Chronic Pain Medicine

ORIGINAL CLINICAL RESEARCH REPORT

Comparison of Pupillometry With Surgical Pleth Index Monitoring on Perioperative Opioid Consumption and Nociception During Propofol–Remifentanil Anesthesia: A Prospective Randomized Controlled Trial

Jong Hae Kim, MD,* Eun Kyung Jwa, MD,† Youjin Choung, MD,‡ Hyo Jin Yeon, MD,‡
Soo Yeon Kim, MD, PhD,‡ and Eugene Kim, MD, PhD§

R2 Chanathip Meerod / Lt.Col.Nattapong Phuvachoterojanaphokin

Background

- Opioid are the most widely used analgesics for providing safe and stable hemodynamic
- Opioid-naïve patients are significant risk for chronic opioid use after surgery
- Particularly, remifentanil dose dependently induces hyperalgesia and tolerance, which might trigger chronic pain and opioid dependence
- Increased opioid consumption is related to the development of postoperative complications
- It is importance to reduce intraoperative opioid use while providing adequate analgesia

Background

- There no definite tools to monitor the appropriate amount of opioids during GA
- Hemodynamic parameter (HR,BP) changes are mostly use in clinical practice
- Surgical pleth index (SPI) is a parameter base on HR and pulse plethysmographic waveforms ; tool to monitor the nociception-antinociception balance under GA
- Pupillary dilation reflex (PDR) is the change of pupil size after stimulus ; *sympathetic contribution of pupil is abolished during GA but division of sympathetic remain functional*
- PDR does not depend on systemic sympathetic activation nor peripheral vascular tone

SPI learning at the beginning of the operation. The number is displayed in grey.

SPI index and trend active during the operation.

Background

- Several study have shown that PDR is superior or noninferior to other measurements for managing nociception during GA
- There has no been randomized study that compared PDR and SPI during laparoscopic surgery
- This study compared efficacy of pupillometry with SPI monitoring for perioperative analgesia

Hypothesis

Intraoperative remifentanil administration guided by pupillometry

would decrease the postoperative pain compared to SPI monitoring

Methods

Study design

prospective , single center, parallel-arm, double blind randomized controlled trial

was conducted in 2 steps

Preliminary stage

clinical feasibility of using pupillometry and SPI compared with conventional hemodynamic monitoring (50 participants)

Main study

Compare the effects between the pupillometer and SPI monitoring

Methods

- Both study were approved by institutional review board of Daegu catholic university medical center
- registered at ClinicalTrial.gov ; (June 30,2018 and January 3,2019)

Methods

Inclusion criteria

- Age 20-65 yr.
- ASA I-II
- Scheduled for laparoscopic cholecystectomy

Exclusion criteria

- History of ophthalmic disease
- Neurologic or metabolic diseases
- History of eye surgery
- Medication interfering ANS ; B blocker , anticholinergics
- History of substance abuse or psychiatric
- Chronic pain / preoperative analgesia within 2 wk.
- Use of pacemakers or arrhythmias

Methods

In the first stage

- 50 patient were randomly assigned to 1 of 3 group
- Control : pupillometry : SPI = 1:2:2
- Investigators were not blinded to PD,SPI, and other parameters

Statistic analysis

- SPSS statistics V.25
- Kolmogorov-Smirnov test , normally and non normally distribution data were presented as mean ± SD and median (1^{st} to 3^{rd} quartile)
- Pilot study, 1 way analysis variance : compare normally distribution data
- Kruskal-Willis test with Dunn post hoc test : compare NRS

Statistic analysis

- Student t test and Mann-Whitney U test : compare normally & non normally distribution from 2 group
- X^2 test or Fisher exact : categorical data
- Non parametric rank based method : analysis longitudinal change of PD, HR , BP , NRS

Sample size calculation

- The sample size was calculated using PASS 15.0 software
- detect the difference of 1.4 in peak NRS between the 2 groups under 2 tails Mann-Whitney U test
- Power 90% with α error of 0.5 , total 86 patients (38 patients / group +10%)

Methods

In the main study

- 86 patients were randomly to allocated to 2 group [PD or SPI] by computer at ratio 1:1
- The random sequence was concealed with in opaque envelopes
- The randomized code was delivered to anesthesiologist who perform anesthesia
- The patient and investigator who measured the PD were blinded
- Patients, attending anesthesiologist, other investigators who measure post operative parameter after PACU were blinded

