Randomized clinical trial

Effect of an individualized *versus* standard pneumoperitoneum pressure strategy on postoperative recovery: a randomized clinical trial in laparoscopic colorectal surgery

O. Díaz-Cambronero[1,2,4], G. Mazzinari[1,2], B. Flor Lorente[3], N. García Gregorio[1,2], D. Robles-Hernandez[6], L. E. Olmedilla Arnal[7], A. Martin de Pablos[8], M. J. Schultz[9,10,11], C. L. Errando[5] and M. P. Argente Navarro[1,2], on behalf of the IPPColLapSe II study investigators*

[1]Research Group in Perioperative Medicine, [2]Department of Anaesthesiology, [3]Department of Colorectal Surgery and [4]Spanish Clinical Research Network (SCReN), SCReN-IIS La Fe, PT17/0017/0035, Hospital Universitario y Politécnico la Fe, and [5]Department of Anaesthesiology, Consorcio Hospital General Universitario de Valencia, Valencia, and Departments of Anaesthesiology, [6]Hospital General Universitario de Castellón, Castellón, [7]Hospital General Universitario Gregorio Marañón, Madrid, and [8]Hospital Universitario Virgen Macarena, Seville, Spain, [9]Department of Intensive Care and Laboratory of Experimental Intensive Care and Anaesthesiology, Amsterdam University Medical Centre, Location AMC, Amsterdam, the Netherlands, [10]Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand, and [11]Nuffield Department of Medicine, University of Oxford, Oxford, UK

Correspondence to: Dr O. Diaz-Cambronero, Perioperative Medicine Research Group, Instituto de Investigación Sanitaria La Fe, Avinguda de Fernando Abril Martorell 106, 46026 Valencia, Spain (e-mail: perioperativemedicine@iislafe.es)

Background: It remains uncertain whether individualization of pneumoperitoneum pressures during laparoscopic surgery improves postoperative recovery. This study compared an individualized pneumoperitoneum pressure (IPP) strategy with a standard pneumoperitoneum pressure (SPP) strategy with respect to postoperative recovery after laparoscopic colorectal surgery.

Methods: This was a multicentre RCT. The IPP strategy comprised modified patient positioning, deep neuromuscular blockade, and abdominal wall prestretching targeting the lowest intra-abdominal pressure (IAP) that maintained acceptable workspace. The SPP strategy comprised patient positioning according to the surgeon's preference, moderate neuromuscular blockade and a fixed IAP of 12 mmHg. The primary endpoint was physiological postoperative recovery, assessed by means of the Postoperative Quality of Recovery Scale. Secondary endpoints included recovery in other domains and overall recovery, the occurrence of intraoperative and postoperative complications, duration of hospital stay, and plasma markers of inflammation up to postoperative day 3.

Results: Of 166 patients, 85 received an IPP strategy and 81 an SPP strategy. The IPP strategy was associated with a higher probability of physiological recovery (odds ratio (OR) 2·77, 95 per cent c.i. 1·19 to 6·40, $P = 0·017$; risk ratio (RR) 1·82, 1·79 to 1·87, $P = 0·049$). The IPP strategy was also associated with a higher probability of emotional ($P = 0·013$) and overall ($P = 0·011$) recovery. Intraoperative adverse events were less frequent with the IPP strategy ($P < 0·001$) and the plasma neutrophil–lymphocyte ratio was lower ($P = 0·029$). Other endpoints were not affected.

Conclusion: In this cohort of patients undergoing laparoscopic colorectal surgery, an IPP strategy was associated with faster recovery, fewer intraoperative complications and less inflammation than an SPP strategy. Registration number: NCT02773173 (http://www.clinicaltrials.gov).

*The IPPColLapSe II study investigators are co-authors of this study and are listed in *Appendix S1* (supporting information)

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Introduction

Although it is recommended to use the lowest possible intra-abdominal pressure (IAP) during laparoscopic surgery at which an acceptable surgical workspace is maintained[1], it is common practice to use a fixed and usually high IAP[2]. Indeed, IAP is frequently set between 12 and 15 mmHg, or even higher depending on the surgeon's

preference[3]. An increase in IAP during pneumoperitoneum for laparoscopic surgery may cause inflammation and injury to the peritoneal mesothelium[4,5]. A low IAP leads to less postoperative pain[6], but definitive evidence for the benefit of a low IAP during pneumoperitoneum with regard to other patient-centred outcomes remains lacking.

