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PAIN

Nociception level-guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial

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A preliminary account of the results has been given in an abstract for the European Anaesthesiology Congress 2020 (*Eur J Anaesthesiol* 2020; **39**(e-Supplement 58): 359).

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Abstract

Background: This RCT investigated the effect of opioid titration by three different nociception monitoring devices or clinical signs during general anaesthesia.

Methods: Ninety-six patients undergoing radical retropubic prostatectomy with propofol/remifentanil anaesthesia were randomised into one of four groups to receive remifentanil guided by one of three nociception monitoring devices (surgical pleth index [SPI], pupillary pain index [PPI], or nociception level [NOL]) or by clinical judgement (control). Intraoperative remifentanil requirement was the primary endpoint, whereas recovery parameters and stress hormone levels were secondary endpoints.

Results: The mean [95% confidence interval {CI}] remifentanil administration rate differed between the groups: control 0.34 (0.32–0.37), SPI 0.46 (0.38–0.55), PPI 0.07 (0.06–0.08), and NOL 0.16 (0.12–0.21) μg kg^{-1} min^{-1}($P<0.001$). Intraoperative cessation of remifentanil administration occurred in different numbers (%) of patients: control 0 (0%), SPI 1 (4.3%), PPI 18 (75.0%), and NOL 11 (47.8%); $P=0.002$. The area under the curve analyses indicated differences in cumulative cortisol levels (mg L^{-1} min^{-1}) amongst the groups: control 37.9 (33.3–43.1), SPI 38.6 (33.8–44.2), PPI 72.1 (63.1–82.3), and NOL 54.4 (47.6–62.1) (mean [95% CI]). Pairwise group comparison results were as follows: control *vs* SPI, $P=0.830$; control *vs* PPI, $P<0.001$; control *vs* NOL, $P=0.001$; SPI *vs* PPI, $P<0.001$; SPI *vs* NOL, $P=0.002$; and PPI *vs* NOL, $P=0.009$.

Conclusions: The nociception monitoring devices and clinical signs reflect the extent of nociception differently, leading to dissimilar doses of remifentanil. Very low remifentanil doses were associated with an increase and higher remifentanil doses were accompanied by a decrease in serum cortisol concentrations. Use of nociception monitoring devices for guiding intra-operative opioid dosing needs further validation.

Clinical trial registration: NCT03380949.

Keywords: adrenocorticotropic hormone; cortisol; general anaesthesia; nociception; opioid analgesics; pain measurement

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Editor's key points

- In this RCT, 96 patients undergoing radical prostatectomy with propofol/remifentanil were randomised to have remifentanil administration guided by surgical pleth index (SPI), pupillary pain index (PPI), nociception level (NOL), or clinical judgement.
- The total amount of remifentanil infused was highest in the control and SPI groups, intermediate in the NOL group, and lowest in the PPI group.
- Adrenocorticotropic hormone and cortisol concentrations were inversely related to remifentanil dose.
- Although all are validated and approved for clinical use, the monitors differently reflect nociception/antinociception balance and guide opioid dosing differently, thus requiring further validation.

Modern general anaesthesia aims to treat nociception induced by surgical stimulation while avoiding an overdose of opioid analgesics and reducing side-effects of opioid administration.[1–3] In recent years, different monitoring devices estimating the effect of nociception during unconsciousness have become commercially available.[2,4] These monitoring devices use several different mechanisms, such as HR variability, pulse wave photoplethysmography, pupil reflex dilation, and skin conductance measurement, and index the nociception/analgesia balance.[4–9] Such monitoring devices should help physicians choose the right dose of opioid analgesics during general anaesthesia. Nevertheless, the impact of nociception-monitor-guided opioid administration on the administered amount of opioid, postoperative short-term recovery, and long-term outcome is inconclusive.[1–4]

In this RCT, the authors compared the effect of nociception-monitor-guided opioid administration with three commercially available monitoring systems and a control group using clinical signs only. We hypothesised that if the monitoring devices were validated correctly, they would deliver the same amount of opioid during the same standardised operation with the same nociceptive stimuli. Thus, the primary endpoint was the intraoperative amount of remifentanil consumption. Secondary endpoints were recovery times, postoperative pain scores and analgesic requirements, and perioperative stress hormone release, and a follow up on persisting postoperative pain and overall satisfaction with anaesthetic care after 3 weeks.

Methods

This prospective RCT was conducted during radical retropubic prostatectomy procedures. The regional ethics review board of the Medical Council of Hamburg, Germany approved the study protocol (reference number: PV5586) on July 31, 2017. The study was registered at the https://clinicaltrials.gov/ database (identifier: NCT03380949) on November 29, 2017 before patient recruitment. Participating subjects gave written informed consent the day before data collection and surgery.

Inclusion and exclusion criteria

All subjects were males, >18 yr, and underwent open abdominal prostatectomy. Patients with robotically assisted minimally invasive prostatectomy were excluded. Further exclusion criteria were previous regular medications influencing the autonomous nervous system (e.g. beta blockers and glycosides) or steroids; history of chronic pain, including treatment with opioids; and patients with pacemaker therapy and a higher degree of cardiac arrhythmias and eye disease.

