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Clinical Investigation

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

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Abstract

Background: Several studies have shown that cholinergic mechanisms play a pivotal role in the anti-nociceptive system by acting synergistically with morphine and reducing postoperative opioid consumption. In addition, the anti-cholinesterase drug physostigmine that increases synaptic acetylcholine concentrations has anti-inflammatory effects.
Methods: In this randomised placebo-controlled trial including 110 patients undergoing nephrectomy, we evaluated the effects of intraoperative physostigmine 0.5 mg h^{-1} i.v. for 24 h on opioid consumption, hyperalgesia, pain scores, and satisfaction with pain control.
Results: Physostigmine infusion did not affect opioid consumption compared with placebo. However, the mechanical pain threshold was significantly higher (2.3 [SD 0.3]) *vs* 2.2 [0.4]; P=0.0491), and the distance from the suture line of hyperalgesia (5.9 [3.3] *vs* 8.5 [4.6]; P=0.006), wind-up ratios (2.2 [1.5] *vs* 3.1 [1.5]; P=0.0389), and minimum and maximum postoperative pain scores at 24 h (minimum 1.8 [1.0] *vs* 2.4 [1.2]; P=0.0451; and maximum 3.2 [1.4] *vs* 4.2 [1.4]; P=0.0081) and 48 h (minimum 0.9 [1.0] *vs* 1.6 [1.1]; P=0.0101; and maximum 2.0 [1.5] *vs* 3.2 [1.6]; P=0.0029) were lower in the study group. Pain Disability Index was lower and satisfaction with pain control was higher after 3 months in the physostigmine group.
Conclusions: In contrast to previous trials, physostigmine did not reduce opioid consumption. As pain thresholds were higher and hyperalgesia and wind-up lower in the physostigmine group, we conclude that physostigmine has anti-hyperalgesic effects and attenuates sensitisation processes. Intraoperative physostigmine may be a useful and safe addition to conventional postoperative pain control.
Clinical trial registration: EudraCT number 2012-000130-19.

Keywords: multimodal analgesia; patient-controlled analgesia; physostigmine; preventive analgesia; quantitative sensory testing

Editor's key points

- Studies have shown that cholinergic mechanisms may act synergistically with morphine to reduce postoperative opioid consumption.
- In this RCT in patients undergoing open nephrectomy, intraoperative infusion of physostigmine in addition to conventional pain therapy did not reduce opioid consumption.
- However, physostigmine did reduce hyperalgesia, wind-up, and pain scores, and increased patient satisfaction with pain control.
- Physostigmine has postoperative anti-hyperalgesic effects, attenuates sensitisation processes, and may be a useful and safe addition to conventional postoperative pain control.

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Physostigmine, a tertiary amine cholinesterase inhibitor that crosses the blood–brain barrier, has been reported to have analgesic properties.[1,2] It increases opioid action after systemic administration[3] and acts synergistically with morphine and clonidine.[4] Several experimental and clinical studies have shown that cholinergic mechanisms play a pivotal role in the anti-nociceptive system. Beilin and colleagues[5] were able to achieve a 42% reduction in morphine dosing with a continuous physostigmine infusion over the first 24 h postoperatively. Compared with the control group, the physostigmine group showed a reduced level of pro-inflammatory cytokines. Increased parasympathetic activity is known to have anti-inflammatory effects,[6] which has been shown to impact neural changes attributable to chronic pain after nerve damage.[7] Beilin and Yardeni[8] have linked increased levels of pro-inflammatory cytokines to postoperative hyperalgesia.

Furthermore, experimental animal data indicate that nicotinic receptors play a role in the anti-nociceptive effects of cholinesterase inhibitors at the spinal level.[9] Concerning direct analgesic effects involving muscarinergic receptors, M_2 muscarinic receptors, and to a lesser extent M_4 receptors are involved at spinal and supraspinal levels.[10] Wehrfritz and colleagues[11] showed anti-hyperalgesic properties of physostigmine in a human pain model. In their study, they induced secondary mechanical hyperalgesia in healthy volunteers by transcutaneous electrical stimulation and evaluated the effect of a single dose of physostigmine. Compared with baseline values, physostigmine resulted in a 47% reduction in the area of mechanical hyperalgesia. These results, however, have not yet been confirmed in a clinical setting.

