PERIOPERATIVE USE OF PHYSOSTIGMINE TO REDUCE OPIOID CONSUMPTION AND PERI-INCISIONAL HYPERALGESIA: A RANDOMISED CONTROLLED TRIAL

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AUTHORS AND ABOUT JOURNAL

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About

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The *British Journal of Anaesthesia* (BJA) publishes high-impact original work in all branches of anaesthesia, critical care medicine, pain medicine and perioperative medicine including fundamental, translational and clinical sciences, clinical practice, technology, education and training. In addition, the Journal publishes review articles, important case reports, correspondence and special articles of general interest.

Metrics

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INTRODUCTION

Overview of Physostigmine and Its Effects

- **Cholinesterase Inhibitor:** Physostigmine increases acetylcholine levels by preventing its breakdown.
- **Crosses Blood-Brain Barrier:** It acts in the brain and has pain-relieving (analgesic) effects.
- **Enhances Opioid Effect:** Boosts the action of opioids like morphine and works well with **morphine** and **clonidine**.

Key Study Findings

Beilin et al. Study:

- **42% Less Morphine Use:** Continuous physostigmine infusion during the first 24 hours post-surgery reduced morphine requirements.
- **Lower Inflammation:** Patients had reduced levels of inflammatory markers (cytokines).

Wehrfritz et al. Study:

- In a human model, a **single physostigmine dose** reduced mechanical hyperalgesia (increased pain sensitivity) by **47%**.
- Clinical confirmation is still needed.

Cholinergic Mechanisms in Pain Relief

- **Nicotinic Receptors:** Help relieve pain at the spinal level.
- **Muscarinic Receptors:**
  - **M2 and M4 receptors** contribute to pain relief in both the brain and spinal cord.

Wind-up Phenomenon

- **Wind-up:** Repeated activation of pain nerves (C-fibers) makes nerve cells fire more, even without injury, causing increased pain sensitivity (central sensitization).

Hyperalgesia Explained

Primary Hyperalgesia:

- Occurs **at the incision site**, caused by sensitization of nerves in the skin (peripheral sensitization).

Secondary Hyperalgesia:

- Happens **around or away from the incision site**, due to changes in how the brain and spinal cord process pain (central sensitization).

- **Postoperative Hyperalgesia** may indicate **central sensitization** and can lead to long-term pain.

- Preventive analgesia is a pain management approach used to improve postoperative pain relief.
- The idea is to administer analgesics before surgical pain occurs to reduce pain sensitivity.
- For it to be considered effective, the analgesic's effect must last well beyond its typical duration—usually more than 5.5 times its half-life—compared to a control group.
- This approach aims to reduce both peripheral and central sensitization that result from painful stimuli.

Hypothesis

- The hypothesis of this prospective, double-blind, randomised, placebo-controlled trial is that continuous i.v. administration of physostigmine during the first 24 h postoperatively reduces opioid consumption and mechanical hyperalgesia by the means of preventive analgesia.

METHODS

- The Physostigmine-Enhanced Opioid Analgesia (PHANOS) study was conducted from June 2013 to October 2018 at the Medical University of Graz, Graz, Austria.

- It was designed as a prospective, double-blind, randomised, placebo-controlled two-armed trial.

- After the approval of the Ethics Committee (review board number: 24e349 ex 11/12) and registration of the study protocol (EudraCT number 2012-000130-19), patients undergoing elective open **nephrectomy** were recruited during routine preoperative anaesthesiological assessment by staff anesthesiologists.

- After eligibility for inclusion was assessed, members of the study team informed potential subjects and obtained written informed consent.