Patient positioning[7], use of deep neuromuscular blockade[8,9], intraoperative ventilation with a low tidal volume[10], and prestretching of the abdominal wall[11] all help to improve the relationship between IAP and intra-abdominal volume. Combining these measures results in an adequate working space at lower IAP in most patients[12]. The present study aimed to assess whether a recently developed individualized pneumoperitoneum pressure (IPP) strategy, which uses all the above-mentioned measures, improves patient-centred outcomes. It was hypothesized that use of an IPP strategy would leads to faster patient recovery than use of standard pneumoperitoneum (SPP).

Methods

The Individualized Pneumoperitoneum Pressure in Colorectal Laparoscopic Surgery *versus* Standard Therapy II (IPPColLapSe II) study was a double-blind two-arm parallel-group multicentre RCT undertaken at four university-affiliated hospitals in Spain (Hospital Universitario y Politécnico la Fe, Hospital General Universitario de Castellón, Hospital General Universitario Gregorio Marañón, Hospital Universitario Virgen Macarena). The Institutional Review Board of Hospital Universitario y Politécnico la Fe in Valencia, Spain, approved the study protocol as well as a subsequent modification concerning extension of recruitment. The study protocol and conduct complied with the Helsinki Declaration and Spanish legislation for biomedical research. Written informed consent was obtained from all subjects before entering the trial. The study was registered before patient enrolment at EudraCT (study 2016-001693-15) and ClinicalTrials.gov (NCT02773173), and the protocol was prepublished[13] and updated[14].

Inclusion and exclusion criteria

Patients were eligible if scheduled for laparoscopic colorectal surgery, aged over 18 years, with an ASA physical status grade below IV, and without cognitive deficits. Exclusion criteria were: absence of written informed consent; emergency or unplanned surgery; pregnancy or breastfeeding; immunological or neuromuscular diseases; advanced stage of cardiopulmonary, renal or hepatic disease; and allergy or contraindications to rocuronium or sugammadex.

Randomization and blinding

Patients were randomized in a 1 : 1 ratio to the IPP or SPP strategy. Local investigators undertook randomization using a web-based automated randomization system. Randomization was performed with random block sizes and stratified by centre. Attending anaesthetists were aware of the group assignment, whereas attending surgeons and patients remained unaware of the assignment at all times, before, during and after surgery.

Pneumoperitoneum strategies

The IPP strategy has been described in detail previously[12]. In short, this strategy comprised: use of a modified lithotomy position, with the hips flexed (between 45 and 90°) and legs raised in padded supports to increase the anteroposterior intra-abdominal space by correcting lumbar lordosis; deep neuromuscular blockade throughout surgery to maintain a train-of-four (TOF) count of 0 and a post-tetanic count of between 1 and 5, both assessed by acceleromyography at the thumb; prestretching of the abdominal wall muscles by maintaining an IAP of 15 mmHg for 5 min at the beginning of carbon dioxide insufflation and insertion of abdominal trocars; IAP titration from 15 to 12 mmHg, and stepwise to 11, 10, 9 and finally 8 mmHg as long as the attending surgeon maintained an adequate workspace after the patient had been placed in a 0–30° Trendelenburg position; and neuromuscular blockade reversal at the end of surgery, before tracheal extubation, with 4 mg/kg sugammadex.

The SPP strategy consisted of: patient positioning according to the surgeon's preference in the Trendelenburg position (0–30°); moderate neuromuscular blockade with rocuronium, cisatracurium or atracurium throughout surgery to maintain a TOF count between 2 and 4; IAP set at 12 mmHg throughout surgery; and neuromuscular blockade reversal, according to usual care with 2·5 mg or 30–50 μg/kg neostigmine.

The two IAP strategies are further detailed in *Table S1* (supporting information). With both strategies, the surgeon could request an increase in IAP if the workspace became inadequate. This was done in steps of 1 mmHg during 1-min intervals until the workspace became adequate, but the IAP was never higher than 15 mmHg; at this point the surgeons were warned that the upper IAP limit had been reached.

Other perioperative management

In both groups, intraoperative ventilation consisted of volume-controlled ventilation, using a tidal volume of 8 ml per kg predicted ideal bodyweight, with a 20 per cent inspiratory pause time, and a positive end-expiratory pressure set at 5 cmH_2O in patients with a BMI of less than 30 kg/m^2 and 10 cmH_2O in those with a higher BMI. The respiratory rate was set between 12 and 15 breaths per min to maintain normal end-tidal carbon dioxide values. Perioperative analgesia included the use of intravenous opioids and non-steroidal anti-inflammatory drugs. Carbon dioxide insufflation was performed with a standard commercial gas that was neither heated nor humidified. Other aspects of perioperative management followed the recommendations of the Spanish enhanced recovery after surgery (ERAS) guidelines, where possible (*Table S1*, supporting information).