Anesthesia

Patient were monitored with HR , NIBP , SpO_2 , TOF , state entropy

↓

SPI monitoring was applied contralateral side of index finger to the arm with a BP cuff computed automatically using normalized HBI & PPGA

↓

Propofol TCI (Ce) 4 mcg/ml + remifentanil 4ng/ml

↓

Once loss of conscious : Rocuronium 0.6 mg/kg

↓

TOF =0 : Tracheal intubation & ventilator support $EtCO_2$ 4-6 kPa with Air : O_2 50%

Anesthesia

- **After intubation** , remifentanil Ce was decreased to 1.5 ng/ml to calibrate baseline of PD

↓

Control

Remifentanil Ce was determine by attending anesthesiologist

Pupillometry group

Remifentanil Ce was controlled q 5 mins due to PD changing

- ↑ PD > 30% : ↑ remifentanil Ce 0.5 ng/ml
- PD ↑ < 30% or ↓ < 5% : not modified
- ↓ PD > 5% : ↓ remifentanil Ce 0.5 ng/ml

SPI group

Target SPI 20-50

- SPI > 50 : ↑ remifentanil Ce 0.5 ng/ml
- SPI < 20 : ↓ remifentanil Ce 0.5 ng/ml
- SPI > 10/min : ↑ remifentanil Ce 0.5 ng/ml

Anesthesia

Propofol Ce was adjusted to maintain the SE between 40-60

↓

Emergence : propofol gradually reduced with the allowance SE up to 65
Remifentanil infusion gradually reduced at the discretion
after CO_2 gas deflated and suturing began

↓

After reversal NMBD ; extubate once the patients opened the eyes on verbal command and recovered spontaneous breathing with TOF ≥0.9

One surgeon performed all the surgeries in a same surgical method

Anesthesia

Hemodynamic instability

- BP or HR ± 20% from baseline

Treatment

- Infusion of crystalloid solution 5ml/kg

- Ephedrine 5 mg for ↓ BP

- Nicardipine 0.5 mg for ↑ BP

At PACU

1) Riker sedation agitation scale (RSAS) evaluate every 10 mins at PACU

Residual sedation : RSAS < 4

2) As patients became alert : NRS (0-10)

Treatment

- **NRS > 4 or analgesic required :** *fentanyl 50 mcg and repeated if pain persisted*
- **Refractory pain (2 dose FTN)** : *ketorolac 30 mg*
- **Persistent pain refractory to ketorolac** : *meperidine 25 mg*

