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Master thesis | Original study

Pupillometry pain index during day care anesthesia using remifentanil: comparison of perioperative analgesic consumption in a double blind RCT

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Abstract

Background: **Communication is impossible in sedated patients. Nowadays there is no single best technology to measure nociception during anesthesia.**
Objectives: **The primary outcome parameter was the postoperative pain intensity queried as pain intensity by numeric rating scale and the amount of pain killer usage. Our hypothesis was that patients with a good titrated remifentanil administration peroperative should have less pain and less need of pain medication. Secondary outcome parameters were the characteristics of the pupillometry introducing a pupillometry pain index chart to individual titrate remifentanil dosage. Tertiary outcome parameters were nausea and vomiting, length of stay at the post anesthesia care unit and health state index.**
Design and setting: **In a single center double blind randomized controlled trial we evaluated if pupillometry controlled use of remifentanil is better than free choice administration of remifentanil by anesthesiologists. Fifty-five patients undergoing elective day care surgery were enrolled. A pupillometry pain index score chart was introduced for remifentanil administration guidance.**
Methods: **After induction, a first pupillary reflex dilation (PRD) measurement was performed using pupillometry. A second identical evaluation was performed six minutes after remifentanil administration and adapted every 10 minutes. Remifentanil dosage was adjusted following the pupillometry pain index score (intervention group) or by the discretion of the anesthesiologist (control group).**
Results: **No statistically significant difference was found in pain intensity and pain killer usage at postoperative day one. The pupillometry pain index chart was usable. Although both groups received 0.21 mcg kg-1 min-1 remifentanil. No Statistically significant difference in opioïd induced side effects, nor health state index was seen.**
Conclusion: **This study showed no additional value for PRD assessment in response to remifentanil administration during daycare procedures with our protocol to titrate remifentanil. A pupillometry pain index score chart could be implemented. Further research to lower the remifentanil administration within this protocol is needed. (Ethics Committee EC17/28/319 of the University Hospital of Antwerp. Registration at clinicaltrials.gov NCT03248908.)**

Keywords: **Pupillometry, Pain index, Anesthesia, Remifentanil, Analgesia.**

Introduction

Pain assessment in non-communicative patients is still challenging despite many novel innovative technologies. Communication under general anesthesia is impossible due to unconsciousness. Adequate measurement of nociception may allow the anesthesiologist to individual titration of analgesics (mostly opioids), avoiding over- or underdosage. More and more anesthesiologists attempt to minimize the dose of opioids used, consequently reducing the well-known side effects. Correct nociceptive assessment and therefore individually based treatment, may be an ideal scenario. Although current research addressing this complex issue provides some promising innovative techniques, no standard objective pain monitoring protocol exists[1,2].

Nowadays there are seven devices for measuring peroperative pain. Ledowski made a review of the

current commercial solutions in 2019[3]. The seven devices use one to four parameters. Our study uses pupillometry, a one parameter device. The conclusion of Ledowski is that the optimum solution for monitoring nociception is not yet known[3].

Pupillary dilation is predominantly driven by the sympathetic nervous system, as the pupillary dilators receive sympathetic innervation.4 The Edinger-Westphal neurons have a resting tone and continuously activate the parasympathetic pupil constrictors. On the other hand there is a sympathetic mediated active dilation. Pain increases the sympathetic activity and gives a central inhibition of the Edinger-Westphal neurons[4].

Infrared pupillometry exists for decades[5]. A light-emitting diode infrared light is directed toward the eye, a sensor detects the reflected infrared light from the iris. The pupil is a blank circle in the center of the reflected image, a computer readily calculates the area and the diameter of the pupil[5]. Although nowadays there are only a few studies about portable video pupillometry in anesthetized patients[3-5]. However, if we want to evaluate the pupil response during noxious procedures (skin incision, pneumoperitoneum, etc.), monitoring of pupillary reflex dilation (PRD) elicited by standardized nociceptive stimulations in anesthetized patients needs to be further examined[3-5].

Barvais et al published, to our knowledge, the first study about pupillometry and remifentanil[6]. The hypothesis was that a different remifentanil administration should be measurable. At twelve patients anesthetized with continuous propofol, he found no significant difference with bisprectral index monitoring when the remifentanil concentration was between 1 and 5 ng/ml. On the other hand, a significant difference was found with pupillometry between 2 and 5 ng/ml remifentanil[6].