Measurements and definitions

The Postoperative Quality of Recovery Scale (PQRS), used to assess the primary endpoint, is a verbal survey tool that assesses recovery in five domains: physiological, nociceptive, emotional, functional and cognitive; it also collects data on overall patient perspective[15]. Each of these domains is assessed by means of multiple items on an ordinal scale and compared with baseline to evaluate recovery (*Table S2*, supporting information). A baseline PQRS score was obtained before surgery. After surgery, the PQRS score was obtained at 15 and 40 min after arrival in the postanaesthesia care unit, and in the ward during the morning of postoperative day (POD) 1 and POD 3. It was anticipated that patients would stay in the hospital of surgery for at least 3 days, based on local experience. If the patient was discharged before day 3, it was planned to censor data from the point of last follow-up within the hospital of surgery. Recovery was a dichotomized outcome defined by a return to at least baseline value or better. Overall recovery was defined as recovery in all domains; failure in any domain meant a lack of overall recovery.

Intraoperative adverse events comprised involuntary patient movements, such as diaphragm or abdominal wall contractions, and spontaneous breathing efforts or coughing. Postoperative complications were defined in accordance with current European standards for perioperative outcomes (*Table S3*, supporting information). The Clavien–Dindo classification was used to evaluate the severity of postoperative complications (*Table S4*, supporting information).

Blood samples were obtained on POD 1 and POD 3 during follow-up visits for PQRS assessment. The neutrophil–lymphocyte ratio (NLR) and C-reactive protein (CRP) level were measured in plasma samples using particle-enhanced immunoturbidimetry at the central laboratory in participating hospitals.

In the IPP group, the individualized IAP was the highest IAP needed to obtain and maintain an adequate workspace until completion of surgery. Adequate workspace was defined as an intra-abdominal workspace sufficient to perform the surgical procedure with no need for an increase in IAP, as judged by the attending surgeon. Inadequate workspace was defined as an intra-abdominal workspace insufficient to perform the surgical procedure.

Endpoints

The primary endpoint was the PQRS score for the physiological domain[15,16]. Secondary outcomes included the PQRS scores for nociceptive, emotional and cognitive recovery and activities of daily living, overall PQRS, occurrence of intraoperative and postoperative complications, duration of hospital stay, and course of plasma markers of inflammation up to POD 3.