- **Inclusion Criteria:**

- Age ≥18 years

- Body weight ≥50 kg

- ASA physical status classification 1 to 3 (mild to moderate health issues)

- Basic eligibility for using patient-controlled analgesia (PCA) based on language and cognitive ability

Exclusion criteria

- Contraindications for physostigmine:
  - Bronchial asthma or severe chronic obstructive pulmonary disease (COPD)
  - Iritis
  - Stenosis or spasms of the intestinal tract, biliary tract, or urinary tract
- Craniocerebral trauma
- Severely impaired left ventricular function (ejection fraction <30%)

- History of myocardial infarction or cerebral insult
- Known allergy, hypersensitivity, or contraindications to hydromorphone or physostigmine
- History of ethanol or drug abuse
- Pregnancy
- Laparoscopic approach for surgery
- History of pain disorders
- Chronic pain medication usage

- The German version of the Pain Disability Index (PDI) was used to assess pre-existing disabilities attributable to pain preoperatively.

- After giving written consent, participants were instructed on how to use PCA(patient controlled analgesia).

- This article was prepared adhering to the Consolidated Standards of Reporting Trials checklist

Randomization and Blinding:

- Randomization was done using **Randomization.com** with a **1:1** allocation ratio.
- The randomization list was securely stored and only accessible to certain nurses with a chip card.
- Nurses prepared the study medication in a private room, following the randomization list.

Study Medication:

- Medication options:
  - **Physostigmine** at 0.125 mg/ml
  - **Saline solution** (NaCl 0.9%)
- The medication was delivered via an infusion pump (CADD®-Solis) with a programmed continuous infusion rate of 4 ml/h (equivalent to 0.5 mg/h for physostigmine).
- Infusion started after anesthesia induction and stopped after 24 hours.

Blinding:

- The pump was labeled "PHANOS study medication" with a unique patient identification number.

- Everyone involved in treating or examining the patients was blinded to the treatment group.

Pre-Operative Medication

- **Midazolam** (7.5 mg, orally) was given 60–90 minutes before anesthesia to help relax patients.

Induction and Maintenance of Anesthesia

- **General anesthesia** was started using:
  - **Remifentanil** at a dose of 0.1–0.3 mg/kg per minute, and
  - **Propofol** at 2–5 mg/kg.

- **Anesthesia maintenance**:
  - **Sevoflurane** was used at 0.7–1.0 MAC (minimum alveolar concentration) along with **remifentanil** at the same dose range (0.1–0.3 mg/kg per minute).

Anti-Nausea Medication

- **Ondansetron** (4 mg) was given about 30 minutes before the surgery ended to prevent nausea and vomiting.

Pain Management

- **Hydromorphone** (0.02–0.03 mg/kg, given intravenously) was administered 20–30 minutes before the skin was closed as a long-acting pain reliever.

Postoperative Pain Management

- **Metamizole** (1 g in saline solution) was administered every 6 hours as a standard pain reliever.