- Discharge when modified Aldrete score > 9

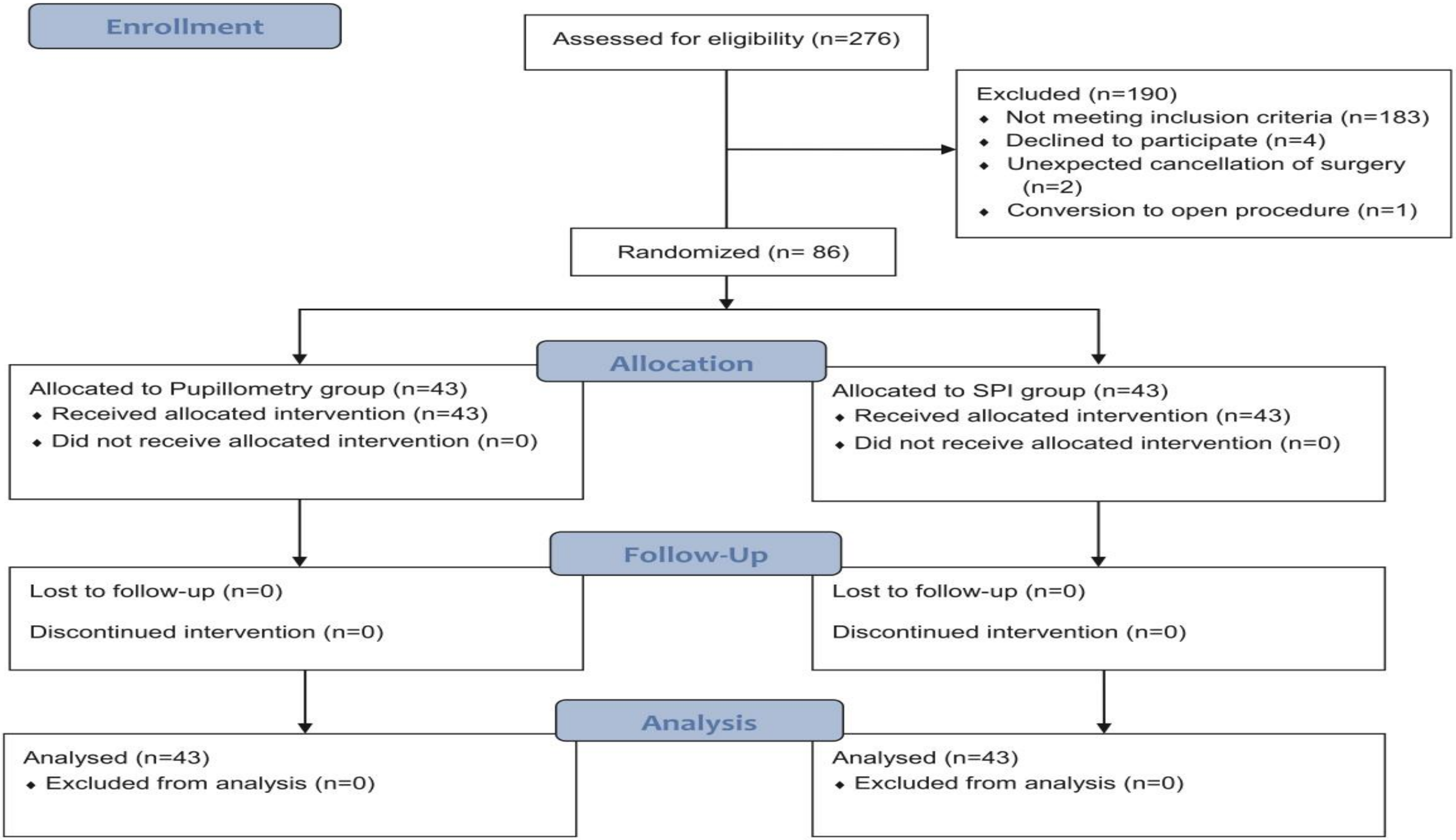
Measurements

Primary outcome

- Peak post operative NRS at PACU

Secondary outcome

- Intraoperative remifentanil consumption rate (mcg/kg/min)
- Postoperative opioid responsiveness
- Number of analgesic administration
- Meperidine administration additional after PACU discharged
- Opioid related complications


Enrollment
Assessed for eligibility (n=276)
Excluded (n=190)
Not meeting inclusion criteria (n=183)
Declined to participate (n=4)
Unexpected cancellation of surgery (n=2)
Conversion to open procedure (n=1)
Randomized (n= 86)
Allocation
Allocated to Pupillometry group (n=43)
Received allocated intervention (n=43)
Did not receive allocated intervention (n=0)
Allocated to SPI group (n=43)
Received allocated intervention (n=43)
Did not receive allocated intervention (n=0)
Follow-Up
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Analysis
Analysed (n=43)
Excluded from analysis (n=0)
Analysed (n=43)
Excluded from analysis (n=0)

Results

Table 1. Results in the Preliminary Phase of the Study

	Pupillometry Group (n = 20)	SPI Group (n = 20)	Control (n = 10)	*P* Value
Demographic data				
Age (y)	50.6 ± 9.3	46.6 ± 10.3	50.2 ± 7.8	…
Body mass index (kg/m^2)	24.5 ± 3.5	24.7 ± 2.8	23.4 ± 3.1	…
Female gender, n (%)	9 (45.0%)	9 (45.0%)	7 (70.0%)	…
Intraoperative				
Remifentanil consumption rate (μg·kg^{-1}·minute^{-1})	0.079 ± 0.024[a]	0.138 ± 0.049	0.108 ± 0.030	<.001
Total remifentanil consumption (μg)	289.4 ± 110.2[a]	545.4 ± 263.2[b]	366.9 ± 74.8	<.001
Propofol consumption rate (mg kg^{-1}·minute^{-1})	0.162 ± 0.025	0.148 ± 0.019	0.168 ± 0.047	.154
Total propofol consumption (mg)	609.0 ± 234.4	582.6 ± 162.6	589.5 ± 196.6	.914
Patients requiring nicardipine, n (%)	6 (30.0%)	5 (25.0%)	2 (20.0%)	.834
Patients requiring ephedrine, n (%)	9 (45.0%)	10 (50.0%)	4 (40.0%)	.869
Extubation time (min)	5.2 ± 2.7[b]	7.3 ± 3.0	9.3 ± 4.8	.008
Eye opening time (min)	4.8 ± 2.7	6.2 ± 2.8	7.7 ± 4.2	.052