Hyperalgesia can be described as primary or secondary. Primary hyperalgesia is present at the site of incision and is caused by sensitisation of peripheral nerve endings (peripheral sensitisation). Secondary hyperalgesia develops in areas adjacent or remote to the site of incision, is related to changes in the processing of sensory information in the CNS, and is hence part of central sensitisation.[12] Postoperative hyperalgesia might be an indicator of central sensitisation[13] and has been linked to persistent postoperative pain.[14]

Wind-up is induced by repeated stimulation of primary afferent C-fibres and leads to an increased firing rate of postsynaptic neurones. This behaviour is also seen when no peripheral sensitisation is present, and is therefore not regarded as a cause of primary hyperalgesia. It has been postulated that enhanced wind-up may be a marker for increased central responsiveness conducted by C-fibres.[12]

Preventive analgesia is a previously described method to enhance pain management in the postoperative period. The effect of preventive analgesia is present when a specific intervention decreases pain or analgesic consumption relative to a comparison group even beyond the duration of the applied medication.[15] The duration of effect is proposed to last beyond 5.5 times the half-life of the applied drug to be regarded as preventive.[16] Therefore, this concept strives to minimise peripheral and central sensitisation attributable to noxious stimuli.[15]

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: 24–349 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 anaesthesiologists. After eligibility for inclusion was assessed, members of the study team informed potential subjects and obtained written informed consent. Inclusion criteria were age ≥18 yr, body weight ≥50 kg, ASA physical status 1–3, and basic eligibility for patient-controlled analgesia (PCA) in terms of language and cognition. Exclusion criteria included contraindications for physostigmine (bronchial asthma/severe chronic obstructive pulmonary disease); iritis; ileus; 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 insult; known allergy, hypersensitivity, or contraindications to hydromorphone or physostigmine; history of ethanol or drug abuse; pregnancy; and laparoscopic approach for surgery. Patients with a history of pain disorders or patients taking chronic pain medication were also excluded. The German version of the Pain Disability Index (PDI) was used to assess pre-existing disabilities attributable to pain preoperatively.[17] After written consent was given, participants were instructed in the use of PCA.

This article was prepared adhering to the Consolidated Standards of Reporting Trials checklist.[18]

Randomisation, blinding, and study medication

The randomisation scheme was generated by using Randomization.com (http://www.randomization.com). The allocation ratio was 1:1. The list was kept in a locked cabinet that could only be opened with a dedicated chip card by nursing staff not further involved in the study or patient care. These nurses prepared the study medication in a closed, unobserved room according to the randomisation list.

The study medication consisted of physostigmine 0.125 mg ml^{-1} (Dr. Franz Köhler Chemie GmbH, Bensheim, Germany) or NaCl 0.9%. The i.v. study medication was delivered to the attending anaesthetist as an infusion pump (CADD®-Solis; Smiths Medical, Minneapolis, MN, USA) with a programmed continuous infusion rate of 4 ml h^{-1} (physostigmine 0.5 mg h^{-1}) and no bolus function. The infusion was started after the induction of anaesthesia but before the incision, and was stopped after 24 h. The pump was labelled as 'PHANOS study medication' and marked with the blinded identification number of the patient. All persons treating or examining the patients were blinded regarding group allocation.

Anaesthesia, surgery, and postoperative management

The patients received midazolam 7.5 mg orally 60–90 min before induction of anaesthesia. General anaesthesia was induced with remifentanil 0.1–0.3 μg kg^{-1} min^{-1} and propofol