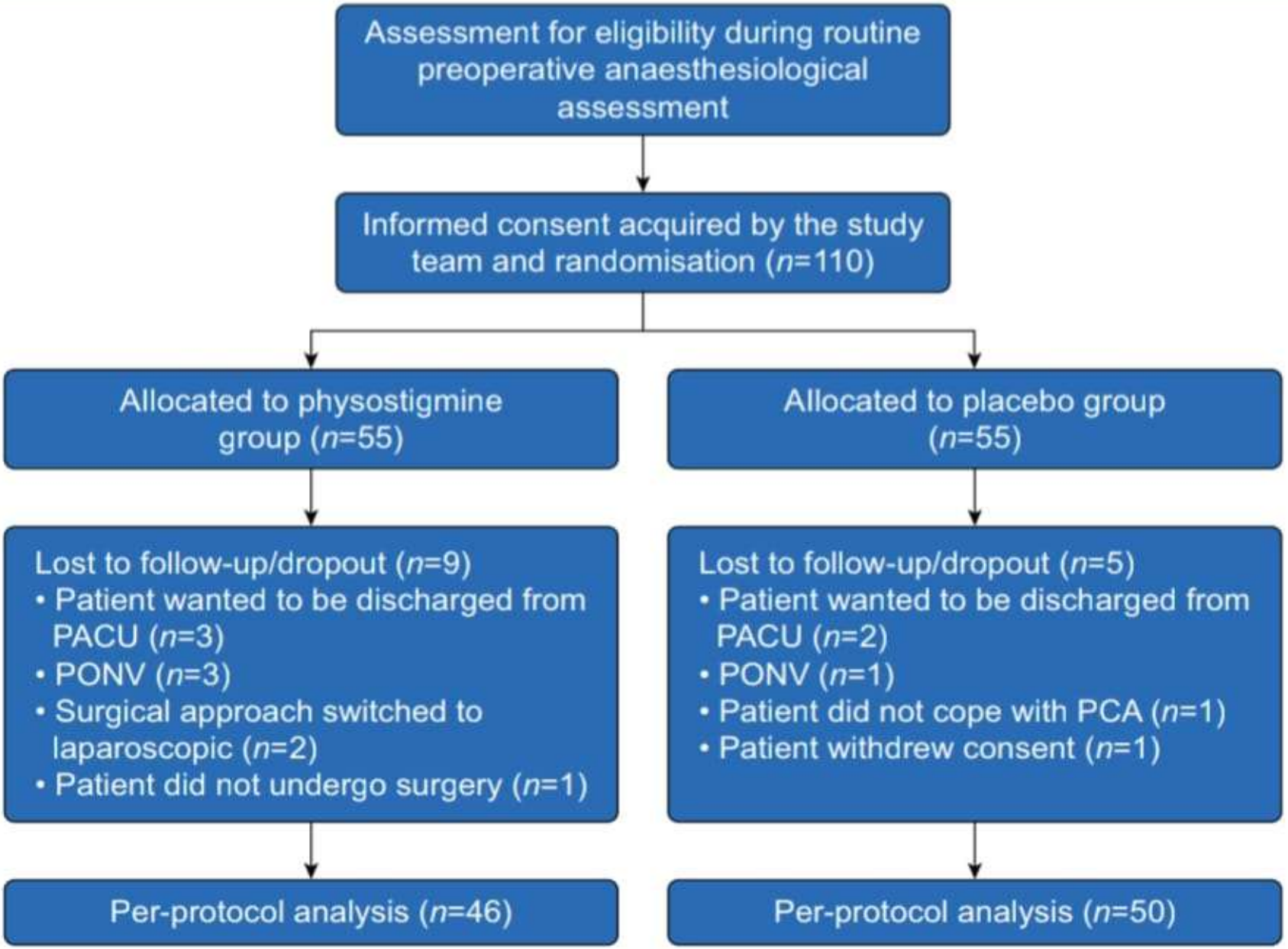
Patient-Controlled Analgesia (PCA):

- A PCA pump containing **hydromorphone** (20 mg in 100 ml saline) was set up with the following settings:
  - **Bolus dose**: 0.2 mg per patient request.
  - **Lockout time**: 10 minutes (prevents overuse).
  - **Maximum usage limits**: 5 boluses per hour and 4 mg in any 4-hour period.
- The PCA pump was available for 72 hours after surgery for patient-controlled pain relief.

Postoperative Monitoring

- Patients were monitored in the PACU (Post-Anesthesia Care Unit) for 24 hours after surgery to ensure safety and stability.

- This protocol aimed to manage pain effectively while minimizing the risk of adverse events by carefully regulating medication dosages and monitoring patients closely.



Flow chart. PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting.

OUTCOMES

- The **primary outcome** of interest is the total opioid consumption measured 24 hours after surgery.

- **Opioid Consumption Measurement:**

- The study defines **total opioid consumption** as the total amount of opioids given at three stages:

  - During the operation (intraoperative),
  - In the post-anesthesia care unit (PACU),
  - Through patient-controlled analgesia (PCA) post-surgery.

Pain Management Satisfaction:

- Satisfaction with pain management was evaluated using a **numeric rating scale** (NRS) where patients rated their satisfaction from 0 (worst) to 10 (best).

- This assessment took place **72 hours after surgery**.

Follow-Up Interview:

- At the study's end, patients were asked to consent to a follow-up telephone interview three months post-surgery to reassess pain management satisfaction and the Pain Disability Index (PDI) for long-term insights.