Up to now, little study is published about using pupillometry to titrate remifentanil dosage. Sabourdin et al illustrated a significant decrease of remifentanil dosage in the pupillometry group (3.8 vs 7.9 mcg kg-1 min-1, $p < 0.001$)[7]. Depending on a 5 to 30% increase of pupil diameter during surgery in comparison before incision, the remifentanil dosage changed or remained the same[7]. Therewith, the postoperative morphine consumption and pain after 3 months was also significant decreased[7]. Kim et al showed a non-significant dose reduction in the pupillometry pain index (PPI) group versus control group (0.079 vs 0.108 mcg kg^{-1} min^{-1} $p = 0.115$)[8]. The method of changing remifentanil was the same as Sabourdin, the starting dose of remifentanil was 1.5 ng/ml. Furthermore, Choi et al did a study with children in which there was a significant remifentanil reduction of 25% (0.117 mcg kg^{-1} min^{-1} vs 0.156 mcg kg^{-1} min^{-1} $p = 0.02$), also at the same manner as Sabourdin[9]. Torrent et al did also a study with pupillometry and remifentanil.10 When at 40 mA the pupil dilation was < 6%, the remifentanil dosage was lowered. He had a 1 point reduction of numeric rating scale (NRS) at 3, 6 and 9h post-operative.10 IV morphine consumption at PACU showed a mean dose of 3.7 mg in the pupillometry group versus 6 mg ($p < 0.001$) in the control group[10].

Unfortunately, all of the above mentioned studies use only the pupil diameter during study and ignore the possibility of increasing stimulation. We believe there is a need for consensus to use and interpret different pupil assessment features as light-induced PRD, nociceptive stimulation induced PRD, constriction velocity, reaction latency or PPI score. Neither the reviews of Ledowski, Packiasabapathy or Larson gave more information about the mentioned features during surgery[3-5]. We used the PPI score (see Table I) IdMed, fabricant of AlgiScan©, delivered upon purchase. This PPI score is not validated.

We anticipated that a PRD evaluation, and in addition PPI score, by increasing tetanic stimulation may be related to analgesic treatment in anesthetized patients. The primary outcome

Table I. — Pupillometry Pain Index score.

Maximum Intensity (mA)	PPI score	Stop stimulation
10	9	Dilatation ≥ 13% stimulating 10 mA
20	8	Dilatation ≥ 13% stimulating 20 mA
30	7	Dilatation ≥ 13% stimulating 30 mA
40	6	Dilatation ≥ 13% stimulating 40 mA
50	5	Dilatation ≥ 13% stimulating 50 mA
60	4	Dilatation ≥ 13% during 1st stimulation 60 mA
60	3	Dilatation ≥ 13% during 2nd stimulation 60 mA
60 (5% < pupil dilatation < 13%)	2	Dilatation ≥ 13% during 3rd stimulation 60 mA
60 (pupil dilatation ≤ 5%)	1	4th stimulation 60 mA
PPI: Pupillometry Pain Index. Note: when pupil dilatation was more than 20% than the resulting score was PPI score + 1.		

parameter was the postoperative pain intensity queried as pain intensity by NRS and the amount of pain killer usage. Our hypothesis was that patients with a good titrated remifentanil administration peroperative should have less pain and less need of pain medication. Secondary outcome parameters were PRD characteristics such as stimulation intensity (Int), baseline pupil diameter, pupil reflex dilation amplitude (PRDA) and PPI score. Total opioid usage during surgery and recovery time were registered. Tertiary, nausea and vomiting, length of stay at the post anesthesia care unit (PACU) and health state index using the EQ5D5L questionnaire.

Materials and methods

Study design and data collection

This was a single center double blind randomized controlled trial at the University Hospital of Antwerp, Belgium. Only day care patients were included. The study was performed in accordance with the ethical standards of ICG-GCP and the Declaration of Helsinki after study approval by the institutional review board and the Ethics Committee (EC17/28/319) of the University Hospital of Antwerp by Dr. G. Ieven at 31/07/2017. Registration at clinicaltrials.gov (NCT03248908) was executed before study inclusion.

The first pilot study was done beforehand with 38 patients (24-74 years) enrolled. Patients were anesthetized with propofol continuous target controlled infusion[11]. One measurement was done before opioid administration, a second measurement after opioid administration. After opioid administration patients needed a higher stimulation intensity (45.26 mA vs 30.79 mA, $p = 0.00001$) to have a pupil dilation of > 13%. Power analysis showed a need of N = 28 to measure a stimulation intensity difference between T0 and T1 measurement of 10 mA (α: 0.05, power 0.9)[11]. The power for a difference of PPI score, to detect a difference of 2 points, was N = 16 (α: 0.05, power 0.9). With N = 28 of each group was estimated to receive statistic significant results. The second pilot study with 34 patients enrolled tested the PPI score. After induction with continuous propofol, administration of remifentanil 5.0 ng/ml started. A PPI score reduction from 8 to 2 ($p < 0.0005$) was noted[12]. An enrollment of 60 patients was carried out to have a margin for dropout. We did not do any interim analyses. There were no stopping guidelines.

