)	0.24 (0.12-1.06)	0.684
POP1	0.32 (0.16-0.71)	0.44 (0.12-1.36)	0.94 (0.51-1.24)	1.71 (0.12-6.77)	0.274
POP2	0.12 (0.12-0.23)	0.37 (0.12-0.47)	0.39 (0.19-0.69)	0.43 (0.18-0.91)	0.186

Plasma levels of hs-CRP and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) were measured at three time points; before operation (PRE), immediately after operation (POP1) and 24 h after operation (POP2).

(r=0.40, p=0.03). Figure 3 shows the jitter plots of the individual values of the NRS scale *versus* pro-inflammatory cytokine IL-1β values postoperatively (POP1) in the placebo group and the three active groups separately. The individual values of the NRS scale *versus* pro-inflammatory cytokine IL-1β values correlated significantly (r=0.38, p=0.04).

Discussion

Since abdominal surgery leads to production of cytokines and acute-phase proteins, physicians have tried to find methods of reducing the inflammatory response to surgery (2). We have previously reported that the inflammatory response in patients with MC *versus* LC was quite similar based on the IL-8, IL-10 and IL-1β values (6), although LC patients reported significantly lower pain score 24 h postoperatively and a shorter convalescence than the MC patients in a randomised trial (8). Okholm *et al*. (2) reviewed 10 studies published between 1999 and 2013, including three randomized trials and seven retrospective studies, and concluded that the stress response to surgery depends on the degree of trauma and the reduction of surgical trauma by laparoscopy-assisted techniques seems to diminish the immune response compared to open surgery.

Spinal analgesia with bupivacaine and morphine eliminates pain but not systemic stress response after abdominal surgery (9, 10). Fares *et al*. (11) studied the effect of thoracic epidural analgesia in 30 patients subjected to oesophagectomy. It was concluded that epidural analgesia might reduce the systemic pro-inflammatory response (IL-8) and could provide optimal post-operative pain relief. Day *et al*. (3) studied in a randomized clinical trial the inflammatory response from two different methods of analgesia after laparoscopy colorectal surgery. In their study, no significant differences in the levels of interleukins between spinal analgesia and intravenous patient-controlled analgesia were found at any time point. However, they concluded that spinal analgesia reduced early neuroendocrine responses and decreased overall parenteral morphine use (3).

The RSB analgesia for pain management has been investigated mostly using a single-dose block. Bashandy and Elkholy (5) investigated the efficacy of the single-injection RSB analgesia in 60 patients randomized to the general anaesthesia-alone group and to the active group with RSB after induction of anaesthesia and before surgical incision. It

Table III. *The inflammatory marker levels for the placebo and RSB groups; three active groups, single-dose, repeated-dose and continuous infusion groups combined. Data are median and interquartile range.*

Marker	Placebo	RSB	*p*-Value
hs-CRP (mg/l)			
PRE	3.48 (1.21-13.05)	3.30 (0.82-48.23)	0.723
POP1	6.60 (1.01-13.24)	4.35 (0.82-59.86)	0.889
POP2	246.11 (82.25-469.10)	189.55 (93.60-302.50)	0.466
IL-1ra (pg/ml)			
PRE	220.31 (185.85-315.85)	294.24 (217.84-450.20)	0.116
POP1	1671.25 (350.53-2000)	1314.10 (623.86-4836)	0.563
POP2	701.17 (495.77-902.33)	621.41 (374.72-879.39)	0.562
IL-6 (pg/ml)			
PRE	3.34 (3.11-4.32)	4.43 (3.11-11.38)	0.251
POP1	85.16 (37.67-165.45)	112.00 (63.46-300.00)	0.253
POP2	66.69 (50.54-128.71)	64.24 (38.53-138.62)	0.751
IL-8 (pg/ml)			
PRE	6.96 (4.84-12.40)	7.86 (5.50-20.29)	0.562
POP1	26.00 (7.94-42.04)	17.23 (8.49-54.65)	0.889
POP2	11.36 (7.45-23.50)	15.55 (7.61-27.35)	0.513
IL-10 (pg/ml)			
PRE	0.77 (0.77-0.77)	0.77 (0.77-1.18)	0.180
POP1	0.77 (0.77-3.50)	5.76 (1.80-14.30)	0.028
POP2	0.78 (0.77-3.23)	0.77 (0.77-2.04)	0.926
IL-1β (pg/ml)			
PRE	0.15 (0.12-0.37)	0.28 (0.12-1.22)	0.267
POP1	0.32 (0.16-0.71)	0.94 (0.12-1.62)	0.191
POP2	0.12 (0.12-0.23)	0.39 (0.14-2.04)	0.053

Plasma levels of hs-CRP and five interleukins (IL-1ra, IL-6, IL-8, IL-10, IL-1β) were measured at three time points; before operation (PRE), immediately after operation (POP1) and 24 h after operation (POP2).

was concluded that ultrasound-guided RSB is easy to learn and more effective in post-operative pain control than general anaesthesia alone. In Crosbie *et al*.'s (4) study, RSB provided a significant postoperative analgesia for patients with major gynaecological surgery and, therefore, the investigators concluded that a randomized clinical trial is needed to confirm the efficacy of RSB. Day *et al*. (3) studied in the randomized clinical trial the stress response from two different methods of analgesia after laparoscopic colorectal surgery. In their study, no significant differences in the levels of interleukins between spinal analgesia and intravenous patient-controlled analgesia were found at any time point. However, they concluded that spinal analgesia reduced early neuroendocrine responses and overall parenteral morphine use (3). Dutton *et al*. (10) used bilateral RSB with catheters in patients undergoing major urological surgery and reported that the use of RSB offers a safe and effective method for perioperative analgesia.

One limitation of the present study, from the methodological point of view, is the small sample size of 46 analyzed patients. However, the issue addressed is quite specific and, therefore, we did not expect high number of patients, a point that has to be taken into account in planning new scientific studies in the future. Also, the timing of the assessment of cytokines needs to be considered since their half-life in blood is usually less than one hour. The under 6-h postoperative time point would be an optimal time point for proinflammatory IL-1β and anti-inflammatory IL-1ra and IL-10 kinetics. Therefore, samples taken at 24 h postoperatively (POP2) are missing the early postoperative peak values and may not allow a fair comparison of the individual NRS values *versus* inflammatory marker values. The peak of CRP is generally between 36-48 h postoperatively and this might be the reason that no difference was identified in our study. In active groups, the wound catheters were inserted at the end of operation and it is unlikely that wound catheters would have affected the inflammatory response immediately after surgery (POP1), in contrast to samples taken at 24 h postoperatively (POP2).

In conclusion, the results suggest that the inflammatory stress marker response in the placebo group and in three active groups was quite similar and there is no clear evidence that the post-surgery placement of the RSB analgesia would reduce the inflammatory stress response following surgery. However, there is some evidence for the main hypothesis of our study; a significant correlation between patients' pain experience, NRS postoperatively and concentrations of inflammatory stress

biomarkers, suggesting that inflammation and pain are related in patients with benign disease and cancer.

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Disclosure

No conflicts of interest exist. The Authors alone are responsible for the content and writing of this original article.

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