Randomisation

The randomisation sequence was generated before patient recruitment by a study nurse, who was not involved in data collection, via a computer-generated list in blocks of 12 using the RAND function in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Allocation was concealed with sequentially numbered sealed opaque envelopes. The principal investigator evaluated eligibility and enrolled the participants by opening the respective concealed envelope on the day of surgery before anaesthesia induction. The subjects were randomised to one of the four treatment groups: remifentanil administration titrated at the discretion of the attending anaesthesiologist (control group) or by one of the three nociception monitoring devices (surgical pleth index [SPI], pupillary pain index [PPI], or nociception level [NOL]).

Nociception monitoring devices

The SPI is derived by the CARESCAPE™ B650 patient monitor (GE Healthcare, Helsinki, Finland). It calculates an index value from normalised HR and pulse wave amplitude derived by photoplethysmography. The index is presented on a scale from 0 (low sympathetic tone) to 100 (high sympathetic tone).[4] Several previous studies used a range of 20–50 as a target that was considered sufficient analgesia without being too deep.[10–13]

The PPI is derived with the AlgiScan® monitoring device (idmed, Marseille, France), which is a video pupillometer that is placed intermittently in front of a patient's eye. It applies a standardised electric nociceptive stimulus to the forearm of the patient, and a camera measures the consecutive extent of pupillary reflex dilation (PRD).[14,15] An algorithm increases the intensity of the electric stimulation stepwise from 10 to 60 mA, and the degree of PRD is then displayed as an index value between 0 (no pain) and 10 (extreme pain).[8,16,17] There is no published evidence on the optimal target range, but the manufacturer states that a PPI of 2 to 3 represents optimal analgesia.

The third nociception index was the NOL index. The PMD-200™ monitoring system (Medasense Biometrics Ltd, Ramat Gan, Israel) provides the multi-parameter NOL index derived from a finger probe that is used to determine pulse rate, pulse rate variability, pulse wave amplitude, skin conductance level, skin conductance fluctuations, skin temperature, and finger motion.[5,18–20] The resulting composite index value ranges from 0 to 100.[4] A low value is a sign of deep analgesia, whereas higher values indicate light to insufficient analgesia. The manufacturer proposes a target range between 10 and 25 that was recently used in clinical trials.[12,20]

Conduct of the study

The anaesthesia protocol is described in the Supplementary material (Expanded methods 1. Anaesthesia protocol).

After the induction of general anaesthesia with continuous infusion of remifentanil at a rate of 0.5 μg kg^{-1} min^{-1}, the dose of remifentanil was reduced to a rate of 0.2 μg kg^{-1} min^{-1}. During the surgery, remifentanil infusion was guided by the

subjects' stress response either by the attending anaesthesiologist observing traditional clinical signs, such as an increase in HR or blood pressure >10%, sign of tearing, movements, a decrease in the respiratory system compliance, and sweating (control group), or by a protocol, including the index values of one of the three nociception monitoring devices. The PPI was reassessed in intervals of 5 min. The SPI and NOL were observed continuously, but changes were considered significant only if the index was above or below the proposed range for more than 30 s. If the NOL was below the lower threshold value for more than 30 s, the remifentanil infusion rate was decreased by 0.03 μg kg^{-1} min^{-1} every 5 min until finally stopped. If the index exceeded the upper threshold value, the patient received a bolus of remifentanil 30 μg, and the continuous infusion rate was increased by 0.03 μg kg^{-1} min^{-1} every 5 min until the index was within the proposed range. The postoperative care of the patients in the PACU is described in the Supplementary material (Expanded methods 2. Post-anaesthesia care unit protocol).

Blood sampling

Perioperative blood samples were taken at baseline (before induction of general anaesthesia), skin closure (at the end of the surgical procedure), after extubation (when the patient entered the PACU), and end of PACU (when the patient was fit for discharge to the ward). In addition to analysis of serum cortisol and plasma adrenocorticotropic hormone (ACTH) concentrations in ethylenediamine tetra-acetic acid (EDTA) samples, the investigators measured total plasma protein to account for blood loss and haemodilutional effects. The EDTA blood samples were cooled in ice water immediately after collection before transport to the central laboratory. The staff analysed serum cortisol levels (cobas e 411 analyzer; Roche Germany, Mannheim, Germany) and plasma ACTH levels (IMMULITE® 2000XPi system; Siemens Healthineers Germany, Marburg, Germany) according to the manufacturers' recommendations.

Measurements and data handling

The cumulative remifentanil consumption was documented during surgery by a study assistant, who was not involved in the patient's treatment. In this prospective study, the staff in the PACU, the outcome assessors, and the patients were blinded to group assignment. In the PACU, all patients were treated by a standardised protocol. During surgery, the study setting precluded blinding of the attending anaesthesiologist. Nevertheless, although the anaesthesiologists in the operation theatre were not part of the study team, they were instructed to strictly follow the study protocol whenever the patients had been randomised to one of the three nociception-monitor-guided groups. During the PACU stay, the blinded staff assessed the data on postoperative pain and consumption of analgesics, nausea and vomiting, shivering, or other anaesthesia-related events. On the second postoperative day, the patients completed quality of recovery and persistence of pain questionnaires blinded to group assignment.[21] Furthermore, the patients received an envelope with a questionnaire to evaluate prolonged persistence of pain and overall satisfaction with anaesthetic care upon discharge from the hospital. The patients voluntarily sent this questionnaire back by mail on postoperative Day 21.