We used CE-approved NeuroLight Algiscan® (IDMed, Marseille, France) pupillometer using infrared video recording allowing quantitative pupil size assessment. The subjects underwent consecutive pupil measurements under general anesthesia.

For nociceptive stimulation, two Ag-AgCl electrodes were placed at the skin area innervated by the median nerve. Optimal skin contact with low electrode impedance was defined on the touchscreen display. Constant current stimulations were generated during pupil measurement, increasing automatically the voltage according to the resistance. Voltage is limited to a maximum of 300 V. Therefore, at a current fixed at 60 mA, the maximum acceptable resistance is 5 kOhm.

The upper eyelid of the measured eye was opened during pupil assessment. A rubber cup placed to the orbit ensured optimal device position, pupil-camera distance and environmental darkness. There was never direct contact with the cornea. By convention the left eye was assessed after confirmation of pupil syndrome disorder absence. The contralateral eye was closed, reducing the effect of the consensual light response. The PPI-modus was selected for dynamic pupil measurement via the touch screen display. This inbuilt measurement protocol generated an automatic electric stimulation pattern. Operating principle is the application of a standardized noxious stimulation (from 10 mA to 60 mA by incremental steps of 10 mA, with a duration of 1s, and pulse width of 200 μs) in increasing intensity, until pupillary dilation of more than 13% ([maximal diameter – minimal diameter] / maximal diameter x 100). When the defined criteria was reached stimulation automatically stopped and PPI score was determined (table 1). When the pupil variation (VAR) was >20%, a +1 was added to the score. The measurable pupil size (diameter) ranged between 0.1 and 10 mm. Furthermore, baseline (as minimum diameter per measurement), PRD, VAR, Int and PPI score were recorded each measurement. Depending on necessary stimulation intensity, pupil measurement duration is between 2 and 16 seconds.

After written consent, patients planned for elective abdominal or gynecological day care surgery were recruited for study inclusion from October 2017 until August 2021. Inclusion criteria were elective abdominal of gynecological surgery, no locoregional anesthetics, age > 18 years and ASA I, II or III. Exclusion criteria were medical history of eye surgery, known bilateral eye disease, known nervus opticus or nervus oculomotorius deficit, active pheochromocytoma, active psychiatric disease, opioid usage > 7 days preoperative and active oncologic treatment with chemotherapy. Also use of medication that

interfere with the pupillary measurements such as use of high dose α-1 or β-blocker (no intake on the day of surgery), use of benzodiazepines on the day of surgery, topical use of atropine or phenylephrine, use of scopolamine or dopamine antagonists were excluded. During anesthesia it was forbidden to give dehydrobenzperidol (DHBP), alizapride, fentanyl and atropine as examined in two studies beforehand[13,14]. Because of the high risk of postoperative nausea or vomiting of some patients, we tolerated the administration of DHBP or alizapride after the last PPI measurement.

Enrolled subjects were randomized into two groups. Group 1 is the remifentanil flowchart group, group 2 is the remifentanil control group. It was a double blind randomized controlled trial, so by the site www.randomization.com a randomization was made. Permuted block randomization was used.

Before induction were demographic data collected. Length and weight were registered. Ideal body (IBW) weight was calculated by length (cm) – 100 for men / 105 for women. If actual body weight was lower dan IBW, then actual body weight was used. When actual body weight was higher than IBW, then corrected body weight (CBW) was used. CBW was calculated by IBW + 0.4 x (weight – IBW). Further ASA-classification, SpO_2 before administration of oxygen, blood pressure, HR and EEG awake were collected. The use of any antihypertensive drug, including β-blocker was checked.

Patients were anesthetized in a fully equipped operation room. No premedication was administered before surgery. On arrival in the operation theatre, standard monitoring and safe surgery checklist were executed. Venous catheter was inserted in a cubital vein. Non-invasive blood pressure was recorded every 5 minutes. Heart rate (HR), ECG, oxygen saturation (SpO_2) and end-tidal-carbon dioxide concentration were recorded continuously. Also a processed electroencephalography (EEG) monitor (NeuroSENSE Monitor©, NeuroWave Systems Inc) recorded continuously[15].

Induction was established, after preoxygenation, by administration of a propofol continuous target controlled infusion (Marsh-Model: injectomat TIVA Agilia, Fresenius Kabi, Germany) up to the value of EEG was between 40 and 60[16]. The effect site concentration of propofol (CE-Prop) was noted. When necessary, lidocaine and dexamethasone were allowed to give, as there is no known interference with pupil measurement[13,14]. Manually assisted ventilation with 100% oxygen began as soon as the patients became apneic.

