TEMPLATE FOR RESEARCH PROPOSAL
Faculty of Medicine, Universiti Malaya

---

a) Project Title

Patient-Controlled Analgesia (PCA) with Ketamine–Morphine (PCA KetaMorph) vs PCA Morphine for Postoperative Analgesia in Idiopathic Scoliosis Surgery – A Randomized Controlled Trial (PCA KetaMorph trial)

b) Team Composition

Principal Investigator: Siti Nadzrah Binti Yunus, Senior Lecturer (Dr.), Anaesthesiology

Co-Researchers: *Name, Designation, Department*

1. Mohd Shahnaz Bin Hasan, Consultant Anaesthesiologist (Professor), Anaesthesiology
2. Muhammad Faeez bin Mohd Yusoh, Medical Officer (Dr.), Anaesthesiology
3. Nur Ainina Binti Zulkeplee, Lecturer (Dr.), Anaesthesiology
4.
5.

c) Executive Summary (less than 300 words)

Tip: Executive summary should be written succinctly in paragraphs format. It should include information regarding the problem statement, objectives, research methodology, expected output/outcomes, and significance/impact of research output

Posterior spinal fusion (PSF) is the definitive surgical treatment for patients with scoliosis. However, the procedure involves extensive tissue dissection, resulting in significant postoperative pain. Although patient-controlled analgesia (PCA) with intravenous morphine remains the current standard, the large doses required are frequently associated with side effects such as nausea, vomiting, pruritus, and sedation [4-6]. These complications delay mobilisation, prolong hospital stay, increase healthcare costs, and may contribute to opioid tolerance, undermining effective pain control.

Enhanced Recovery After Surgery (ERAS) protocols strongly promote multimodal analgesia, which combines opioid and non-opioid agents to achieve synergistic pain relief while minimising opioid exposure. This strategy has been shown to reduce side effects, improve recovery, shorten hospital stay, and lower the risk of opioid-related tolerance, hyperalgesia, and potential long-term dependence. Despite these advantages, evidence for the use of ketamine–morphine PCA in scoliosis surgery remains limited, and subanaesthetic ketamine—though effective intraoperatively as an opioid-sparing agent—remains underutilised in postoperative PCA regimens. Our previous study demonstrated that co-administration of subanaesthetic ketamine (0.5 mg/kg) at induction reduced postoperative pain sensitivity and hyperalgesia typically associated with high-dose remifentanil infusion, a strong opioid analgesic [13]. This finding underscores the potential role of ketamine as an opioid-sparing adjunct.

Building on this, we propose a single-centre, double-blind, randomised controlled trial in 114 idiopathic scoliosis patients undergoing elective PSF at University Malaya Medical Centre. Participants will be randomised to receive PCA containing ketamine–morphine (1 mg/mL + 1 mg/mL) or morphine (1 mg/mL) alone, with identical syringes to ensure allocation concealment. The primary endpoint is cumulative morphine consumption at 48 hours, while secondary outcomes include pain scores, opioid-related side effects, time to ambulation, and patient satisfaction.

This study aims to provide the first Malaysian evidence on an opioid-sparing PCA regimen, addressing national ERAS priorities and contributing to global opioid stewardship.

d) Research Background and Rationale

Tip: Introduce the problem at hand including its current burden/challenges, and highlight the need(s) for the proposal. Provide a focused literature review with references and highlight current gaps as well as scientific rationale for the proposal. State concretely the unique features or the novelty of your research proposal. Provide examples of your team's track record in the field or previous/ongoing work leading to this proposal (e.g., preliminary data), if available.

Posterior spinal fusion (PSF) is a surgical procedure and the only effective medical treatment for severe idiopathic scoliosis, the most common structural spinal deformity. This condition primarily affects adolescents and is characterized by abnormal spinal curvatures greater than 50 degrees.

Due to the extensive nature of the surgery, PSF is recognized as one of the most painful pediatric operations. Prospective studies report numeric rating scores (NRS) ≥7/10 in up to 80% of patients during the first 24 hours, and inadequately treated pain can lead to chronic postsurgical pain in as many as 40% of cases [4–6]. This severe pain burden necessitates prolonged monitoring and nursing, thereby increasing hospital length of stay (LOS).

Patient-controlled analgesia (PCA) with intravenous morphine is the standard approach for managing postoperative pain. It allows patients to decide when and how much morphine to receive through an electronic infusion device, giving them direct control over their pain relief. PCA is widely used because it is safe and effective, providing on-demand analgesia with preset doses and lockout intervals tailored to individual needs, without nurse-mediated delays. These safety features ensure adequate pain control while preventing overdose, making PCA a reliable and patient-centered method of postoperative pain management.