Mechanical Hyperalgesia (Secondary Outcome):

- Mechanical hyperalgesia was tested **48 hours** after surgery.
- **Four points** were chosen around the surgical site, each **5 cm** from the suture in four directions (up, down, left, right).
- **von Frey filaments** were used to apply light pressure at each point, ranging from **0.25 to 512 mN**.
- Patients described each pressure as either **sharp** or **blunt**. If they felt it as **sharp**, this set their pain sensitivity threshold.

- The average pain sensitivity level was calculated after adjusting the data.

- To see how far the sensitivity (hyperalgesia) spread, a **128 mN filament** was used in four lines around the suture, pressing every **5 mm** until the patient no longer felt sharp pain.

- This gave an average distance of sensitivity from the suture.

Wind-Up Phenomenon:

- **Wind-up** checks if pain feels worse with repeated identical pressure.

How It Was Tested:

- A **pinprick tool** applying **256 mN** was used on the side of the body.
- Patients rated their pain after the **first pinprick** on a **0–10 scale** (0 = no pain, 10 = worst pain).
- Then, the pinprick was applied **10 times in a row**, once per second, over a **1 cm^2 area**.
- Patients rated their pain again after the **10th pinprick**.
- The **wind-up ratio** was calculated by comparing pain ratings after the first and the last pinprick.

Sample Size Calculation and Statistical Analysis

- The study's **sample size** was calculated based on data from a pilot study, which showed a **30% difference** in 24-hour hydromorphone use between two groups (physostigmine and placebo).

- To detect this difference with **80% power** and a **5% significance level**, and allowing for a **5-10% dropout rate**, a total of **110 subjects** was needed.

- Because **nausea and vomiting** are common side effects, the dose of physostigmine was lowered to **0.5 mg per hour**.

Data Analysis:

- ANOVA, Student's t-test, Wilcoxon–Mann–Whitney, or Fisher's exact test were used based on the data type.
- Categorical data was tested with the chi-squared test.
- Analyses were conducted with NCSS software (version 12.0.13).

RESULTS

- **110 subjects** were included in the study, divided equally between the physostigmine and control groups.
- **14 subjects did not complete the study** (9 in the physostigmine group and 5 in the control group).
- This difference was **not statistically significant**.
- **Patient characteristics** (like age, sex, health factors) were similar between the two groups.
- The study ended in **October 2018**, and analysis was conducted as planned.

Table 1 Subject characteristics. Data are presented as mean (range or SD).

	Physostigmine	Placebo
N (M/F)	46 (35/11)	50 (35/15)
Age (yr)	62.9 (40–86)	59.6 (31–73)
Height (cm)	172.8 (10.2)	170.6 (8.7)
Weight (kg)	81.0 (15.7)	83.4 (15.9)
BMI (kg m^{-2})	27.0 (4.0)	28.8 (5.8)
Pain Disability Index preoperative	0.4 (2.1)	2.96 (8.6)
ASA physical status 1/2/3 (*n*)	5/32/9	9/28/13

DISCUSSION

- This study examined if **physostigmine** could improve opioid-based pain relief, lower opioid use, and reduce sensitivity to pain after surgery.

- **Opioid-Sparing Effect**:

  - No reduction in opioid use was found with physostigmine, contrary to previous studies (including our pilot) that showed it reduced opioid use.

  - The dose was halved (from 1 mg/h to 0.5 mg/h) to minimize side effects, which may have been too low to observe an opioid-sparing effect.

Pain Reduction:

- Physostigmine lowered pain at 24 and 48 hours, suggesting a **preventive effect**.

- By 72 hours, pain levels were similar in both groups as pain naturally decreased over time.

Reduced Pain Sensitivity:

- Physostigmine reduced **mechanical pain sensitivity, hyperalgesia, and wind-up**, potentially decreasing post-surgery sensitivity. The effect may involve both central and peripheral mechanisms.

Table 2 Main study results. NRS, numeric rating scale.