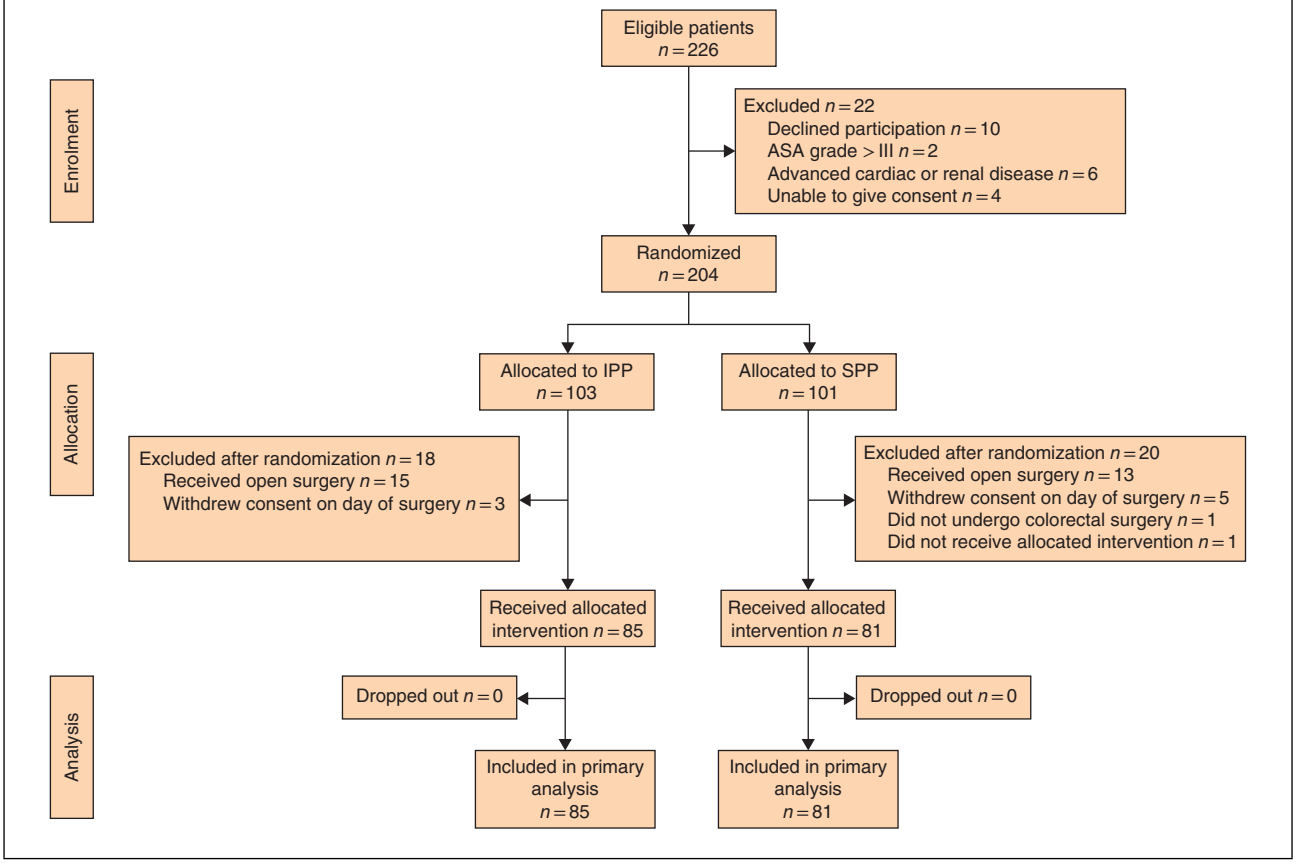
Statistical analysis

In the absence of studies that used the PQRS in the setting of intraoperative IAP management during laparoscopic surgery, a sample size calculation was undertaken assuming an odds ratio (OR) of 2·65 between groups in the recovery of physiological PQRS score, which is equivalent to a difference of 0·5 units in the logit scale. A sample size of 170 patients was required to achieve 80 per cent power at an α of 5 per cent, with a drop-out rate of 20 per cent.

During the conduct of the study it was decided to proceed with an open surgical approach in a larger than expected number of patients. Therefore, an extension to recruit 205 patients was requested, which was approved by the Institutional Review Board of the Hospital Universitario y Politécnico la Fe, Valencia, Spain. The primary evaluation comprised a modified intention-to-treat analysis based on the target condition, that is patients who actually underwent laparoscopic colorectal surgery, and in whom the surgical procedure was not converted to open abdominal operation[17].

Continuous variables are reported as median (i.q.r.). Normality was checked by examination of the quantile–quantile plot. Categorical variables are reported as percentages and proportions. Where there were more than 5 per cent missing data, imputation was performed using the mice package for R software (R Foundation for Statistical Computing, https://www.r-project.org). Values

Fig. 1 CONSORT diagram for the trial



IPP, individualized pneumoperitoneum pressure; SPP, standard pneumoperitoneum pressure.

were imputed by chained equation with predictive mean matching, creating five data sets that were used jointly to fit regression models[18].

To assess the association between the pneumoperitoneum strategy (IPP or SPP) and PQRS scores, a mixed logistic regression model was fitted with age, BMI, duration of surgery and sex as co-variables, and patient as a random factor to account for interindividual variability. The association between the two strategies and the incidence of intraoperative adverse events was assessed by Fisher's exact test. To assess the association between the pneumoperitoneum strategy and postoperative complications, an ordinal model was fitted with postoperative complications introduced as an ordinal scale according to Clavien–Dindo severity score, and age, BMI, ASA grade, duration of surgery and sex as co-variables. To assess the association between the pneumoperitoneum strategy and duration of hospital stay, a Cox regression model was fitted with introduction of an interaction term between incidence and severity of complications.

PQRS scores were also analysed as ordinal variables[13]. With this approach there is no dichotomization of PQRS outcomes, and scores are treated as variables in ordered categories.

A mixed linear regression model, with age, BMI and duration of surgery as co-variables, was fitted to assess the association between the two pneumoperitoneum strategies and the course of NLR and CRP plasma levels. The study protocol prespecified a missing data threshold of 5 per cent for performing imputation. NLR and CRP level had a missing rate of 6·4 and 13·2 per cent respectively, so analysis of these outcomes was undertaken after imputation of missing values.

A *post hoc* decision was made also to report risk ratio (RR) for significant logistic regression results, to avoid misleading interpretation of ORs[19]. RRs were estimated by modified Poisson regression with robust error variance with sandwich estimator to account for repeated measures in patients, with age, BMI, duration of surgery and sex as co-variables[20].