The observer performed the first, T0, measurement at the moment the patient had a EEG value between 40 and 60. When necessary, mask ventilation with minimal manipulation was conducted during measurement. The minimal manipulation does not have significant nociceptive influence in comparison with the standardized nociceptive stimulation by the pupillometer. For note, no opioid or curare were given before the T0 measurement. After the first measurement the anesthesiologist gave the opioid as noted by the right group follow the randomization. When necessary, curare was also administered after the first measurement.

After a waiting time of 6 minutes, the T1 measurement was performed. Whereafter every 10 minutes a new measurement was conducted. The intervention group followed the Minto model and started at 5.0 ng ml-1 using CBW[17]. After each measurement the remifentanil infusion was adapted in the intervention group. When the PPI score was 1 or 2, then the concentration was lowered by 0.2 ng ml^{-1}. When the PPI score was 3 or more, than the concentration was raised by 0.2 ng ml^{-1} (see figure 1). At the remifentanil control group had the anesthesiologist a free choice of the amount of remifentanil to give. The last measurement happened at start closure the wound or when there was no wound at the end of surgery. At each measurement we collected also the blood pressure, HR, movement and EEG.

At the end of the surgery the observer noted time of stop CE-Prop, stop surgery time, temperature, neuromuscular transmission monitoring by train-of-four (TOF) test (TOF-watch®, Draeger), SpO_2 and EEG. Also the time of extubation was noted. At the anesthesiologist was asked if acetaminophen, NSAID, tramadol, morphine or local wound infiltration was given. Also if anti-emeticum dexamethasone or ondansetron was given. In need we tolerated the gift of DHBP or alizapride, but only after the last measurement to prevent measurement influence.

The anesthesiologist had to fill in a blind form with the study group and the total dose of remifentanil. The form went in a closed envelop and only went open after all the measurements.

By the PACU staff a second form was filled in. At this file we collected time of arrival and departure of the recovery. The Aldrete score at arrival and departure, the need of anti-emeticum, vomiting and/or nausea was noted. The need of supplemental oxygen and so needed the oxygen flow was noted. Also pain was questioned and if necessary which and how much rescue pain killer was given, followed by pain reassessment.

At home the patients were asked to fill in an online questionnaire during five days. The use

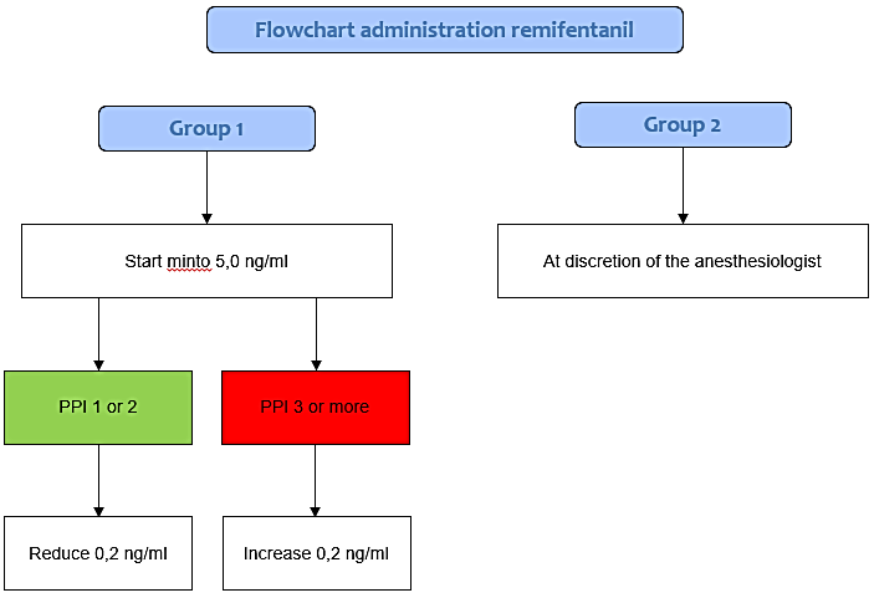

Fig. 1 — Flowchart administration remifentanil. PPI: Pupillometry Pain Index.

of pain killers was asked and calculated by the Medication Quantification Scale. NRS of pain with 0 is no pain and 10 is maximal pain, NRS activity with 0 is no activity and 10 is very active and NRS sleep with 0 equals "did not sleep" and 10 means "did sleep very well" were asked using an online evaluation dairy. The questions "Did you have nausea in the last 24 hours?" and "Did you throw up last 24 hours?" were also asked. Also the EQ-5D-5L questionnaire was used, the calculation was by the United Kingdom score as there is no Belgian score. At least patients were asked to place a dot on the EQVAS-score about their feeling of health whereby 0 equals the worst health imaginable and 100 is the best health imaginable.