Primary and secondary endpoints

The primary endpoint was the intraoperative amount of remifentanil administered. The secondary endpoints were the time from the stop of remifentanil and propofol infusion to extubation; duration of time in the PACU until fit for discharge; postoperative pain (numeric rating scale) in the PACU; total amount of morphine equivalents administered in the PACU; perioperative plasma ACTH and serum cortisol concentrations; pain on the second postoperative day; and patient satisfaction with general anaesthesia and pain management evaluated on postoperative Day 21.

Sample size calculation

For the sample size calculation, the investigators collected pre-test data because there were no published data on remifentanil consumption during open prostatectomy. The pre-test data revealed a mean remifentanil dose of 0.21 (standard deviation [SD] 0.02) μg kg^{-1} min^{-1} in the control group, and 0.23, 0.17, and 0.20 μg kg^{-1} min^{-1} in the SPI, PPI, and NOL intervention groups, respectively. As calculated from these data, using a two-sided two-sample *t*-test, adjusting alpha for six pairwise group comparisons, and assuming a normal data distribution, it was estimated that group sample sizes of 22 patients would achieve 80% power to detect a difference of 0.02 μg kg^{-1} min^{-1} between groups with a significance level of 0.00830 (0.05/6); this estimate was computed by the software package PASS 2008 version 08.0.6 (NCSS LLC, Kaysville, UT, USA). The investigators scheduled 24 subjects/group to account for a dropout rate of approximately 10%.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics Inc., Armonk, NY, USA). Data for population descriptions are shown as the mean (SD) and counts (%). The predefined primary and secondary endpoints were evaluated by general linear models (analysis of variance [ANOVA]) and *post hoc* pairwise contrasts for intergroup comparison as planned *a priori*. Perioperative data were analysed using ANOVA or Kruskal–Wallis tests for continuous outcome variables as appropriate, and using binary logistic regression analysis for dichotomous outcome variables. For group comparisons regarding binary outcome variables, logistic regression models were used to estimate odds ratios with 95% confidence limits for subjects with intraoperative movements and marginal frequencies with 95% confidence interval for the occurrence of remifentanil discontinuation. The progression of ACTH and cortisol concentrations during the day of surgery was evaluated using a linear mixed model (SPSS routine GENLINMIXED) with random intercepts for patients, assuming a variance component covariance structure. The fixed effects were the study group, time point (treated as a categorical variable), time slot (surgery in the morning *vs* at noon, to account for circadian rhythm), and the interaction between the study group and time point. The authors adjusted for current total plasma protein concentrations at the different time points to account for eventual hormone dilution effects caused by blood loss and fluid therapy.

Areas under the curve (AUC) were calculated for ACTH plasma and cortisol serum concentrations over time (after natural logarithm [ln] transformation, because they were right