Table 1 Baseline characteristics

	All patients ($n = 166$)	Individualized pneumoperitoneum pressure ($n = 85$)	Standard pneumoperitoneum pressure ($n = 81$)
Age (years)*	68 (59–74)	68 (58–74)	67 (59–77)
Sex ratio (F : M)	63 : 103	27 : 58	36 : 45
BMI (kg/m^2)*	27·0 (24·0–30·0)	27·0 (24·2–29·9)	26·6 (23·8–29·0)
ASA physical status grade			
I	25 (15·1)	13 (15)	12 (15)
II	96 (57·8)	47 (55)	49 (60)
III	45 (27·1)	25 (29)	20 (25)
Respiratory disease	15 (9·0)	9 (11)	6 (7)
Diabetes	38 (22·9)	17 (20)	21 (26)
Hypertension	85 (51·2)	41 (48)	44 (54)
Ischaemic disease	19 (11·4)	8 (9)	11 (14)
Previous pregnancies			
0	31 of 63 (49)	11 of 27 (41)	20 of 36 (56)
1	6 of 63 (10)	3 of 27 (11)	3 of 36 (8)
2	16 of 63 (25)	8 of 27 (30)	8 of 36 (22)
3	6 of 63 (10)	4 of 27 (15)	2 of 36 (6)
4	3 of 63 (5)	1 of 27 (4)	2 of 36 (6)
5	1 of 63 (2)	0 of 27 (0)	1 of 36 (3)
Type of surgery			
Lower anterior rectal resection	45 (27·1)	24 (28)	21 (26)
Right hemicolectomy	61 (36·7)	30 (35)	31 (38)
Left hemicolectomy	5 (3·0)	4 (5)	1 (1)
Sigmoidectomy	33 (19·9)	17 (20)	16 (20)
Total colectomy	2 (1·2)	1 (1)	1 (1)
Other†	20 (12·0)	9 (11)	11 (14)
Previous laparoscopic procedures			
0	90 of 128 (70·3)	50 of 69 (72)	40 of 59 (68)
1	31 of 128 (24·2)	16 of 69 (23)	15 of 59 (25)
2	4 of 128 (3·1)	1 of 69 (1)	3 of 59 (5)
3	3 of 128 (2·3)	2 of 69 (3)	1 of 59 (2)
Oncological surgery	149 (89·8)	79 (93)	70 (86)
Recruiting hospital			
La Fe, Valencia	86 (51·8)	44 (52)	42 (52)
Gregorio Marañón, Madrid	26 (15·7)	13 (15)	13 (16)
General, Castellón	29 (17·5)	15 (18)	14 (17)
Virgen Macarena, Seville	25 (15·1)	13 (15)	12 (15)
Surgeons' previous laparoscopic colorectal surgery experience (years)*	10 (8–15)	10 (8–15)	1 (8–15)

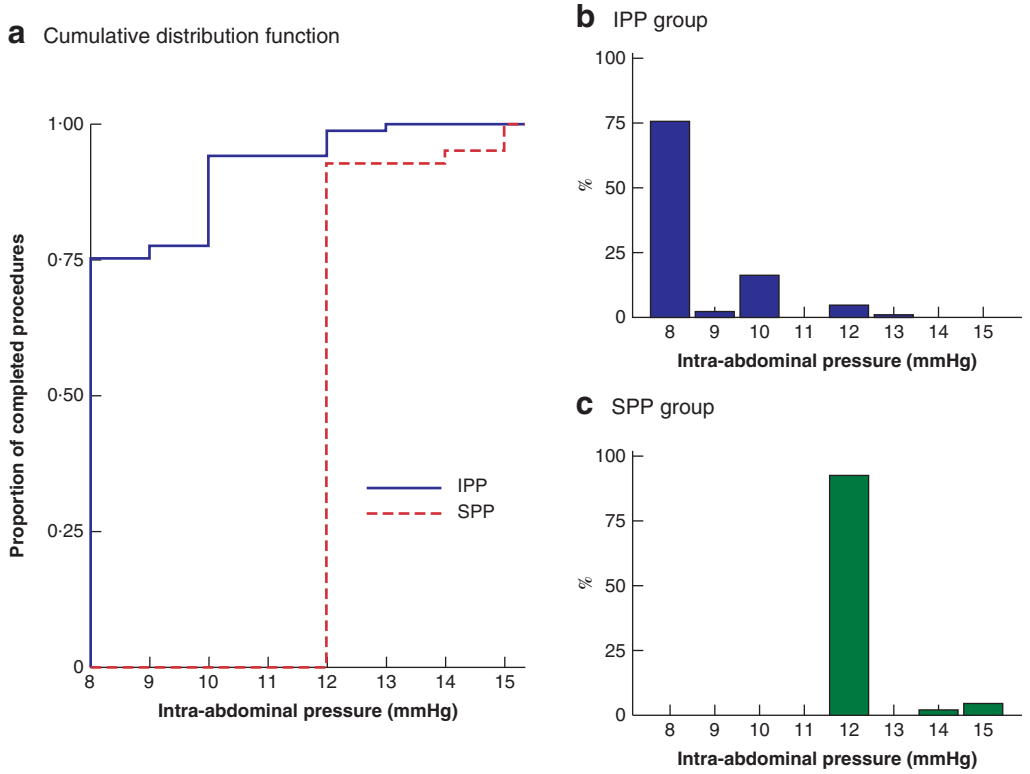
Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). † Ileocaecal resection, perineal amputation, segmental resection.