Our previous study in adolescent idiopathic scoliosis patients at University Malaya Medical Centre (UMMC) undergoing PSF demonstrated that wound pain trajectories in the first two postoperative weeks were substantial, with morphine consumption peaking at 12 hours postoperatively, confirming the necessity of PCA morphine in this cohort [7]. The high cumulative morphine doses required (30–60 mg in the first 48 h) drive dose- dependent nausea, vomiting, pruritus, urinary retention and, most importantly, respiratory depression [8]. Efforts to reduce opioid load with non-steroidal anti-inflammatory drugs risk impairing bony fusion, while gabapentinoids add dizziness without consistent opioid-sparing benefit in children [8]. Our previous study aimed at reducing opioid requirements and optimizing analgesia in scoliosis surgery, we investigated perioperative intravenous lignocaine infusion. While this approach was safe, it did not reduce postoperative morphine consumption [10].

Global opioid stewardship efforts focus on reducing opioid use while promoting safer, multimodal approaches to pain management. The aim is to reduce opioid-related harm such as misuse, dependence, and overdose while still providing effective pain management for patients who need it. The key principles therefore include rational prescribing by using the lowest effective dose for the shortest possible duration and multimodal analgesia by combining opioids with non-opioid medications to minimize opioid requirement. In surgery, including spine surgery, opioid stewardship means reducing unnecessary opioid exposure through strategies like PCA combinations (e.g., ketamine–morphine) or by using non-opioid medications like regional anesthesia.

More importantly, they run counter to the Ministry of Health’s opioid-stewardship agenda and the Enhanced Recovery After Surgery (ERAS) objectives, which prioritize safe opioid use, early ambulation, and shorter hospital stay.

Ketamine is a non-opioid medication that provides pain relief and anesthesia in a dose-dependent manner. It helps reduce the need for opioids because it works on different receptors than morphine, while still offering effective pain control. By combining ketamine with morphine in a PCA regimen, it is possible to achieve effective pain relief while lowering overall opioid use, thereby reducing side effects and supporting opioid stewardship goals.

Our previous research has focused on optimizing analgesia in scoliosis surgery. In a UMMC study examining intraoperative opioid exposure, we found that co-administration of subanesthetic ketamine (0.5 mg/kg) at induction was able to prevent undesirable postoperative hyperalgesia and increased pain sensitivity that are otherwise associated with high-dose remifentanil infusion [13]. This finding supports ketamine's role as an NMDA-receptor antagonist in reducing opioid-induced hyperalgesia and highlights its potential as an effective opioid-sparing adjunct.

Therefore, the present study will evaluate whether a ketamine–morphine PCA regimen (PCA KetaMorph) can achieve meaningful opioid-sparing effects while maintaining effective analgesia.

e) Objective(s) of the Research

Tip: Objectives should be Specific, Measurable, Achievable, Relevant, and Time-bound (SMART).

Primary objective

To determine whether adding ketamine to morphine patient-controlled analgesia (PCA) reduces cumulative morphine consumption during the first 48 hours after posterior spinal fusion compared with morphine PCA alone.

Secondary objectives

1. To compare patient-reported pain intensity (visual analogue scale) at 6, 12, 18, 24, 30, 36, 42 and 48 hours post-operatively between the two treatment groups.
2. To evaluate and compare the incidence of opioid-related adverse events (nausea, vomiting, pruritus, excessive sedation or respiratory depression) occurring within 48 hours of surgery.
3. To compare overall hospital length of stay, time to first flatus and time to first ambulation and the proportion of patients who report high satisfaction (Likert score ≥ 4 / 5) at discharge in each group.

Objective tier	Specific	Measurable	Achievable	Relevant	Time-bound
Primary	Effect of adding ketamine to PCA on total morphine usage.	Percentage reduction in PCA morphine dose (mg) in intervention arm.	Sample size (n = 113) with standardized effect size of 0.55.	Directly addresses opioid-reduction gap in PSF	PCA pump summary at 6-hour intervals up to 48 h post-surgery
Secondary (i)	Effect on pain score while reducing opioids	Mean VAS pain score difference between groups	Self-reported pain scores every 6 h; target ≥1-point reduction in intervention arm	Ensures opioid reduction does not worsen pain	Pain recorded at 6, 12, 18, 24, 30, 36, 42 & 48 h post-surgery