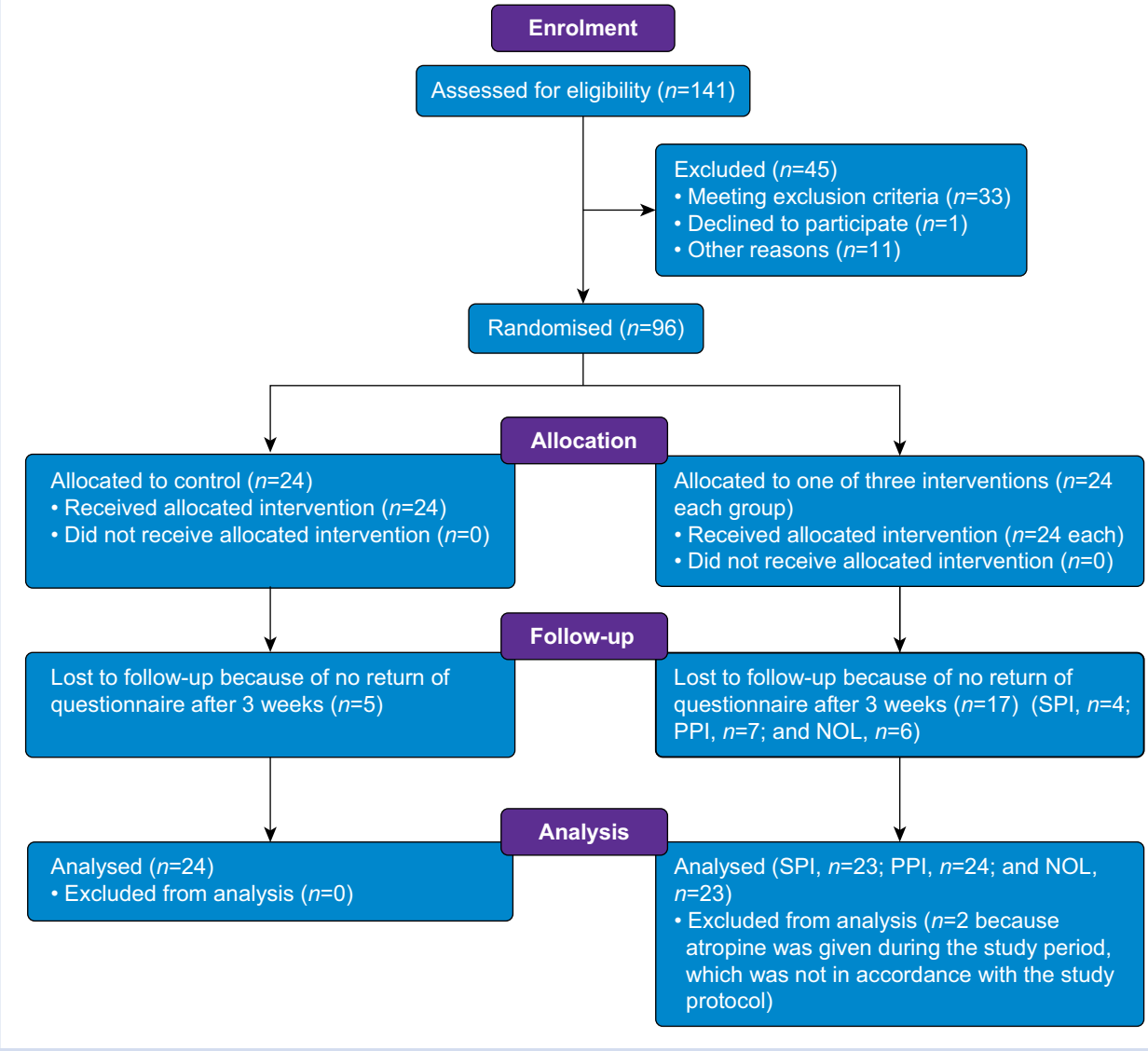

Fig 1. Consolidated Standards of Reporting Trials diagram (study flow chart). NOL, nociception level; PPI, pupillary pain index; SPI, surgical pleth index.

skewed), and analysed by general linear models with study group and onset of surgery (as time slot) as fixed effects and adjusting for $\log_2$-transformed plasma protein levels. Their estimated marginal group means with their 95% confidence limits were back-transformed and presented.

All tests were two tailed with alpha set to 0.05. The significance level for group comparisons of the primary endpoint was Bonferroni adjusted, whereas the significance level for the AUC of ACTH and cortisol levels was sequentially Šidák adjusted to account for the six pairwise group comparisons. All other secondary outcome variables were analysed in an explorative manner.

Results

Ninety-six subjects were enrolled between December 2017 and April 2018. All patients underwent open radical retropubic prostatectomy and were thus males. After obtaining written informed consent, subjects were randomised to one of the four study groups. Figure 1 displays the Consolidated Standards of Reporting Trials flow diagram, including the details of assessment and exclusion. The subjects were Caucasian men at a mean age of 63 (8) yr mean (SD), all American Society of Anesthesiologists (ASA) physical status 2–3, and had a BMI of 26.9 (2.3) kg m^{-2} mean (SD). Table 1 shows the baseline characteristics in more detail.

The primary endpoint investigated remifentanil consumption adjusted for body weight and duration of surgery. Table 2 and Figure 2 show that remifentanil consumption was different in the study groups, with higher infusion rates in the SPI and control groups, and lower rates in the NOL and PPI groups. The results of sensitivity analyses with ln-transformed data and adjustment for variance inhomogeneity amongst groups showed comparable results.

Table 1 Baseline characteristics of the four treatment groups: control (Ctrl), surgical pleth index (SPI), pupillary pain index (PPI), and nociception level (NOL). Values are displayed as the means (standard deviation) and counts (%). According to the study protocol, patients with chronic pain taking any long-term pain medication (opioids and non-opioids) were excluded from the study. *Cardiovascular: antihypertensive (angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, and angiotensin II Type 1-receptor antagonists) and anti-arrhythmic medication, except beta-blocker therapy (exclusion criterion). NRS, numeric rating scale.

Biometric data	Ctrl (n=24)	SPI (n=23)	PPI (n=24)	NOL (n=23)
Age (yr)	63 (10)	62 (7)	63 (6)	63 (7)
Height (cm)	179 (9)	177 (4)	179 (7)	181 (4)
Weight (kg)	84 (12)	83 (11)	88 (13)	88 (13)
BMI (kg cm^{-2})	26.3 (2.7)	26.7 (3.5)	27.4 (2.8)	27.0 (4.0)
ASA physical status, n (%)				
2	21 (87.5)	20 (87)	21 (87.5)	19 (82.6)
3	3 (12.5)	3 (13)	3 (12.5)	4 (17.4)
Medication, n (%)				
Metabolic	4 (17.4)	4 (17.4)	8 (33.3)	4 (17.4)
Anticoagulants	3 (12.5)	1 (4.3)	3 (12.5)	4 (17.4)
Cardiovascular*	9 (37.5)	5 (21.7)	11 (45.8)	8 (34.8)
Others	14 (58.3)	11 (47.8)	13 (54.2)	15 (65.2)
None	9 (37.5)	9 (39.1)	6 (25)	5 (21.7)
NRS=0 before surgery, n (%)	22 (91.7)	18 (78.3)	23 (95.8)	22 (95.7)

Thus, we report the results of the unadjusted data as planned *a priori*.

There was no evidence found for differences between the four study groups regarding the prospectively defined secondary endpoints, except for the perioperative time course of the stress hormones cortisol and ACTH (Table 2).

The AUC analysis indicated differences in cumulative cortisol levels and cumulative plasma ACTH levels adjusted for plasma protein levels amongst the groups. Pairwise group comparisons of cortisol levels showed differences between all groups and the influence of a morning surgery time slot or a noon surgery time slot on the AUC of cortisol and ACTH are reported in Table 2. Figure 3a shows that, in addition to the total amount of serum cortisol differing between the study groups, evolution over time also varied. Figure 3b displays the association between the individual remifentanil dose during surgery (μg kg^{-1} min^{-1}) and the serum cortisol level at the end of surgery (μg L^{-1}).