One of the authors took care of the informed consent of the patient. The same author did also all the peroperative measurements. The syringe was hidden for the observer, so it was not possible to make an estimation of the used amount of opioid. Also the participants, because they were under anesthesia, were blinded. The staff of the recovery ward was blinded, because the anesthesiologist did not tell them in which group the patient was allocated.

The primary outcome parameter was the postoperative pain intensity queried as pain intensity by NRS and the amount of pain killer usage. Our hypothesis was that patients with a good titrated remifentanil administration peroperative should have less pain and less need of pain medication. Secondary outcome parameters were the characteristics of the pupillometry introducing a pupillometry pain index chart to individual titrate remifentanil dosage. Also opioid induced side effects nausea and vomiting and length of stay at the PACU ward were examined. Further the wellbeing of the patients was examined using health state index and EQ5D5L questionnaire.

Statistical analysis

Results were expressed as mean and standard deviation for continuous variables, as median and interquartile range for ordinal variables and as numbers and percentages for categorical variables. Normality of continuous variables per group was tested with Kolmogorov-Smirnov and Shapiro Wilk test. At normal distribution and independent samples T-test was used. In case of non-normality or ordinal variables, Mann-Whitney U test was used. For categorical variables chi-square test or Fisher's exact test was used as appropriate. In the study were also repeated measures for which paired samples test was used. Statistical significance was set at a P-value of <0.05 for all tests. Statistical analysis was performed using IBM SPSS Statistics version 28.0.0.0.

Initially, we wanted to analyze the use of pain medication, pain score and health state index at day 5. Unfortunately, because of a 80% drop out of not filled in online questionnaires we decided to only statistically analyze postoperative day 1.

Results

Demographic data

In total 59 patients participated to the PUP-AIT study. By randomization 30 patients were allocated to the "remifentanil flowchart group" or intervention group, 29 allocated to the "remifentanil free use" group or control group (see consort flow diagram). From both groups were two patients not analyzed because of a deviation from the study protocol.

So 28 patients were analyzed for the intervention group and 27 for the control group.

Baseline demographic data are presented in Table II. Patients had no significant difference in age, sex, discipline, CBW, SpO_2, HR, use of antihypertensive drugs and CE-Prop. There were in both groups only 14% males included due to the amount of gynecologic patients with 78% in both groups. The EEG was calculated as (EEG right + EEG left) divided by two and called EEG mean (EEGm). There was no significant difference in EEGm.

The pupillometry baseline measurement at T0 was after induction with propofol, but before administration of remifentanil or curare. Results of the T0 measurement are presented in Table III. There was no significant difference in baseline pupil diameter, PRDA, VAR, Int or PPI. Respectively, the mean pupil diameter baseline was 4.1 and 3.9 mm and the mean PRDA was 1.0 and 1.1 mm. The variation was 26% and 28% at a median intensity of 30 mA in both groups. Both median PPI were 8. There was also no statistical significance in SBP, HR or EEGm. The EEGm reached in 89 and 93% the target value of 40 – 60.

Peroperative measurements

Results are presented in Table III. The first peroperative measurement was conducted 6 minutes after start administration of remifentanil and called T1 measurement. Between the two groups there was no significant difference between baseline pupil diameter, PRDA, VAR, Int or PPI. At T1 there was a significant difference in heart rate with respectively 57 and 64 bpm ($p = 0.021$). SBP and EEGm did not show a significant difference.
If we compared baseline reduction of the PPI score T0 versus T1 for both groups, there was a significant reduction of 46.8% and 49.8% with both $p < 0.001$. The comparison T0 versus T1 of PPI gave for the flowchart group a significant reduction of 62.4% ($p < 0.001$). The control group had also a significant PPI reduction of 74.8% ($p < 0.001$). The wanted PPI-score of 1 or 2 was reached in 20 cases (71.4%) of the flowchart group and 25 cases (92.6%) of the control group ($p = 0.078$).

The last measurement was at the beginning of closing the operative wound(s). This measurement called end-measurement. A significant difference at baseline pupil diameter was noted. Further there was no significant difference at PRDA, VAR, Int or PPI. Also the SBP, HR and EEGm did not show any significant difference. In 26 of the 28 cases (92.9%) the end PPI was 1 or 2 in the flowchart group, at the free use group this was 25 of 27 cases (92.6%) ($p = 0.970$).