	Physostigmine	Placebo	P-value
Time from incision to closure (min)	136 (43)	130 (34)	0.5075
Mean intraoperative remifentanil ($\mu g\ kg^{-1}\ min^{-1}$)	0.17 (0.04)	0.16 (0.04)	0.4110
Intraoperative hydromorphone (mg)	2.2 (0.6)	2.0 (0.5)	0.1060
Hydromorphone after 24 h (mg)	7.2 (4.0)	7.3 (3.0)	0.9396
Hydromorphone after 48 h (mg)	10.2 (4.5)	10.3 (4.4)	0.9276
Hydromorphone after 72 h (mg)	11.6 (5.2)	12.1 (5.8)	0.6104
Minimal pain (NRS 0–10), 24 h	1.84 (1.0)	2.4 (1.2)	0.0451
Minimal pain (NRS 0–10), 48 h	0.9 (1.0)	1.6 (1.1)	0.0101
Minimal pain (NRS 0–10), 72 h	0.3 (0.5)	0.6 (0.8)	0.1111
Maximum pain (NRS 0–10), 24 h	3.2 (1.4)	4.2 (1.4)	0.0081
Maximum pain (NRS 0–10), 48 h	2.0 (1.5)	3.2 (1.6)	0.0029
Maximum pain (NRS 0–10), 72 h	1.0 (1.2)	1.4 (1.1)	0.1248
Pain sensitivity threshold (logarithm of all the mean of all four measurement points)	2.3 (0.3)	2.2 (0.4)	0.0491
Distance of hyperalgesia (cm)	5.9 (3.3)	8.5 (4.6)	0.0060
Mechanical pain sensitivity for first pinprick application (0–10)	1.6 (1.5)	2.4 (1.8)	0.0425
Wind-up ratio	2.2 (1.5)	3.1 (1.5)	0.0389
Satisfaction with pain management, 72 h (0–10; higher is better)	9.3 (0.9)	8.0 (1.9)	0.0001
Satisfaction with pain management, 3 months (0–10; higher is better)	9.6 (0.7)	8.8 (0.7)	0.0302
Pain Disability Index 3 months postoperative	2.6 (5.2)	16.4 (9.5)	0.0046