Secondary (ii)	Ketamine and opioid-related adverse events (AEs)	Incidence of nausea, vomiting, pruritus, sedation, desaturation, psychotropic effects	Daily AE assessment by researcher plus real-time reporting by ward nurses; aim: fewer opioid AEs and no ketamine psychotropic events	Confirms safety of ketamine adjunct	AEs monitored continuously to 48 h post-surgery
Secondary (iii)	Enhance recovery parameters	Mean time to first flatus, time to first ambulation and hospital length of stay (LOS)	LOS SD ≈ 1 day from previous studies	Improve time to first flatus, time to first ambulation and shorter LOS aligns with ERAS & cost-saving aims	Discharge date vs surgery date
Secondary (iv)	Improve patient satisfaction	Likert scale score on pain management experience	Previous surveys show > 70 % baseline satisfaction	Captures patient-centred benefit	Survey on day of discharge

f) Methodology

i. Description of Methodology including study design and research plans. Ideally, researchers should demonstrate how the research plans will help to achieve the proposed objectives and the feasibility of the project within the stipulated timeline.

Study design and setting

Prospective, single-centre, double-blind pilot randomised controlled trial at the University Malaya Medical Centre (UMMC).

Study participants

Inclusion criteria

1. Aged > 10 years old
2. Idiopathic scoliosis scheduled for single-stage posterior spinal fusion (PSF).
3. American Society of Anaesthesiologists (ASA) physical status I–II.

Exclusion criteria

1. Known hypersensitivity to morphine, ketamine or formulation excipients.
2. Hepatic dysfunction (ALT or AST > 2 × upper limit of normal).
3. Renal impairment (eGFR ≤ 60 mL min^{-1} 1·73 m^{-2}).
4. Uncontrolled asthma or severe restrictive lung disease.
5. Cardiac disease or clinically significant arrhythmia.
6. Epilepsy.
7. Intellectual disability precluding PCA use.
8. Chronic opioid therapy or pre-operative pain > 3 months.
9. Concomitant monoamine-oxidase inhibitor or tricyclic antidepressant therapy.
10. History of severe postoperative delirium.

Sample size

From our previous study (7), the mean ± SD for postoperative PCA morphine usage from 0 to 24 hours was 30.84 ± 22.33 mg. We hypothesized that by adding ketamine to PCA morphine postoperatively, morphine consumption at 24 hours would be reduced by 40% compared with the Usual Care Group. The mean after reduction was 18.5 mg, and the calculated G*Power effect size was d ≈ 0.55. The sample size for an independent t-test with 80% power and a two-tailed alpha of 0.05 was 102. Assuming a 10% dropout rate due to incomplete data, the final sample size was calculated as 102 / 0.9 = 113 (~114) patients, which is approximately 57 patients per group.

Study intervention, randomisation and blinding

Informed consent (and assent where appropriate) will be obtained pre-operatively. An independent statistician will generate a computerised sequence in blocks of four. Sequentially-numbered opaque sealed envelopes (SNOSE; n = 114) will assign patients 1:1 to:

- **Group A** Ketamine–Morphine PCA (K-M)
- **Group B** Morphine-only PCA (M)

An Acute Pain Service (APS) nurse not otherwise involved in the study will prepare identically labelled 30 mL polypropylene syringes (patient name + study ID only). Investigators, ward staff, surgeons and patients will remain blinded. In recovery, Group A receives a ketamine–morphine PCA solution (1 mg mL^{-1} + 1 mg mL^{-1}); Group B receives morphine alone (1 mg mL^{-1}). Both devices deliver a 1 mL bolus, enforce a five-minute lock-out and cap delivery at 20 mL per four hours, with no background infusion.

Anaesthetic protocol

All patients will fast for 6 hours, with clear fluids allowed up to 2 hours prior to surgery. No premedication will be given. TIVA will be administered via target-controlled infusion (TCI) of remifentanil at 3–5 ng/ml and TCI propofol at 3–5 µg/ml, guided by bispectral index readings of 40–60 throughout surgery. After establishing baseline neuromonitoring tracing and prior to skin incision, IV Dexmedetomidine infusion will be started at a rate of 0.4 mcg/kg/hr; this infusion of IV Dexmedetomidine will be discontinued 20 minutes before the end of surgery.

Mechanical ventilation will be set at 6–8 ml/kg tidal volume and 12–16 breaths per minute. Continuous monitoring will include invasive blood pressure, heart rate, oxygen saturation, and electrocardiogram.

Intraoperative analgesia will consist of IV ketamine 0.5 mg/kg administered prior to skin incision, IV paracetamol 15 mg/kg, and IV morphine 0.1 mg/kg given 45 minutes before the end of surgery. Local anaesthetic infiltration with bupivacaine 0.25% (maximum 2 mg/kg) will be performed by the surgeon prior to wound closure.