Table 3 shows further perioperative parameters. Differences between groups were observed regarding the subjects with an intraoperative discontinuation of remifentanil that occurred frequently in the PPI and NOL groups, but in only one patient in the SPI group and in no patient in the control group. There was a tendency towards a higher incidence of intraoperative movement in the PPI and NOL groups, but no evidence for differences regarding the haemodynamic parameters, recovery in the PACU, or in the short-term and long-term follow up.

Discussion

The results of the present study showed that the total amount of infused remifentanil varied depending on the nociception monitoring device used for nociception-monitor-guided opioid administration. Compared with the control group, the patients in the SPI group received more remifentanil, whereas the patients in the NOL group received less remifentanil and those in the PPI group received the least amount of remifentanil. The reduction of opioids in the PPI and NOL groups compared with the control group was associated with an increased release of stress hormones during surgery, whereas in the control and SPI groups, the stress hormone concentration decreased from the preoperative baseline level during surgery. There were more subjects in the PPI and NOL groups with an intraoperative discontinuation of remifentanil than in the SPI and control groups, and unintended intraoperative movements occurred with a clinically relevant higher probability in subjects in those groups with lower remifentanil amounts. In addition, less opioid infusion was accompanied by increased intraoperative amounts of hypnotics and muscle relaxants. There was no evidence for a difference found during the recovery in the PACU in the first two postoperative days or in the follow up after 21 days.

Several previous studies compared the effect of opioid titration with one of the three nociception monitoring systems with a control group that was guided by clinical signs only. On the one hand, some studies showed a reduction in intraoperative opioid use, lower postoperative opioid consumption or pain scores, and more intraoperative haemodynamic stability in the groups with a nociception-monitor-guided opioid administration.[10,11,14,16,20,22] On the other hand, other studies revealed equal or even increased opioid demand, and could not find differences in postoperative recovery between a nociception-monitor-guided opioid administration and the control group.[12,13,23,24] These previous studies were summarised in recent meta-analyses.[1–3] Thus, current data are inconclusive regarding the effect of nociception monitoring on intraoperative opioid consumption and outcome parameters. One of the main problems comparing these different studies is that there is no ‘standard care’ for the control group. Opioid titration in the control group is an individual decision of the attending anaesthesiologist based on clinical parameters. In addition, one may assume that baseline administration rates of opioids are also influenced by local standards of opioid dosing. Furthermore, studies were inhomogeneous regarding the surgical procedure, analgesic and hypnotic drugs, and patient age and sex. This might have explained the controversial results of the previous studies. The present randomised clinical trial showed that the choice of different nociception indices in one standardised surgical setting still

Table 2 Primary and secondary endpoints of the four study groups. Values are displayed as estimated marginal means (95% confidence interval [CI]) with *P*-values of group effects (*F*-test) or median [quartiles] with *P*-values for group comparison (Kruskal–Wallis test). Numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain). *n=22 in the SPI group. Pairwise group comparisons of cortisol AUC: control *vs* PPI 0.53-fold [0.41; 0.68], *P*<0.001; control *vs* NOL 0.7-fold [0.55; 0.88], *P*=0.001; PPI *vs* SPI 1.87-fold [1.45; 2.40], *P*<0.001; NOL *vs* SPI 1.41-fold [1.12; 1.78], *P*=0.002; and NOL *vs* PPI 0.75-fold [0.61; 0.94], *P*=0.009); no difference found for SPI *vs* control (0.98-fold [0.81; 1.18], *P*=0.830); all data: back-transformed (ex) marginal mean differences [95% CI], *P*-value). For ACTH, pairwise group comparisons of the AUC showed differences between some of the groups (control *vs* PPI 0.53-fold [0.29; 0.95], *P*=0.028; control *vs* NOL 0.54-fold [0.30; 0.95], *P*=0.028; PPI *vs* SPI 2.89-fold [1.52; 5.48], *P*<0.001; NOL *vs* SPI 2.83-fold [1.51; 5.28], *P*<0.001), but not for control *vs* SPI (1.52-fold [0.89; 2.59] *P*=0.150) or NOL *vs* PPI (0.98-fold [0.61; 1.59], *P*=0.934; all data: back-transformed (ex) marginal mean differences [95% CI], *P*-value). The time slot for the onset of surgery had an influence on the AUC levels of cortisol (μg L^{-1} min^{-1}; mean [95% CI]: at noon 45.5 [41.4; 49.9] *vs* in the morning 52.6 [48.0; 57.7], 0.86-fold [0.76; 0.99], *P*=0.030) and ACTH (ng L^{-1} min^{-1}; mean [95% CI]: at noon 28.5 [22.6; 36.0] *vs* in the morning 19.2 [15.2; 24.1], 1.49-fold [1.07; 2.07], *P*=0.018). †n=19 in the control group, n=19 in the SPI group, n=17 in the PPI group, and n=17 in the NOL group. ‡Rated on the 21st postoperative day on a scale from 1 ('full satisfaction') to 6 ('no satisfaction'). ACTH, adrenocorticotropic hormone; AUC, area under the curve; Ctrl, control group; NOL, nociception level; PPI, pupillary pain index; SPI, surgical pleth index.