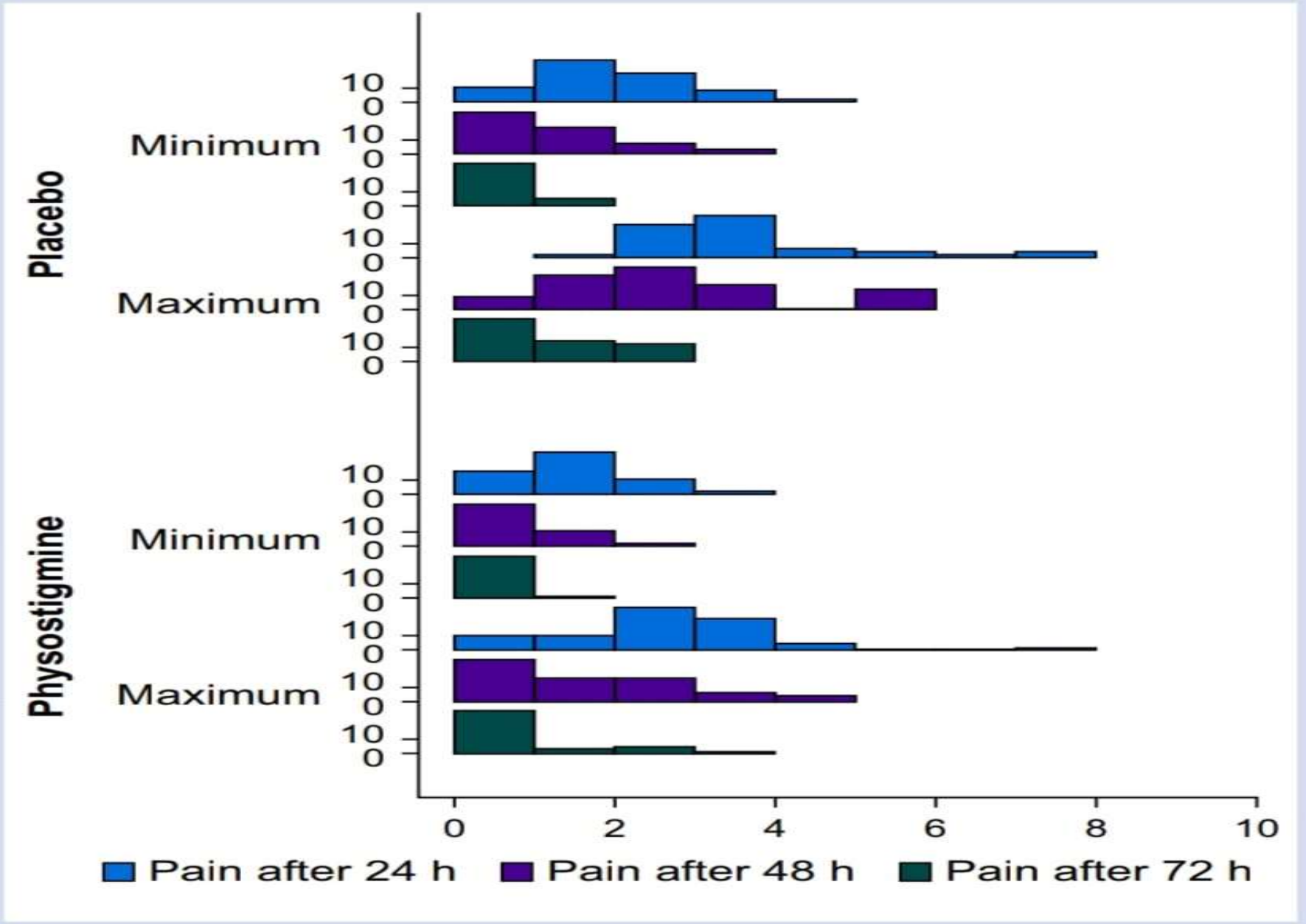


Fig 2. Histogram of pain values by time point and group.

❖ Long-Term Pain:

- Three months after surgery, those who received physostigmine had **lower Pain Disability Index (PDI) scores**, indicating less persistent pain.

- However, since only some patients completed this follow-up, more studies are needed to confirm this finding.

❖ Patient Satisfaction:

- **Satisfaction with pain management** was higher in the physostigmine group, both immediately after the study and at the 3-month follow-up.

Study Limitations:

- **12.7% of subjects dropped out**, mainly because of the 24-hour stay in the recovery room, which some found inconvenient.

- The dropout rate due to nausea and vomiting was low in both groups and did not differ significantly.

- These results suggest physostigmine could help reduce pain sensitivity and possibly lower long-term pain, though more research is needed to fully understand its effects.

Side Effects of Physostigmine

- **Rare Side Effects** (when used as an antidote for anticholinergic effects):
  - **Vomiting** (2.1%)
  - **Corrected QT prolongation** (1%) — a change in heart rhythm
  - **Seizures** (1%)

- In a previous study, **nausea and vomiting** were common, especially in the first 2 hours after surgery.

- In this study, the only side effect was **postoperative nausea and vomiting (PONV)**.

Recommendations:

- Since side effects were minimal, **shorter monitoring** might be possible during physostigmine treatment, which could simplify future studies and clinical use.

- Using **anti-nausea medication** (anti-emetics) could also be helpful when giving physostigmine to prevent nausea and vomiting.

Limitations

- **Recruitment Issues:** Midway, urologists switched to laparoscopic surgery (an exclusion criterion), slowing recruitment and extending the timeline.
- **3-Month Follow-Up:** Conducted by phone instead of in-person, limiting detailed pain assessments.
- **Unclear Optimal Dose/Duration:** The best dose and duration of physostigmine for pain relief remain unknown.
- A single dose may be effective but likely provides only short-term relief (around 30 minutes).

CONCLUSION

- **No reduction in opioid use** was found with adding physostigmine to standard pain therapy (given as 0.5 mg/h for 24 hours).

- However, physostigmine did provide **significant pain relief**, improved **patient satisfaction**, and reduced **pain sensitivity** (hyperalgesia).

- More research is needed to find the **best dose** of physostigmine and to better understand and manage any side effects.