Pupillometry reduced intraoperative remifentanil consumption compared to SPI monitoring

P = < 0.001

Results

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No difference between the pupillometry and control

P = 0.115

Results

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Age (y)	50.6 ± 9.3	46.6 ± 10.3	50.2 ± 7.8	...
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No difference between 3 groups

Results

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pupillometry monitoring were extubated earlier than conventional monitoring

P=0.007

Results

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Eye opening time (min)	4.8 ± 2.7	6.2 ± 2.8	7.7 ± 4.2	.052

Pupillometry monitoring **VS** SPI monitoring

P=0.124

Results

Table 1. Results in the Preliminary Phase of the Study

	Pupillometry Group (n = 20)	SPI Group (n = 20)	Control (n = 10)	*P* Value
Postoperative				
NRS				
Peak	5.0 (3.1–6.0)[b]	6.0 (4.3–8.0)	6.0 (5.8–8.3)	.010
At admission	4.0 (3.0–6.0)	5.0 (4.0–6.0)	6.0 (4.8–7.0)	.112
10 min after	3.0 (3.0–5.0)[a,b]	5.0 (4.0–6.8)	5.5 (3.8–7.3)	.007
20 min after	3.0 (2.0–4.0)[a,b]	5.0 (3.3–6.0)	4.8 (3.5–7.5)	.002
30 min after	3.0 (2.0–4.0)[a,b]	5.0 (3.0–6.0)	5.0 (4.0–7.0)	.010
At discharge	2.0 (2.0–3.0)[a,b]	3.5 (2.6–5.0)	3.8 (3.0–4.6)	.009

Significant at P = 0.018

Results

Table 1. Results in the Preliminary Phase of the Study

	Pupillometry Group (n = 20)	SPI Group (n = 20)	Control (n = 10)	*P* Value
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NRS				
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30 min after	3.0 (2.0–4.0)[a,b]	5.0 (3.0–6.0)	5.0 (4.0–7.0)	.010
At discharge	2.0 (2.0–3.0)[a,b]	3.5 (2.6–5.0)	3.8 (3.0–4.6)	.009

No difference at P = 0.074

Results

Table 2. Patient Characteristics and Intraoperative Parameters in the Main Study

	Pupillometry Group (n = 43)	SPI Group (n = 43)	*P* Value[a]
Age (y)	49.1 ± 10.3	49.4 ± 10.0	…
Female gender, n (%)	19 (44.2%)	25 (58.1%)	…
Body mass index, (kg/m^2)	24.0 ± 3.1	24.0 ± 3.2	…
ASA PS, I/II	29/14	22/21	…
Duration of operation (min)	36.7 ± 12.5	40.3 ± 15.0	.230
Duration of anesthesia (min)	58.7 ± 12.7	62.2 ± 15.2	.252
Duration of PACU stay (min)	27.8 ± 9.8	31.4 ± 8.8	.081
Hospital stay after the operation (d)	2.3 ± 1.1	2.7 ± 2.0	.200
Remifentanil consumption rate (μg·kg^{-1}·minute^{-1})	0.078 ± 0.019	0.130 ± 0.051	<.001
Total remifentanil consumption (μg)	264.4 ± 91.6	458.1 ± 233.2	<.001
Propofol consumption rate (mg kg^{-1}·minute^{-1})	0.160 ± 0.025	0.149 ± 0.025	.042
Total propofol consumption (mg)	551.9 ± 198.4	526.0 ± 157.7	.504
Extubation time (min)	6.4 ± 3.5	7.0 ± 3.3	.429
Eye opening time (min)	5.8 ± 3.5	6.0 ± 3.2	.822