Table IV compares the two groups intra operatively. Time between start and stop propofol had a median of 27 and 36 minutes ($p = 0.228$) respectively. The time between stop propofol and extubation was median 12 and 10 minutes ($p = 0.812$). For wake up conditions there was no significant difference at temperature, SpO_2 or EEG. The TOF-count was 4 at all neuromuscular blocked patients. At one patient in the flowchart group it was < 80% with wake-up time 9 minutes. Three patients of the control group had TOF < 80% with wake-up times of 15, 17 and 18 minutes. There was no significant difference of intra-venous pain medication. 14% versus 44.4% received wound infiltration ($p = 0.014$) which differed significant. Dexamethasone was respectively given to 43 and 59% of the patients ($p = 0.224$). Ondansetron to 7 and 33% ($p = 0.015$), which was significantly more in the control group. DHBP or alizapride was given in 11 and 4%, only after the last measurement. As

Table II. — Demographic data.

TOTAL	Remifentanil flow chart	Remifentanil free use	p-value
N = 55	28	27	
Age (years)	45 (14.1)	40 (12.8)	0.172
Male	4 (14.3%)	4 (14.8%)	0.956
Discipline	78% gynecologic	78% gynecologic	0.943
Corrected body weight (kg)	65 (8.7)	65 (8.0)	0.773
SpO_2 start (%)	99 (1.4)	96 (1.9)	0.856
Systolic blood pressure (mmHg)	133 (21.1)	133 (18.9)	0.931
Heart rate (bpm)	72 (13.5)	79 (15.9)	0.072
Antihypertensive drug use	4 (14.3%)	2 (7.4%)	0.413
EEGm	92 (2.1)	92 (2.3)	0.240
C_E-Prop induction	6.9 (0.87)	7.5 (1.26)	0.107

CBW: male = (weight - 100) + (0.4 x (weight - 100)) ; female = (weight - 105) + (0.4 x (weight - 105))
EEGm: Electroencephalography mean = (EEG left + EEG right) / 2; C_E-Prop: effect-site concentration propofol.

Table III. — Peroperative measurements.

TOTAL	Remifentanil flow chart	Remifentanil free use	p-value
N = 55	28	27	
T0 Baseline (mm)	4.06 (1.069)	3.88 (1.061)	0.520
T0 PRDA (mm)	1.03 (0.419)	1.09 (0.509)	0.626
T0 Var (%)	26 (11.8)	28 (14.0)	0.209
T0 Int (mA) (median)	30 (10)	30 (20)	0.330
T0 PPI (median)	8 (2)	8 (2)	0.959
TO SBP (mmHg)	121 (17.6)	117 (17.6)	0.539
T0 HR (bpm)	71 (11.2)	77 (12.5)	0.077
TO EEGm	48 (6.9)	49 (8.1)	0.315
T0 EEGm (% between 40 - 60)	25 (89.3%)	25 (92.6%)	0.670
T1 Baseline (mm)	2.16 (1.022)	1.95 (0.392)	0.946
T1 PRDA (mm)	0.27 (0.364)	0.15 (0.087)	0.266
T1 VAR (%)	11.1 (10.99)	9.4 (12.78)	0.209
T1 Int (mA) (median)	60 (0)	60 (0)	0.166
T1 PPI (median)	2 (2)	2 (1)	0.148
T1 SBP (mmHg)	98 (15.1)	101 (19.3)	0.926
T1 HR (bpm)	57 (10.3)	64 (11.4)	0.021
T1 EEGm	53 (14.9)	44 (12.5)	0.871
T0-T1 baseline reduction	46.8% (1.14) $p < 0.001$	49.8% (1.07) $p < 0.001$	
T0-T1 PPI reduction	62.4% (3.07) $p < 0.001$	74.8 (2.13) $p < 0.001$	
T1 PPI 1 or 2	20 (71%)	25 (93%)	0.078
Tend baseline	1.81 (0.274)	1.98 (0.229)	0.017
Tend PRDA	0.93 (0.108)	0.13 (0.117)	0.084
Tend VAR	4.7 (6.13)	6.0 (6.02)	0.249
Tend Int (median)	60 (0)	60 (0)	0.959
Tend PPI (median)	1 (1)	1 (1)	0.434
Tend SBP	93 (12.3)	94 (22.0)	0.419
Tend HR	55 (11.5)	58 (9.8)	0.177
Tend EEGm	42 (8.9)	44 (10.3)	0.564
Tend PPI 1 or 2	26 (93%)	27 (93%)	0.970
PRDA: Pupillary Reflex Dilation Amplitude; VAR: Pupil Variation; Int: Intensity; PPI: Pupillometry Pain Index; SBP: Systolic blood pressure; HR: Heart rate; EEGm: Electroencephalography mean = (EEG left + EEG right) / 2			

mentioned before, this was a deviation from the study protocol, but because there are no further pupillary measurement it did not have influence. In the intervention group, the mean dose of remifentanil was 422 mcg, in the control group was the mean dose 595 mcg without significant difference ($p = 0.351$). When we corrected the dose to CBW and length of propofol infusion, we had 0.21 mcg kg-1 min-1 for both groups ($p = 0.926$).