All analyses were undertaken using R software version 3.5.2. Two-tailed $P < 0·050$ was considered statistically significant and no correction for multiple comparisons was preplanned.

Results

In total, 204 patients were included and randomized between February 2017 and November 2018. Of these, 38 patients did not receive the allocated intervention, mainly because it was decided to perform open surgery instead of the planned laparoscopic intervention. A total of 166 patients were included in the modified intention-to-treat analysis (*Fig. 1*). Baseline characteristics were well balanced and intraoperative characteristics were no different between the two groups (*Table 1*). Follow-up for the primary endpoint was complete up to POD 3, as all patients stayed in hospital for at least 3 days after surgery.

Fig. 2 Intra-abdominal pressure at which surgery could be performed



a Empirical cumulative distribution function for the individualized pneumoperitoneum pressure (IPP) and standard pneumoperitoneum pressure (SPP) groups. Distribution of intra-abdominal pressure in **b** IPP and **c** SPP groups.

Intervention

The empirical cumulative distribution function and relative percentages of IAP used during pneumoperitoneum in the two groups are shown in *Fig. 2*. In 80 patients in the IPP group (94 per cent), IAP remained below 12 mmHg during pneumoperitoneum. A rise in IAP was requested in 20 (24 per cent) and seven (9 per cent) patients in the IPP and SPP group respectively ($P < 0{\cdot}001$). This need for a higher IAP resulted in an increase to 10 (95 per cent c.i. 10 to 10) and 15 (14 to 15) mmHg respectively. The request for an increase in IAP was made mainly during the pelvic phase of the surgical procedure.