Demographic data between the group ; no difference

Results

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Extubation time (min)	6.4 ± 3.5	7.0 ± 3.3	.429
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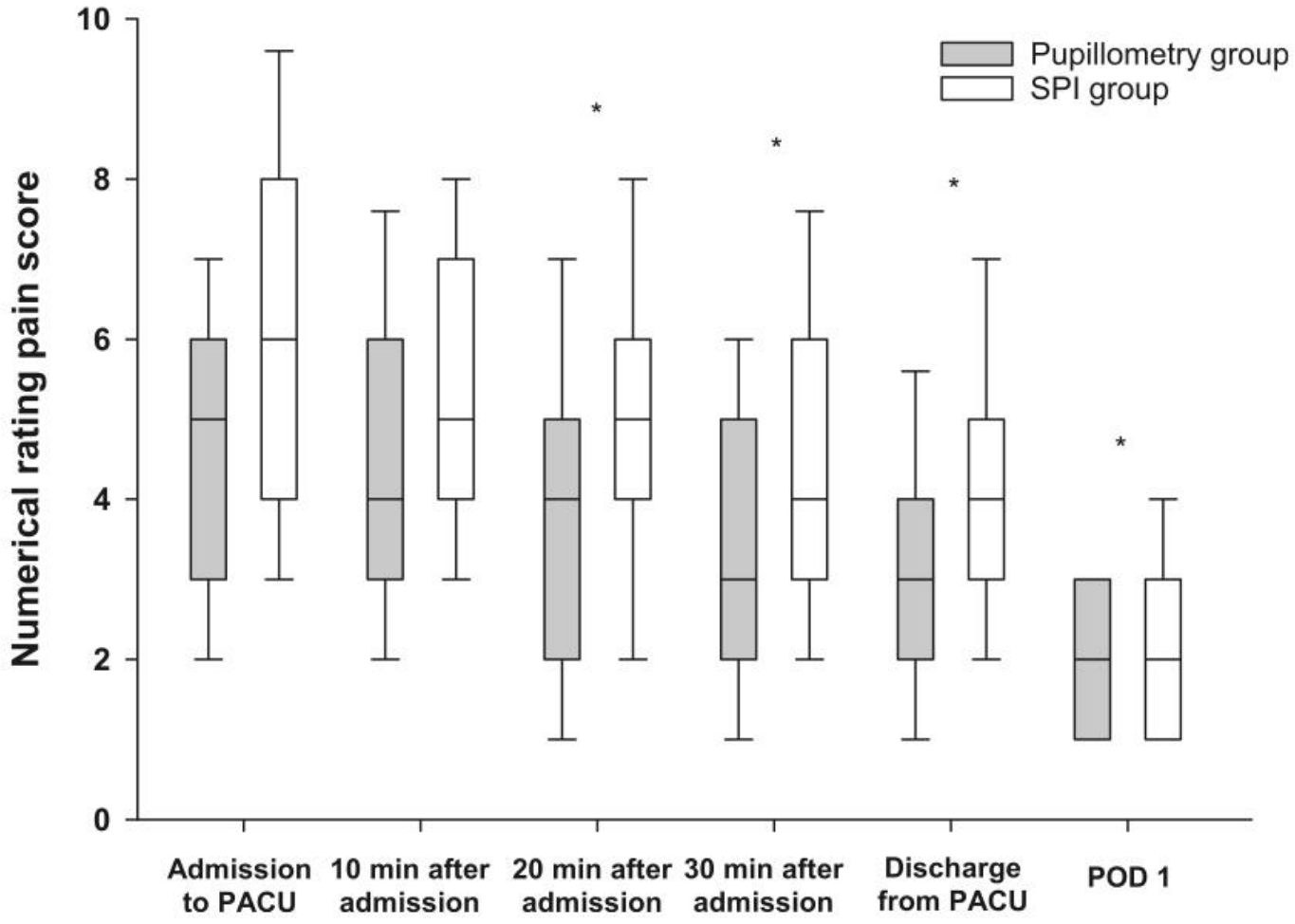
Statistically significant $P < 0.001$

Results



NRS scores

Pupillometry VS SPI

5[4-6] VS 7[5-8]