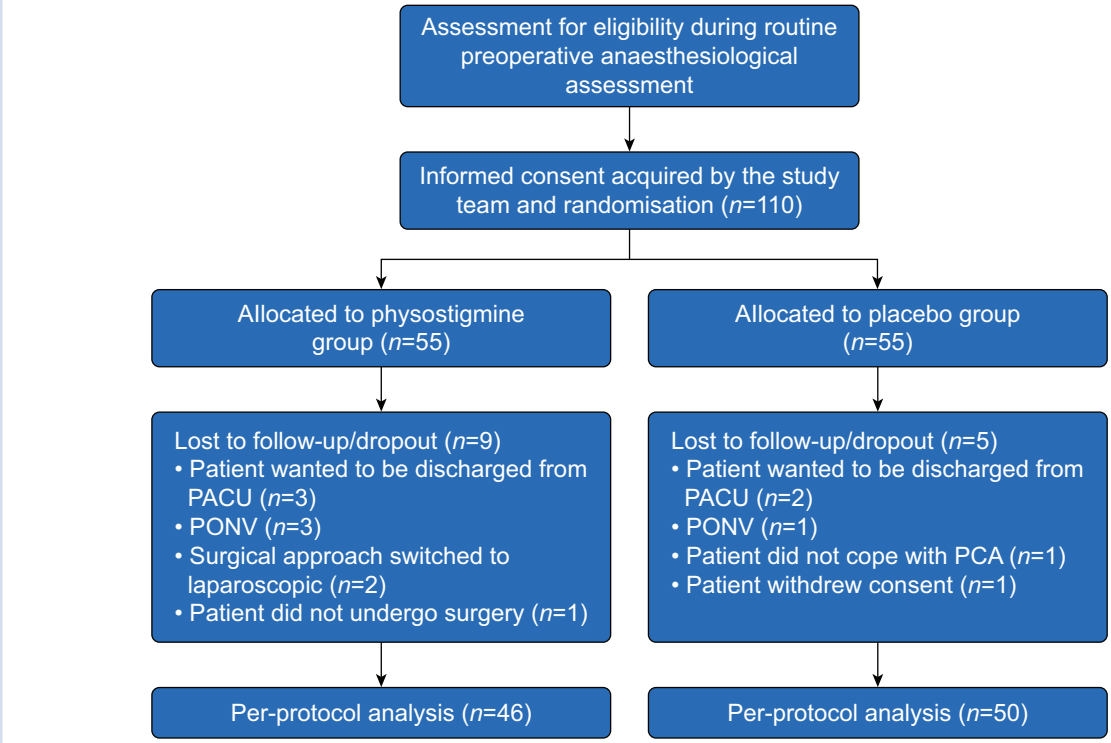

Fig 1. Flow chart. PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting.

2–5 mg kg^{-1}, and maintained with sevoflurane (0.7–1.0 minimum alveolar concentration) and remifentanil 0.1–0.3 μg kg^{-1} min^{-1} i.v.

Ondansetron 4 mg was applied ~30 min before the end of surgery. As a long-acting analgesic, hydromorphone 0.02–0.03 mg kg^{-1} i.v. was administered 20–30 min before skin closure.

Postoperatively, metamizole 1 g in NaCl 0.9%, 100 ml was administered every 6 h. An i.v. PCA pump (CADD-Solis) with hydromorphone (20 mg in NaCl 0.9%, 100 ml) was applied with the following settings: bolus dose 0.2 mg, no continuous infusion rate, lockout time 10 min, maximum five boli per hour, and 4 h maximum 4 mg. The PCA was administered for 72 h postoperatively. No additional medication was used to treat pain throughout the study. All subjects remained in the PACU under monitoring for 24 h postoperatively.

Outcomes

These methods have been reported from our centre.[19–21] Total opioid consumption was defined as the sum of intraoperative opioid use, opioid use in the PACU, and opioid administration *via* PCA postoperatively. The primary outcome was defined as opioid consumption at 24 h postoperatively.

Satisfaction with pain management was assessed with a numeric rating scale from 0 (worst) to 10 (best) at 72 h. At the end of the study, the subjects were asked if they consent to being interviewed by telephone 3 months postoperatively. This follow-up was conducted as a telephone interview, and satisfaction with pain management and the PDI were assessed once more.

Assessment of mechanical hyperalgesia

Personnel involved in testing were blinded to the group allocation of the subjects.

Hyperalgesia was defined as a secondary outcome parameter and was examined 48 h postoperatively. Mechanical hyperalgesia was assessed at four points, each 5 cm proximal, caudal, ventral, and dorsal of the corresponding edge of the suture. Von Frey filaments (OptiHair$_2$ set; Marstock Nervtest, Schriesheim, Germany) were applied with calibrated forces between 0.25 and 512 mN according to the methods of limits.[22] The patients were instructed to categorise the stimuli as sharp or blunt. When a stimulus was described as sharp, the pressure of the corresponding von Frey filament was defined as the threshold for mechanical pain sensitivity. After logarithmic transformation, a mean value of single measurements was calculated.

Afterwards, von Frey filaments with a force of 128 mN were used to quantify the distance of hyperalgesia.[11,13,23,24] In four radial lines from the suture line (cranial and caudal from the centre of the wound, and medial and dorsal from the edges of the wound), the von Frey filament was applied every 5 mm to determine the border of the hyperalgesic area.[20,21] The mean distance from the suture line was then calculated.