Acknowledgements

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Declarations of interest

The authors declare that they have no conflicts of interest.

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CRITICAL APPRAISAL

Title

"Perioperative use of physostigmine to reduce opioid consumption and peri-incisional hyperalgesia: a randomised controlled trial"

Suggested Title

"Perioperative use of physostigmine to reduce opioid consumption and peri-incisional hyperalgesia: a placebo-controlled,randomized trial."

CRITICAL APPRAISAL BASED ON CONSORT CHECKLIST

Sr no.	Title	Justified	Not Justified	Comments
1.	Title & Abstract	✓		Study can be identified as randomized trail from the title Structured summary of trial design, methods, results, and conclusions are given
Introduction				
2a	Background	✓		Study Explain the scientific background and rationale for the trial
2b	Objectives	✓		Specific objectives are given

Methods

Trial design

Sr no.	Title	Justified	Not Justified	Comments
3a	Description of trial design (such as parallel, factorial) including allocation ratio	✓		Trial design is mentioned. Allocation ratio is mentioned
3b	Important changes to methods after trial commencement (such as eligibility criteria)	✓		No changes in methods after trial commencement

Participants				
Sr no.	**Title**	**Justified**	**Not Justified**	**Comments**
4a	Eligibility criteria for participants	✓		Inclusion and exclusion criteria are mentioned
4b	Settings & locations where the data were collected	✓		study was conducted at the Medical University of Graz, Graz, Austria.
Intervention				
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	✓		The medication was administered via a CADD®-Solis infusion pump at 4 ml/h (0.5 mg/h physostigmine), starting after anesthesia induction and stopping after 24 hours.

Outcomes & Sample size

Sr no	Title	Justified	Not Justified	Comments
6	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	✓		The primary and secondary outcomes are described, including when and how they will be assessed.
7a	How sample size was determined	✓		Based on pilot data showing a 30% difference in 24-hour hydromorphone use, a sample size of 110 was calculated to achieve 80% power at a 5% significance level, accounting for a 5-10% dropout rate
7b	When applicable, explanation of any interim analyses and stopping guidelines	----	----	NA

Randomisation

Sr no.	Title	Justified	Not Justified	Comments
8a	Method used to generate the random allocation sequence	✓		The randomisation scheme was generated by using Randomization.com (http://www.randomization.com).
8b	Type of randomization		✓	Not mentioned
9	Mechanism used to implement the random allocation sequence		✓	Not mentioned

Sr no	Title	Justified	Not Justified	Comments
10	Implementation		✓	Information regarding investigator who generated the random allocation sequence, who enrolled participants and who assigned intervention is not given.
11	Blinding	✓		Double blinded study
12	Statistical methods	✓		Data were analysed using ANOVA, Student's t-test, and WilcoxoneManneWhitney or Fisher's exact test, as appropriate. Categorical data were analysed by c2 test. The analysis was performed with NCSS version 12.0.13

Result

Sr no	Title	Justified	Not Justified	Comments
13	Participants flow	✓		Information regarding numbers of participants who were randomly assigned, received treatment and analysed for the primary outcome is given but given in methods.
14	Recruitment	✓		Dates defining the periods of recruitment is mentioned from June 2013 to October 2018 but given in methods.
15	Baseline data	✓		Baseline data is given but in outcome part.

Sr no.	Title	Justified	Not Justified	Comments
16	Outcomes & estimation		✓	The study has presented the results for each outcome, but it is missing information regarding confidence intervals. Study results are also given in discussion part.
		Discussion		
17	Limitations	✓		Trial limitations are mentioned
18	Generalisability	✓		The small participant size reduces the generalisability of findings.
19	Interpretation	✓		Study has provided an interpretation of the results in the context of existing evidence, considering both benefits and harms.

Other Information

Sr no.	Title	Justified	Not Justified	Comments
20	Registration	✓		Registration number and name of trial registry is mentioned
21	Protocol		✓	Information regarding study protocol is not mentioned.
22	Funding	✓		This study was funded by: Institutional and departmental resources and the Styrian Provincial Government (16.A-99/2012e1).


Thank You!