Primary outcome

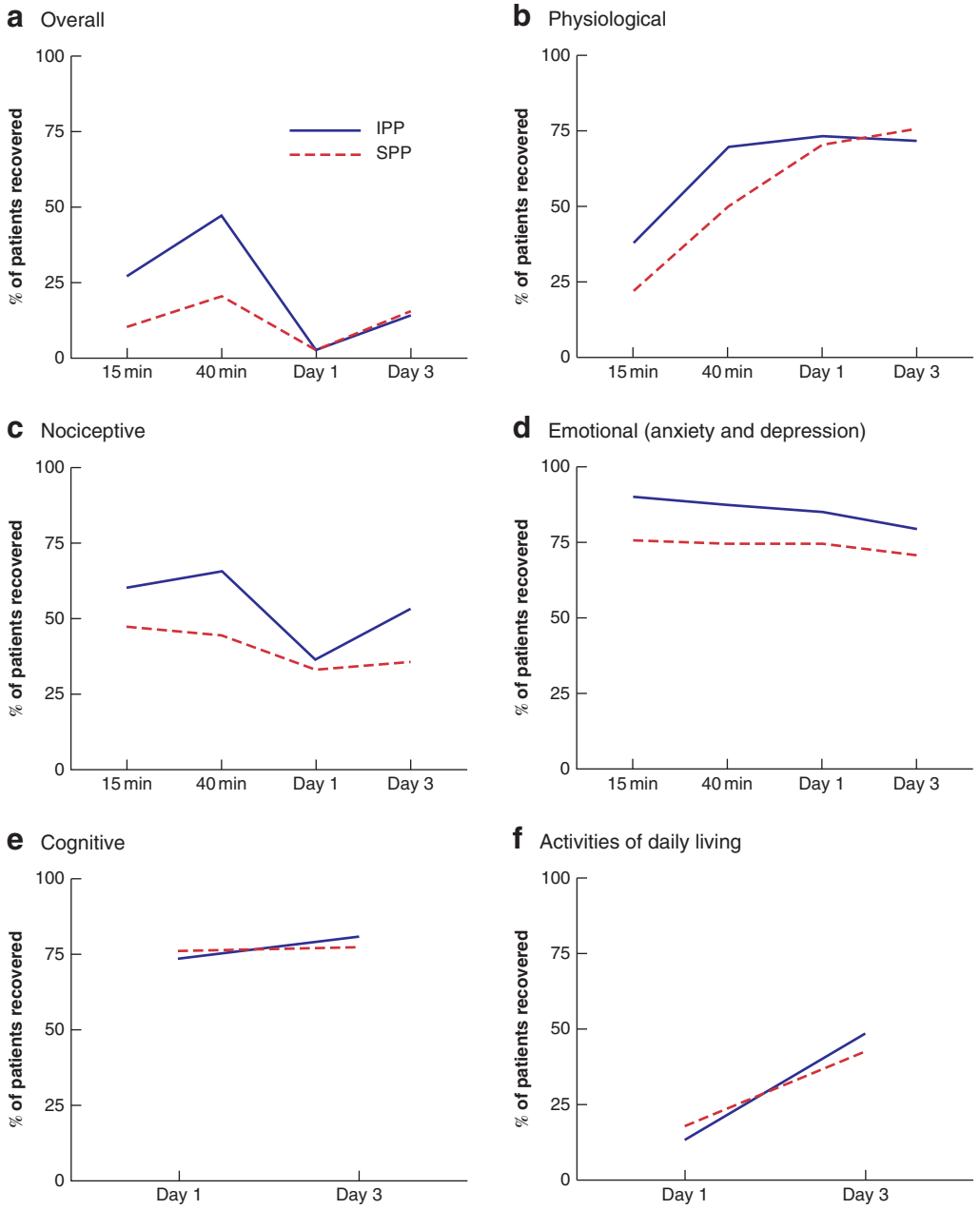
PQRS scores results are shown in *Fig. 3*. Patients in the IPP group had a higher probability of physiological recovery (OR 2·77, 95 per cent c.i. 1·19 to 6·40, $P = 0{\cdot}017$; RR 1·82, 1·79 to 1·87, $P = 0{\cdot}049$). Of note, the interaction between time and group assignment was significant, with the probability of recovery equalizing on POD 3 (*Table S5*, supporting information).

Secondary outcomes

The probability of emotional recovery was higher in the IPP group (OR 4·59, 95 per cent c.i. 1·37 to 15·29, $P = 0{\cdot}013$; RR 1·18, 1·16 to 1·21, $P < 0{\cdot}001$), with no significant time interaction (*Table S6*, supporting information). Patients in the IPP group had a higher probability of overall recovery (OR 3·68, 1·35 to 10·03, $P = 0{\cdot}011$; RR 2·70, 1·29 to 5·66, $P = 0{\cdot}016$), with a significant interaction between time and group assignment (*Table S7*, supporting information). The quality of recovery in the other domains was not affected by the IPP strategy (*Fig. 3*; *Tables S8–S10*, supporting information).

The PQRS ordinal regression analysis yielded similar results for all PQRS domains except nociceptive PQRS score, which was significantly lower in the IPP group (OR 0·47, 0·22 to 0·99, $P = 0{\cdot}047$; RR 0·29, 0·16 to 0·78, $P = 0{\cdot}023$).

Fig. 3 Postoperative quality of recovery



a Overall, **b** physiological, **c** nococeptive (pain and nausea), **d** emotional and **e** cognitive recovery, and **f** recovery of activities of daily living (eating, walking, standing and dressing) of all participants in the individualized pneumoperitoneum pressure (IPP) and standard pneumoperitoneum pressure (SPP) groups after surgery. **a** $P = 0{\cdot}011$, **b** $P = 0{\cdot}017$, **a** $P = 0{\cdot}079$, **d** $P = 0{\cdot}013$, **e** $P = 0{\cdot}536$, **f** $P = 0{\cdot}506$ (mixed logistic regression).

The incidence of intraoperative cough or movement was lower in the IPP group than in the SPP group (1 *versus* 54 per cent; $P < 0{\cdot}001$). No differences were observed in the incidence of postoperative complications or in duration of stay between the two randomized groups.

The plasma NLR was lower in the IPP compared with the SPP group ($P = 0{\cdot}029$) (*Fig. S1* and *Table S11*, supporting information). Plasma CRP levels were not affected by the IPP strategy (*Table S12*, supporting information). Inflammatory markers were not associated with

recovery (*Tables S13* and *S14*, supporting information). Additional information on PQRS sensitivity analysis, postoperative complications and length of stay is reported in *Tables S15–S22* (supporting information).