Wind-up was measured with a calibrated pinprick with a force of 256 mN and a flat contact area 0.2 mm in diameter (PinPrick stimulator set; MRC Systems, Heidelberg, Germany). The patients were asked to rate the amount of pain with the aforementioned numeric rating scale from 0 (no pain) to 10 (worst pain) when the pinprick was applied to the medial part of the flanks. Afterwards, wind-up was induced by applying

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

the pinprick once per second 10 consecutive times in an area of 1 cm^2. The patients were then asked to rate the pain of the 10th application of the pinprick. A ratio of wind-up was calculated by dividing the first single pain measure by the pain value of the 10th application during the wind-up.

Sample size calculation and statistical analysis

Our *a priori* sample size calculation was based on a pilot study,[25] in which mean 24 h hydromorphone consumption was 0.05 *vs* 0.07 [SD 0.035] mg kg^{-1} in the physostigmine group compared with the placebo group. Based on these data that suggest a 30% difference between groups and expecting a dropout rate of 5–10%, a sample of 110 subjects in total was deemed sufficient for a power of 80% at a significance level of 0.05. As nausea and vomiting have been established as relevant side-effects, we decided to lower the applied dosage of physostigmine to 0.5 mg h^{-1}.

Data were analysed using ANOVA, Student's *t*-test, and Wilcoxon–Mann–Whitney or Fisher's exact test, as appropriate. Categorical data were analysed by χ^2 test. The analysis was performed with NCSS version 12.0.13 (NCSS, LLC, Kaysville, UT, USA).

Results

A total of 110 subjects with an allocation ratio of 1:1 were included. Fourteen subjects did not finish the study (nine physostigmine and five control; P=0.25248; Fig. 1) for the following reasons: quit the study because they wanted to be discharged from the PACU (three physostigmine and two control; P=0.59815), postoperative nausea and vomiting (PONV) (and consecutively withdrew consent) (three physostigmine and one control; P=0.28839), surgery switched to a laparoscopic procedure (two physostigmine), subject did not undergo surgery (one physostigmine), subject did not tolerate PCA (one control), and subject withdrew consent for other reasons (one control). Subject characteristics did not differ between groups (Table 1).

The end of trial was reached in October 2018. Analysis was conducted as per protocol. The main study results are presented in Table 2. A histogram of pain values is presented in Fig. 2.

Discussion

In this clinical study, we examined whether physostigmine can enhance opioid-based analgesia, reduce opioid consumption, and dampen the effects of hyperalgesia. We could not detect an opioid-sparing effect. This finding was surprising, as our pilot study[25] and that of Beilin and colleagues[5] showed reduced opioid consumption when physostigmine was used. Physostigmine dosage was halved (0.5 mg h^{-1} compared with 1 mg h^{-1} in the pilot study[25]) to reduce side-effects and potentially increase patient safety. As there are no available data on optimal dosage, the infusion regimen used might have fallen short of the threshold to induce an opioid-sparing effect. The physostigmine group had significantly lower pain values both at 24 and 48 h postoperatively, although the physostigmine infusion was applied only for the first 24 h. As the half-life of physostigmine is in the range of minutes and the duration of clinical action less than 1 h, this effect can be attributed to preventive (or pre-emptive)

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 (μg 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

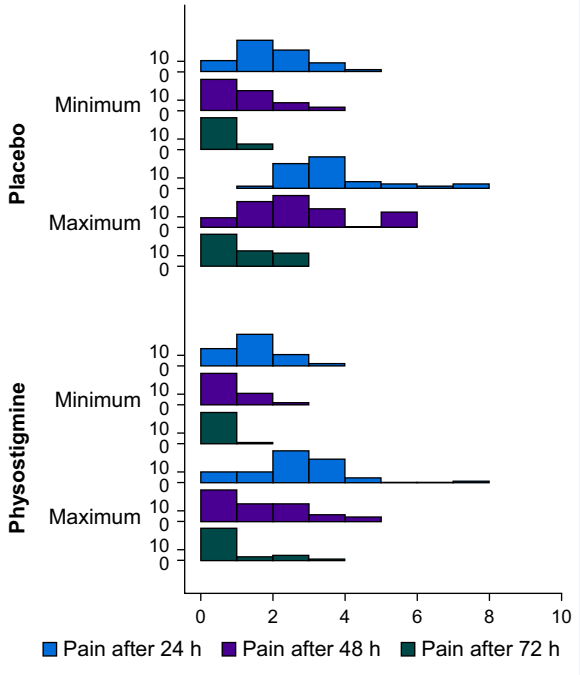

Fig 2. Histogram of pain values by time point and group.

analgesia.[26,27] After 72 h, there was no difference in either group. This could be attributed to the fact that, at this time, pain was well controlled in both study arms, which is usually also the case in clinical practice, as postoperative pain expectedly lessens over time (Fig. 2).