P = 0.003

Results

Table 3. Postoperative Results in the Main Study

	Pupillometry Group (n = 43)	SPI Group (n = 43)	*P* Value
During PACU stay			
No. of administration of analgesics	2 (1–2)	2 (1–3)	.048[a]
FTN responsiveness[b]	35/40 (84.6%)	24/40 (61.0%)	.005[c]
Adverse events, n (%)	16 (37.2%)	22 (51.2%)	.193[c]
Residual sedation[d]	12 (27.9%)	14 (32.6%)	.639[c]
Nausea and vomiting	1 (2.3%)	3 (7.0%)	.616[e]
Desaturation[f]	4 (9.3%)	6 (14.0%)	.501[c]
Bradycardia[g]	0	3 (7.0%)	.241[e]
Dizziness	2 (4.7%)	1 (2.3%)	1.000[e]
Pruritus	0	1 (2.3%)	1.000[e]
Others	2 (4.7%)	4 (9.3%)	.676[e]

Results

Table 3. Postoperative Results in the Main Study

	Pupillometry Group (n = 43)	SPI Group (n = 43)	*P* Value
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Bradycardia[g]	0	3 (7.0%)	.241[e]
Dizziness	2 (4.7%)	1 (2.3%)	1.000[e]
Pruritus	0	1 (2.3%)	1.000[e]
Others	2 (4.7%)	4 (9.3%)	.676[e]
After PACU discharge			
Patients requiring additional meperidine, n (%)	1 (2.3%)	4 (9.3%)	.360[e]
Adverse events, n (%)	21 (48.8%)	30 (69.8%)	.048[c]
Residual sedation	1 (2.3%)	1 (2.3%)	1.000[e]
Nausea and vomiting	16 (37.2%)	20 (46.5%)	.382[c]
Pulmonary complications[h]	0	4 (9.3%)	.116[e]
Urinary distension	5 (11.6%)	5 (11.6%)	1.000[c]
Dizziness	3 (7.0%)	5 (11.6%)	.713[e]
Pruritus	3 (7.0%)	4 (9.3%)	1.000[e]
Others	0	1 (2.3%)	1.000[e]

Discussion

Pupillometry can decrease intraoperative opioid consumption , Post operative pain,

numbers of postoperative analgesic administrations

Discussion

Possible reason

- SPI increases promptly in response to sympathetic tone enhanced by nociceptive stimuli but decreases slowly with the abolishment of stimuli (delayed response of SPI)
- PDR faster responds to noxious stimuli faster than other , returns quickly once stimuli disappears
- Maintain hemodynamic stability , the use of vasopressors & vasodilators which significant influence SPI
- Hypercapnia dilates peripheral vessel as well as coronary & cerebral vasculature ; CO_2 pneumoperitoneum induced hypercapnia might affect SPI value

Limitations

- **Intraoperative pupillometry** , opioid block nociceptive stimulation dose-dependently (high dose opioids completely suppress PDR)

  It should not be generalized to surgeries requiring high dose opioid administration

- Postoperative pain can be affected by many variables beyond opioid use ,

  exclude the effects of confounding factors by randomization and standardization of anesthetic and surgical technique

Limitations

- SPI was recorded continuously while PD was measured every 5 mins , during the 5 mins, a significant change in nociceptive can not be detected by pupillometry
- Ideal SPI score might be affected by age and maintained SPI value between 20 and 50 as previous study (no validated range is presently available)

Critical Appraisal : RCT

Does this study address a clear question?

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical Appraisal : RCT

- Are the results of this single trial valid?

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?	✓		
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical Appraisal : RCT

- Are the results of this single trial valid?

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes ✓	Can't tell	No
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Critical Appraisal : RCT

- What were the results?

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	no
10. How precise were the results? Were the results presented with confidence intervals?	yes

Critical Appraisal : RCT

- Can I apply these valid, important results to my patients?

11. Do these results apply to my patient?	Yes	Can't tell	No
• Is my patient so different from those in the trial that the results don't apply?		✓	
• How great would the benefit of therapy be for my particular patient?		✓	
12. Are my patient's values and preferences satisfied by the intervention offered?			
• Do I have a clear assessment of my patient's values and preferences?	✓		
• Are they met by this regimen and its potential consequences?	✓		