	Ctrl (n=24)	SPI (n=23)	PPI (n=24)	NOL (n=23)	*P*-value
Primary endpoint					
Remifentanil consumption (μg kg^{-1} min^{-1})	0.349 (0.297; 0.401)	0.501 (0.448; 0.554)	0.072 (0.020; 0.124)	0.189 (0.136; 0.242)	<0.001
Secondary endpoints					
Time from end of narcotics to extubation (min)	13 (11; 15)	14 (12; 16)	12 (9; 14)	11 (9; 13)	0.352
Duration of time in PACU until fit for discharge (min)	138 (121; 154)	132 (115; 149)	147 (130; 163)	127 (110; 144)	0.389
Maximum NRS in PACU	5.5 (4.8; 6.1)	5.8 (5.1; 6.4)	5.5 (4.9; 6.2)	5.5 (4.9; 6.2)	0.896
Total amount of morphine equivalents in the PACU (mg)	9.8 (7.7; 11.9)	10.5 (8.4; 12.6)	8.4 (6.3; 10.5)	9.8 (7.7; 11.9)	0.570
AUC of cumulative serum cortisol levels (μg L^{-1} min^{-1})*	37.9 (33.3; 43.1)	38.6 (33.8; 44.2)	72.1 (63.1; 82.3)	54.3 (47.6; 62.1)	<0.001
AUC of cumulative plasma ACTH levels (μg L^{-1} min^{-1})*	18.9 (13.7; 26.1)	12.5 (89.0; 17.4)	35.9 (25.9; 50.1)	35.2 (25.2; 49.2)	<0.001
NRS on postoperative Day 2 at rest†	0.7 (0.2; 1.3)	1.7 (1.1; 2.3)	0.9 (0.3; 1.5)	0.6 (0; 1.2)	0.056
NRS on postoperative Day 2 during movement†	3.9 (3.1; 4.7)	4.6 (3.8; 5.5)	4.0 (3.0; 4.7)	4.4 (3.6; 5.2)	0.520
Quality of recovery score on postoperative Day 2†	14.9 (14.3; 15.5)	14.5 (13.6; 15.3)	15 (14.4; 15.6)	14.7 (14.2; 15.2)	0.696
Long-term follow up					
Persistence of pain on postoperative Day 21, *n* (%)	12 (63.2)	15 (78.9)	10 (58.8)	9 (52.9)	0.420
NRS on postoperative Day 21	1 [0–3]	2 [1–3]	1 [0–3]	1 [0–2]	0.344
Satisfaction with anaesthetic management after 21 days‡	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–1]	0.381

led to different amounts of opioid administration. Thus, the indices displayed surgical stress and nociceptive events in comparable standardised operations differently. This is in contrast with the results from the well-validated monitoring systems on the depth of hypnosis, because the assessment of the depth of hypnosis does not greatly differ between the various electroencephalographic monitoring systems.[25]

The type of nociception monitoring affected the total amount of cumulative stress hormone release during and initially after surgery. The SPI and control groups were associated with a decrease in serum cortisol concentration during surgery, whereas in the PPI and NOL groups, serum cortisol concentration increased. The association between the remifentanil dose during surgery and the serum cortisol level at the end of surgery shows an increase in the cortisol concentration if the average dose of remifentanil was below 0.2 μg kg^{-1} min^{-1}. These findings suggest that approximately 0.2 μg kg^{-1} min^{-1} might be a threshold for the average dose of remifentanil below, which the cortisol release increases as a surrogate of an unintended intraoperative stress response. Yet, nociception during general anaesthesia is a multidimensional continuum. Even supra-clinical doses of opioids do not suppress nociception in total in fMRI.[26]

The aim of validation of nociception monitoring devices has been the detection of nociceptive stimuli so far. However, because there is no 'gold standard' for validation of nociception monitoring devices, the aim should rather be the guidance of opioid doses to a level of nociception that is low enough for an optimal clinical outcome with minimal opioid side-effects. The fact that some devices cause less opioid consumption whereas others do not, and the association with the stress hormones and unwanted intraoperative movement suggest that using a specific nociception device can even be counterproductive in reducing stress hormones. The use of PPI with an index of 2–3 yields reduced opioid consumption, higher stress hormone levels, and a tendency towards a higher occurrence of unwanted intraoperative movement. The present results suggest that guidance of opioids by some of these monitors with the current threshold values may even worsen the intraoperative well-being. Thus, these monitors are not yet optimised for use in the clinical routine, although commercially available, and their clinical benefit still has to be proved.

Limitations

The study has some limitations. (1) This study focused only on radical retropubic prostatectomy for better comparability of the results. Therefore, only male patients were included. (2) Threshold values for upper and lower index values of the nociception monitoring devices were used as currently recommended.[1–4] These values were recommended by the manufacturers, and some have already been used in other