The use of physostigmine decreased mechanical pain sensitivity, hyperalgesia, and wind-up ratios. Our study was, by design, unable to differentiate between central and peripheral aspects of sensitisation, but in light of previous studies,[5,6,8,13] it is conceivable that both mechanisms play a role in postoperative pain. Therefore, we conclude that physostigmine attenuates the sensitisation processes. Further research is warranted to evaluate and uncover its precise role in sensitisation processes.

The PDI 3 months after surgery was significantly lower in the study group. Our data suggest that physostigmine might be able to reduce the incidence of persistent postoperative pain. The small sample size should be considered when interpreting these findings, as not all subjects consented to being contacted by telephone 3 months after surgery. Further investigations to confirm this effect are needed.

Satisfaction with pain management was higher in the study group immediately after the completion of the study and in the 3 month follow-up questionnaire. When interpreting our results, the high dropout rate of 12.7% should be considered. Most often, dropout was caused by the prolonged observation period of 24 h in the PACU, which was unsatisfactory for many subjects. This observation is affirmed by the fact that five subjects quit the study to be released from the recovery room before the planned discharge time. Dropout attributable to nausea and vomiting was low in both groups with no significant difference. Arens and colleagues[28] conducted a retrospective cohort study over the span of 10 yr to evaluate possible side-effects of physostigmine when used as an anticholinergic antidote. Side-effects were rare and consisted of emesis (2.1%), corrected QT prolongation (1%), and seizures (1%). The most significant side-effects that occurred in the study by Beilin and colleagues[5] were nausea and vomiting, especially in the first 2 h postoperatively.

As side-effects in our study were limited to PONV and have been described as rare previously, it might be feasible to shorten the duration of monitoring whilst physostigmine is applied to make future studies and the clinical application easier to conduct. Likewise, anti-emetic prophylaxis seems reasonable when administering physostigmine.

Limitations

After the initial steady recruitment and inclusion of subjects, the surgical technique that was preferably used by urologists of our centre shifted towards the laparoscopic approach, which was listed as an exclusion criterion for this study. Recruitment has, therefore, become more complicated and led to prolongation of the study.

When designing the study, we were doubtful that a 3 month follow-up would lead to satisfactory levels of participation and, consequently, to a small sample size. Therefore, the 3 month follow-up was carried out as a telephone interview. It would have been interesting to examine the patients after 3 months, including assessment of primary and secondary hyperalgesia instead of the telephonic assessment.

Even though our data show a beneficial role of physostigmine for postoperative pain, it is still unclear which dose and duration of administration are most effective. Theoretically, if a single intraoperative bolus is as effective as a continued infusion, the need for prolonged observation would also be obsolete. However, findings from Petersson and colleagues[3] showed that the duration of action for a single bolus of physostigmine to decrease pain in a 'non-preventive analgesia' setting lasted about 30 min.

Conclusion

Although we were unable to show an opioid-sparing effect from the addition of physostigmine to conventional pain therapy as a continuous infusion of 0.5 mg h^{-1} for 24 h, we showed significant benefits on pain values and satisfaction with pain therapy. We were also able to show reduced hyperalgesia and sensitisation processes.

Further studies are needed to determine the most appropriate dosage of physostigmine and to evaluate the resulting occurrence and therapy of side-effects. Those future findings might help define precise indications, a clinically feasible modality of application, and the need for observation when used in clinical practice.

Authors' contributions

Study design: GR-S, SF, HB-C
Patient recruitment: CK, GR-S, CD, KL-I, SF
Data collection: CK, LS, NS
Data analysis: HB-C
Data interpretation: CK
Writing of paper: CK
Revising of paper: GR-S, CD, KL-I, SF, LS, NS, SF, HB-C

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Declarations of interest

The authors declare that they have no conflicts of interest.