Discussion

The main finding of this study of patients undergoing laparoscopic colorectal surgery was that an individualized insufflation strategy was associated with quicker physiological, emotional and overall recovery in the early postoperative period than a standard strategy. In addition, the IPP strategy was associated with less intraoperative coughing and movements, and a lower plasma NLR.

This study has several strengths. It tested a previously designed and evaluated IPP strategy that was easy to perform and maintain during surgery, with no deviations from the protocol. There was a clear separation between the two strategies with respect to the pneumoperitoneum pressure, while keeping sufficient surgical working space with the individualized approach. The primary outcome was assessed using a previously validated comprehensive scoring system that evaluates early postoperative recovery with a focus on clinical rather than surrogate measures or preclinical endpoints[21]. Patients and surgeons were kept blinded to the group assignment, thereby reducing bias in terms of recovery scores, surgical conditions and conversion rate. The statistical analysis accounted for the longitudinal nature of the primary outcome using a mixed-effect model including individual variability and the effect of time, with adjustment for prerandomization and postrandomization co-variables to control for attrition bias[22].

Findings of previous systematic reviews assessing the effect of a low IAP on perioperative outcomes in patients undergoing laparoscopic surgery were conflicting, either showing a significant reduction in pain scores[23] or no effects[6,24]. Significant decreases in perioperative complications were found in prospective studies[25–27]. Only one study[28] that reported on the quality of recovery found no difference between a low and standard IAP strategy. In that study of laparoscopic nephrectomies, quality of recovery was evaluated using another assessment tool, the QoR-40 questionnaire[29], and differently from in the present analysis; moreover, no longitudinal analysis was performed.

Several studies[12,30,31] have shown a low pneumoperitoneum pressure to be feasible during laparoscopic surgery. However, none of them assessed the effects on quality of recovery. In the present trial, an IPP strategy was associated with faster recovery in the early postoperative period. Of note, although parts of the bundle of measures applied in the intervention arm were prespecified and, in fact, standard, the IPP strategy protocol aimed for an IPP at which surgeons could perform the intervention. The lithotomy position, deep neuromuscular blockade, and prestretching the abdominal wall are crucial elements allowing better individualization of the intraoperative pneumoperitoneum pressure[12]. Surgical experience was comparable between the two study groups, as in each participating centre the surgical procedure was performed by a staff surgeon experienced in colorectal and laparoscopic surgery.

Patients in the IPP group had a much lower incidence of intraoperative adverse events, mainly intraoperative cough or patient movements, at least in part because of the deeper neuromuscular blockade, but a definitive association could not be established because the IPP intervention consisted of several procedures. Deep neuromuscular blockade has been associated with better surgical conditions in previous studies[8,32], but robust evidence for its benefit is still lacking[33]. Intraoperative complications have been linked to increased postoperative morbidity and mortality[34,35], so reducing them can improve surgical outcomes.

Plasma NLR, but not plasma CRP levels, were lower with the IPP strategy, although statistical significance was borderline. The physiological effect of carbon dioxide insufflation on the diaphragm and other tissues surrounding the abdominal cavity is well known[5,36,37]. The present findings suggest that insufflation at an individualized IAP could reduce these injurious effects, although the differences found here are hypothesis-generating at best. Future studies should focus on the clinical significance of these differences.

This study has some limitations. The long-term effects of an IPP strategy remain uncertain, as follow-up was limited to the early postoperative period. This study considered a restricted number of intraoperative adverse events. Future studies could include more or other adverse events as endpoints, like those reported elsewhere[38,39]. Although reported adverse events, such as major intraoperative bleeding, and injury to bowel and intra-abdominal organs, were no different between the two groups, these outcomes were not recorded as part of the present study. The number of patients recruited was lower than planned, which reduces the statistical power especially to show differences in the secondary outcomes. A modified intention-to-treat analysis was undertaken based on the target condition, that is patients who actually underwent laparoscopic colorectal surgery, and in whom the surgical procedure was not converted to an open abdominal operation. This approach is appropriate for pragmatic RCTs[40,41]. The validity of the results among surgical teams with a different level of experience requires further investigation, as not only technical but also teamwork skills may be involved. The study protocol advised postoperative nausea and vomiting

prophylaxis according to ERAS guidelines, but data regarding administration of drugs such as dexamethasone were not collected. Finally, corrections were not made for multiple comparison, meaning that the findings regarding the secondary outcomes should be viewed as exploratory.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.