Postoperative outcome

The median time at recovery was respectively 40 and 47.5 minutes, with $p = 0.966$. See Table IV, the number of missing observations is reported. Aldrete at arrival was in both groups 8. At departure only one patient of the flow chart group had Aldrete 9, all the other patients of both groups had Aldrete 10. Only one patient suffered from postoperative nausea or vomiting, it was a patient of the control group. Respectively 1 and 3 patients needed supplemental oxygen ($p = 0.246$). 39 and 44% of the patients received piritramide ($p = 0.728$).

Follow-up

At day 1 the medication use was comparable between the two groups. Results are presented in table 5. After the results the number of answers are shown. The median NRS was 3 for the flowchart group and 3 for the control group ($p = 0.758$). The level of activity median of both groups was 4 ($p = 0.492$). The level of subjective sleep quality median was respectively 5 and 7 ($p = 0.297$). One patient of the intervention group had nausea while none of the control group ($p = 0.382$). No vomiting was noted.

Table IV. — Peroperative time, medication and PACU.

TOTAL	Remifentanil flow chart	Remifentanil free use	p-value	
N = 55	28	27		
Time start to stop propofol (min) (median)	27:00 (17:30)	36:00 (40:00)	0.228	
Time stop propofol to wake-up (min) (median)	12:00 (06:00)	10:00 (6:30)	0.812	1 and 2 cases missing
Temperature (°C)	36.0 (0.35)	36.0 (0.49)	0.634	1 and 1 case missing
Train-of-four measurement	1 too low. wake-uptime 9 min	3 too low. wake-up time 18. 15 and 17 min		
SpO_2 % < 97%	1 case (4%)	0 (0%)		
EEGm at stop propofol	44 (9.1)	47 (10.2)	0.191	
Paracetamol %	27 (96.4%)	27 (100%)	>0.999	
NSAID %	24 (85.7%)	24 (88.9%)	0.724	
Contramal %	4 (14.3%)	5 (18.5%)	0.671	
Morfine %	0 (0%)	0 (0%)	NA	
Wound infiltration %	4 (14.3%)	12 (44.4%)	**0.014**	
Dexamethasone %	12 (42.9%)	16 (59.3%)	0.224	
Ondansetron %	2 (7.1%)	9 (33.3%)	**0.015**	
Dehydrobenzperidol / alizapride post last measurement	3 (10.7%)	1 (3.6%)	0.299	
Total dose remifentanil (µcg)	422 (203.5)	595 (527.1)	0.351	2 and 2 cases missing
Total dose remifentanil/ corrected body weight/time (µcg kg^{-1} min^{-1})	**0.21 (0.077)**	**0.21 (0.055)**	**0.926**	2 and 2 cases missing
Time recovery (median) (min)	40 (32:30)	47:30 (26:15)	0.966	3 and 5 cases missing
Aldrete arrival (median)	8 (1)	8 (3)	0.678	1 and 2 cases missing
Aldrete departure (median)	10 (0)	10 (0)	>0.999	1 and 5 cases missing
Postoperative nausea or vomiting	0 (0%)	1 (4.0%)	0.285	0 and 2 cases missing
Supplemental oxygen	1 (3.6%)	3 (12.0%)	0.246	0 and 2 cases missing
Piritramide used	11 (39.3%)	11 (44.0%)	0.728	0 and 2 cases missing
EEGm: Electroencephalography mean = (EEG left + EEG right) / 2				

The Health State Index of the flowchart group was 0.76, the control group 0.68 (p = 0.108). The EQVAS score at D1 was respectively 65 and 63 (p = 0.793).

Discussion

Our primary outcome parameter was postoperative pain intensity. Patients in both groups had a NRS of 3 without statistical significance. According to our opinion, it is good to have low pain scores in the study. The in-hospital goal for discharge is NRS 3 or less. The pain medication use in both groups was also comparable. Unfortunately there was already a drop out of patients not or partially filled in the online questionnaire at day 1.

The second outcome parameter, namely the PRD characteristics were comparable in both groups. Already after 6 minutes 71 and 92% of the patients had a PPI score of 1 or 2. At the end had 92% of the patients the right PPI score. The reduction of PPI score was comparable with the second pilot study[12]. To our opinion, introducing a PPI score during surgery succeeded.