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References

1. Romano JA, Shih TM. Cholinergic mechanisms of analgesia produced by physostigmine, morphine and cold water swimming. *Neuropharmacology* 1983; **22**: 827–33
2. Yaksh TL, Dirksen R, Harty GJ. Antinociceptive effects of intrathecally injected cholinomimetic drugs in the rat and cat. *Eur J Pharmacol* 1985; **117**: 81–8
3. Petersson J, Gordh TE, Hartvig P, Wiklund L. A double-blind trial of the analgesic properties of physostigmine in postoperative patients. *Acta Anaesthesiol Scand* 1986; **30**: 283–8
4. Abram SE, Winne RP. Intrathecal acetyl cholinesterase inhibitors produce analgesia that is synergistic with morphine and clonidine in rats. *Anesth Analg* 1995; **81**: 501–7
5. Beilin B, Bessler H, Papismedov L, Weinstock M, Shavit Y. Continuous physostigmine combined with morphine-based patient-controlled analgesia in the postoperative period. *Acta Anaesthesiol Scand* 2005; **49**: 78–84
6. Tracey KJ. The inflammatory reflex. *Nature* 2002; **420**: 853–9
7. Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. *Physiol Rev* 2002; **82**: 981–1011
8. Beilin B, Yardeni I. Effects of preemptive analgesia on pain and cytokine production in the postoperative period. *Anesthesiology* 2003; **98**: 151–5
9. Yoon MH, Choi JI, Jeong SW. Antinociception of intrathecal cholinesterase inhibitors and cholinergic receptors in rats. *Acta Anaesthesiol Scand* 2003; **47**: 1079–84
10. Wess J, Duttaroy A, Gomeza J, et al. Muscarinic receptor subtypes mediating central and peripheral antinociception studied with muscarinic receptor knockout mice: a review. *Life Sci* 2003; **72**: 2047–54
11. Wehrfritz AP, Ihmsen H, Schmidt S, et al. Interaction of physostigmine and alfentanil in a human pain model. *Br J Anaesth* 2010; **104**: 359–68
12. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev* 2009; **89**: 707–58
13. Dirks J, Møiniche S, Hilsted K-L, Dahl JB. Mechanisms of postoperative pain: clinical indications for a contribution of central neuronal sensitization. *Anesthesiology* 2002; **97**: 1591–6
14. Wilder-Smith OH, Schreyer T, Scheffer GJ, Arendt-Nielsen L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J Pain Palliat Care Pharmacother* 2010; **24**: 119–28
15. Katz J, McCartney CJL. Current status of preemptive analgesia. *Curr Opin Anaesthesiol* 2002; **15**: 435–41
16. Katz J, Clarke H, Seltzer Z. Review article: preventive analgesia: quo vadimus? *Anesth Analg* 2011; **113**: 1242–53
17. Tait RC, Pollard CA, Margolis RB, Duckro PN, Krause SJ. The Pain Disability Index: psychometric and validity data. *Arch Phys Med Rehabil* 1987; **68**: 438–41
18. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c869
19. Dahaba AA, Mueller G, Mattiassich G, et al. Effect of somatostatin analogue octreotide on pain relief after major abdominal surgery. *Eur J Pain* 2009; **13**: 861–4
20. Bornemann-Cimenti H, Lederer AJ, Wejbora M, et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. *Br J Anaesth* 2012; **108**: 845–9
21. Bornemann-Cimenti H, Wejbora M, Michaeli K, Edler A, Sandner-Kiesling A. The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial. *Minerva Anestesiol* 2016; **82**: 1069–76
22. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; **123**: 231–43
23. Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. *Pain* 2000; **86**: 19–24
24. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**: 147–55
25. Farzi S, Bornemann H, Dorn C, Rumpold-Seitlinger G. PHANOS—physostigmine and postoperative opioid consumption: 14AP2-11. *Eur J Anaesthesiol* 2012; **29**: 197
26. Urman R, Vadivelu N, Mitra S, Kodumudi V, Kaye A, Schermer E. Preventive analgesia for postoperative pain control: a broader concept. *Local Reg Anesth* 2014; **7**: 17–22
27. Hartvig P, Wiklund L, Lindström B. Pharmacokinetics of physostigmine after intravenous, intramuscular and subcutaneous administration in surgical patients. *Acta Anaesthesiol Scand* 1986; **30**: 177–82
28. Arens AM, Shah K, Al-Abri S, Olson KR, Kearney T. Safety and effectiveness of physostigmine: a 10-year retrospective review. *Clin Toxicol (Phila)* 2018; **56**: 101–7

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