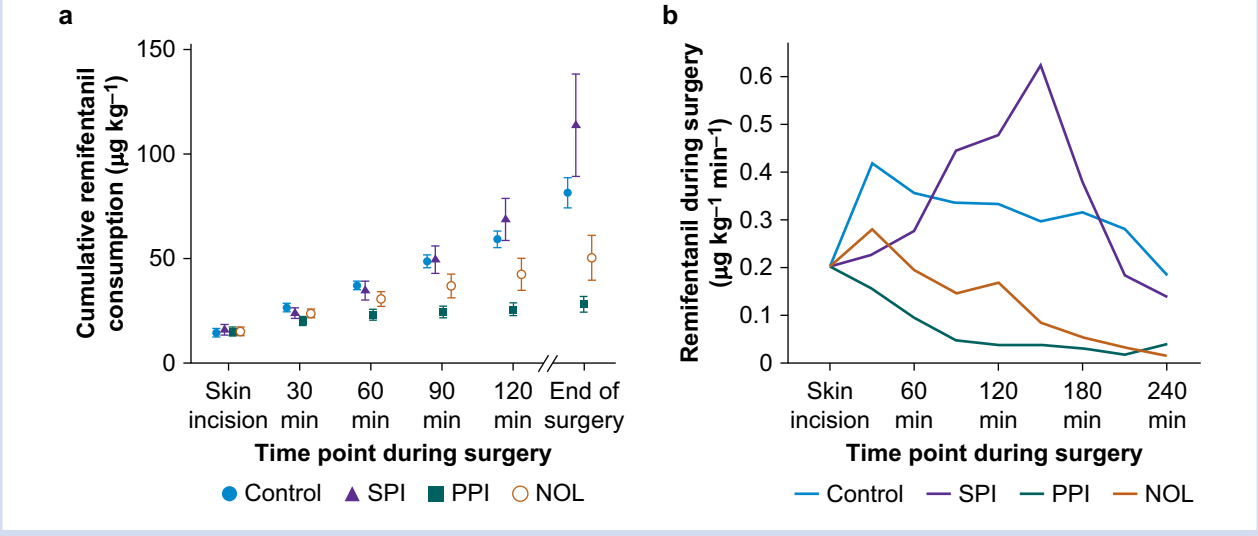

Fig 2. Intraoperative remifentanil consumption. (a) Increase in cumulative remifentanil administration (μg kg^{-1}) over time during the first 2 h of anaesthesia and at the end of surgery. Pairwise group comparisons of cumulative remifentanil consumption adjusted to body weight and the duration of surgery for the induction and maintenance of anaesthesia: control *vs* NOL, $P<0.001$; control *vs* PPI, $P<0.001$; control *vs* SPI, $P=0.001$; NOL *vs* PPI, $P=0.015$; NOL *vs* SPI, $P<0.001$; and PPI *vs* SPI, $P<0.001$ (P-values were Bonferroni adjusted to account for six pairwise group comparisons). (b) Median remifentanil administration per kilogram body weight and minute during the operation. All subjects had baseline infusion rate of 0.2 μg kg^{-1} min^{-1} between anaesthesia induction and skin incision. During surgery, remifentanil rate was guided according to the study protocol. Further data distribution with median and inter-quartile ranges (25th–75th percentile) can be found in Supplementary Table S1. NOL, nociception level; PPI, pupillary pain index; SPI, surgical pleth index.

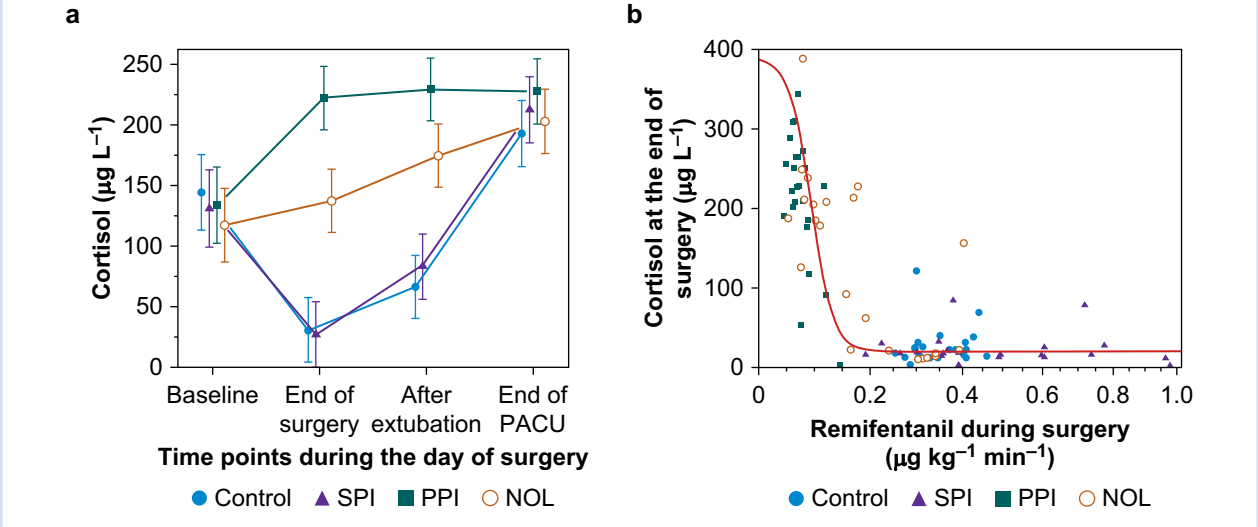

Fig 3. Release of cortisol in the study groups. (a) Serum levels of cortisol at four different time points during the day of surgery ('baseline' before induction of general anaesthesia, 'end of surgery' at skin closure, 'after extubation' on arrival at the PACU, and 'end of PACU' before discharge to the ward). Data are mixed-model-estimated marginal means, and error bars are 95% confidence interval adjusted for plasma protein=64 g L^{-1}. (b) Scatter plots of serum levels of cortisol at the end of surgery *vs* the total remifentanil consumption during surgery analysed by study groups. The reference line represents the pharmacodynamic relationship between serum cortisol levels at the end of surgery and the mean remifentanil dose during surgery. NOL, nociception level; PPI, pupillary pain index; SPI, surgical pleth index.