On the contrary, the titration of remifentanil has to be studied further. We followed Barvais et al and started at 5.0 ng/ml because there was statistic difference between 2.0 and 5.0 ng/ml[6]. On the contrary other Kim et al started as low as 1.5 ng/ml[8]. We used incremental steps of 0.2 ng/ml, other authors used 0.5 ng/ml.[7-9]. One of our goals was to better titrate remifentanil with lower dosage regimens and both study groups received the same amount of remifentanil in mcg kg^{-1} min^{-1}. So further studies could start with lower starting doses.

The recovery ward times in minutes were respectively 40 (min 25 - max 99) and 47,5 (min 15 – max

Table V. — Online questionnary day 1.

TOTAL	Remifentanil flow chart	Remifentanil free use	p-value
Medication tracking	15.3 (5.9) (n = 25)	17.7 (4.7) (n = 24)	0.238
NRS pain (median)	3 (4) (n = 15)	3 (3) (n = 11)	0.758
NRS activity (median)	4 (4) (n = 15)	4 (3) (n = 11)	0.492
NRS sleep (median)	5 (3) (n = 15)	7 (2) (n = 11)	0.297
Nausea (%)	1 (6.7%) (n = 15)	0 (0%) (n = 11)	0.382
Throwing up	0 (0%) (n = 15)	0 (0%) (n = 11)	NA
Health State Index	0.76 (0.138) (n = 21)	0.68 (0.172) (n = 17)	0.108
EQVAS score	65 (16.7) (n = 21)	63 (20.0) (n = 17)	0.793
NRS: Numeric rating scale			

110). Probably due to the use of remifentanil had 39 and 44% of the patients need for supplemental postoperative analgesics.

At least are the conclusions of the wellbeing at day one postoperative. The health state index and the EQVAS score were comparable in both groups. Only one patient of the flow chart group had nausea, none of the control group.. Because there was only a small difference of opioid administration in the two groups, not surprisingly, no statistical difference was shown.

There was no report of a serious adverse event during the whole study follow up period.

To our opinion both groups were comparable. We included patients from October 2017 until August 2021. The long inclusion time was due to another study running in our center and because of the Covid 19 pandemic period.

One of the limitations was the investigation of only day care patients. This trial included gynecologic and abdominal patients, resulting in a mainly female study population. The most operations were rather short. More evidence is needed for pupillometry application during major surgery like thoracic surgery.

Another limitation of our trial is the big drop out of the online questionnaire. Unfortunately it made it more difficult to reach statistic difference. Participation was always voluntary.

The post operative pain management was not standardized because we did different operations. Paracetamol, NSAID and tramadol use are very similar. Between the two groups there was only a statistic significance in the amount of patients receiving wound infiltration. As this is used for skin infiltration, it can also make the laparoscopic versus non-laparoscopic surgeries more equal.

We described a RCT in a pragmatic daycare surgery population. Adequate postoperative analgesia is a prerequisite for successful day surgery but at the same time it is challenging for several reasons. Most studies analyzing postoperative pain have focused on the immediate postoperative course and classified the different types of surgery to a wide range of surgical disciplines[18,19]. This RCT was limited to abdominal and gynecological procedures. An optimal identification of painful surgical procedures is a prerequisite for the development of future preventive, procedure-specific, individual nociceptive activation specific pain-treatment schedules. Moreover, to reduce moderate to severe postsurgical pain, additional measures, such as objective nociceptive assessments, should be considered. Therefore, a more profound understanding of the variability of acute postsurgical pain after different types of day surgery is needed.

Also the anti-emeticum management was not standardized. Questions can raise about the lower NRS-score post-operative after dexamethasone. At the start of the study there was no meta-analysis to state the lower NRS-score or lower morphine usage. Mitchell et al publicized a meta-analysis in 2022. At 24 hours postoperative a -0.38 (-0.52 to -0.24) lower NRS-score with $p < 0.05$ was noted.20 In our study 43% of the intervention group and 59% of the control group ($p = 0.224$) received dexamethasone. This was not a significant difference.

Conclusion

This study examined the usefulness of pupillometry in combination with remifentanil. Our first conclusion is that no significant difference was found at NRS score day 1 with both groups had a median NRS score of 3.

The second conclusion is that a PPI score is usable during daycare anesthesia using remifentanil. Unexpectedly, the corrected dosage of remifentanil was more or less the same in both groups. So there was no dose reduction of remifentanil, hence there was no diminishing of side effects. Probably, starting dose could be lower than 5.0 ng/ml and the incremental steps to titrate remifentanil could be bigger than 0.2 ng/

ml. Although we conclude that a PPI score chart is usable with Algiscan©. But further research need to be done to titrate remifentanil.

Possibly because of the same opioid titration in both groups, we have similar wellbeing between the two groups. There is no difference in post operative nausea or vomiting, post anesthesia care unit stay nor health state index.

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