Table 3 Perioperative data of the four study groups. Values are displayed as the estimated marginal means (95% confidence interval [CI]) (*P*-values for group effect from analysis of variance testing), median [quartiles] (*P*-values for group comparison by Kruskal–Wallis test), or *n* (%) (*P*-values for group effect by logistic regression analysis). Total mivacurium and propofol doses were adjusted to individual body weight and the duration of surgery. Numeric rating scale (NRS 0–10) from 0 (no pain) to 10 (worst pain). Quality of recovery score: nine questions with 0–2 points each. *The estimated marginal frequencies for an intraoperative stop of remifentanil with *P*-values for pairwise comparison with the control group (0%) were SPI 4% (95% CI [1%; 25%], *P*=0.307); PPI 75% (95% CI [54%; 88%], *P*<0.001); and NOL 48% (95% CI [29%; 68%], *P*<0.001). †The odds ratios for patients having at least one event of unintended intraoperative movement compared with the control group (with one patient with intraoperative movement) were SPI 2.2 (95% CI [0.2%; 26.0%], *P*=0.534), PPI 11.5 (95% CI [1.3; 101.2], *P*=0.028), and NOL 4.8 (95% CI [0.50; 47.1], *P*=0.174). Ctrl, control group; NOL, nociception level; PONV, postoperative nausea and vomiting; PPI, pupillary pain index; SPI, surgical pleth index.

	Ctrl (*n*=24)	SPI (*n*=23)	PPI (*n*=24)	NOL (*n*=23)	*P*-value
Intraoperative data					
Duration of surgery (min)	193 (173; 213)	183 (168; 198)	184 (169; 198)	181 (165; 198)	0.777
Intraoperative blood loss (ml)	675 [425–875]	600 [300–700]	775 [500–975]	600 [500–800]	0.516
Norepinephrine infusion (μg kg^{-1} min^{-1})	0.080 [0.050 –0.123]	0.09 [0.06 –0.11]	0.070 [0.040 –0.080]	0.070 [0.050 –0.098]	0.323
Patients with intraoperative stop of remifentanil, *n* (%)*	0 (0)	1 (4.3)	18 (75.0)	11 (47.8)	0.002
Patients with occurrence of intraoperative movement, *n* (%)†	1 (4.2)	2 (8.7)	8 (33.3)	4 (17.4)	0.063
Adjusted total dose of mivacurium (μg kg^{-1} min^{-1})	5.2 (4.6; 5.8)	5.6 (4.9; 6.4)	7.7 (7.0; 8.4)	7.0 (6.4; 7.8)	<0.001
Adjusted total dose of propofol (mg kg^{-1} h^{-1})	4.3 (4.0; 4.5)	4.6 (4.3; 5.0)	5.1 (4.7; 5.5)	4.9 (4.5; 5.2)	0.001
Postoperative data					
HR at arrival to the PACU (beats min^{-1})	69 (64; 74)	69 (64; 74)	74 (67; 80)	69 (64; 74)	0.566
NRS at arrival to the PACU	1 [0–6]	4 [0–5]	4 [0–5]	2 [0–5]	0.672
Number of applications of analgesics	3.7 (2.9; 4.5)	3.2 (3.1; 4.9)	3.2 (2.5; 4.0)	3.7 (2.9; 4.5)	0.565
Occurrence of PONV (yes/no), *n* (%)	5 (20.8)	1 (4.3)	3 (12.5)	1 (4.3)	0.264
Occurrence of shivering (yes/no), *n* (%)	2 (8.3)	4 (17.4)	2 (8.3)	1 (4.3)	0.527

clinical studies.[11–14,20] Nevertheless, there is a lack of studies that have specifically validated these thresholds, and thus, these values might be adapted in the future. The PPI target range was based on the manufacturer's recommendations, and results could have been different when using the changes in pupil size over time without the underlying algorithm of the device. (3) Next, the study size was calculated for the primary endpoint, and the secondary endpoints were additionally prospectively defined. Nevertheless, we analysed perioperative and postoperative data, and investigated differences between the study groups that were not prospectively defined secondary endpoints. (4) Furthermore, long-term follow up is multifactorial. Larger study populations are needed to differentiate between the effects from intraoperative opioid titration and surgical factors and the individual risk factors for postoperative pain and recovery in each patient.

Conclusion

Each nociception monitoring device and the anaesthesiologists in the control group interpreted the extent of nociception differently, and nociception-monitor-guided opioid administration led to different doses of remifentanil. Very low remifentanil doses were associated with a significant increase in ACTH and cortisol concentrations, whereas higher remifentanil doses were accompanied by a decrease in ACTH and cortisol concentrations during surgery. Thus, the devices do not seem to be sufficiently validated yet, and the best opioid strategy remains unclear.

Authors' contributions

Study design: SF, HOP, RN
Study conduct: SF, CB, SW, BB, MF, RN
Data collection: SF, CB, SW, BB, MF, RN
Data analysis: SF, HOP, CB, RN
Writing of paper: SF, RN
Critical revision/approval of paper: all authors

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Declarations of interest

The authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.09.051.

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