All patients will receive crystalloid infusion at 7 ml/kg/hour, with additional fluid boluses (5 ml/kg) if MAP falls below 65 mmHg, heart rate increases by 20%, or urine output decreases below 0.5 ml/kg/hour. Intraoperative cell salvage will be used. Allogeneic transfusion will be considered if haemoglobin falls below 8 g/dl despite completion of cell salvage blood reinfusion, adequate fluid resuscitation, and in patients with persistent haemodynamic instability.

Postoperatively, patients will be extubated and monitored in the recovery area.

In the recovery area, pain score will be assessed by the recovery nurse every 5 minutes. Rescue analgesia of IV Fentanyl 10 mcg/bolus will be administered if pain score ≥ 4. Patient-controlled analgesia (PCA) will be initiated once the patient has returned to the ward and continued for up to 48 hours.

Patients will also receive oral paracetamol 15 mg/kg every 6 hours and oral celecoxib 200 mg once or twice daily, in the ward.

Data collection

Demographics, surgical details and intra-operative drug doses are recorded on data collection sheet and transcribed to SPSS. Primary outcome data (cumulative morphine use) will be recorded from the PCA pumps at 24 and 48 hours. Secondary data comprise pain scores at 6, 12, 24, 36 and 48 hours; opioid-related adverse events (nausea, vomiting, pruritus, sedation ≤ RASS -1, or oxygen saturation < 92%); time to first ambulation; total length of stay; and discharge-day satisfaction (five- point Likert scale). Feasibility metrics include recruitment velocity, protocol deviations and accuracy of blinding guesses. All SPSS records will be kept in an electronic database with two-factor authentication; data are retained for seven years before anonymised archiving.

Statistical analysis

Analyses follow the intention-to-treat principle and use SPSS v26. Distribution normality is assessed with the Kolmogorov-Smirnov test. The primary outcome is compared by independent-samples t-test or, if non-parametric, the Mann–Whitney U test. Repeated pain scores are modelled with linear mixed-effects analysis. Incidences of adverse events are compared using χ^2 or Fisher's exact tests, and time to ambulation is evaluated with Kaplan–Meier curves and log-rank testing. Multiple imputation addresses missing data ≥ 5 %. A two-sided $p < 0{\cdot}05$ defines statistical significance.

Safety

The investigational ketamine dose (≤ 1 mg kg^{-1} day^{-1}) is beneath psychotomimetic thresholds and within formulary limits. Continuous cardiorespiratory and sedation monitoring is maintained for forty-eight hours. A Data and Safety Monitoring Board will review unblinded data and may suspend enrolment if drug-related serious adverse events occur or if psychotropic or haemodynamic serious events exceed 20%.

Ethics and registration

Approval from the University Malaya Research Ethics Committee, and the trial will be registered on ClinicalTrials.gov before the first participant is enrolled, in accord with the Declaration of Helsinki and ICH-GCP guidance.

ii. Graphical abstract / Flow chart of research activities

As appended

iii. Gantt chart of research activities

Year	2025					2026												2027												2028
Month	**A**	**S**	**O**	**N**	**D**	**J**	**F**	**M**	**A**	**M**	**J**	**Ju**	**A**	**S**	**O**	**N**	**D**	**J**	**F**	**M**	**A**	**M**	**J**	**Ju**	**A**	**S**	**O**	**N**	**D**	**J**
Proposal Preparation	X	X																												
Ethics application			X	X	X																									
Training of APS nurse						X																								
Data recruitment							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Data analysis																									X	X				
Manuscript preparation																											X	X		
Submit for publication																														X

iv. Milestones and Dates (according to the template below)

Milestone description	***Estimated Completion Date***	***Cumulative Project Completion Percentage (%)***
Protocol finalisation	*1 September 2025*	*5*
Ethics approval and clinical trial registration	*31 December 2025*	*10*
Pharmacy admixture validation and APS staff training	*30 January 2026*	*15*
First participant enrolled	*2 February 2026*	*20*
25% recruitment achieved (n=10)	*1Jun 2026*	*35*
50% recruitment achieved (n=20)	*1 August 2026*	*50*
75% recruitment achieved (n=30)	*1 December 2026*	*65*
Last patient complete 48 h follow up	*1 July 2027*	*80*
Data lock and statistical analysis completed	*1 October 2027*	*90*
Manuscript submitted to Q1 journal & abstract submitted to national meeting	*31 December 2027*	*95*
Final grant report	*30 january 2028*	*100*

g) Expected Output/Outcomes

i. Research Publications - number of publications and journal targets

ii. Human Capital Development - number of PhD and/or Masters students (including Clinical Masters students)

iii. Intellectual Property (IP)/ Patent

iv. Specific or Potential Applications

Category	**Target**
Publications	At least one (1) publication in a Q1/Q2-indexed journal as Corresponding Author.

Human Capital	1 Clinical Master student trained as co-author 1 Research assistant
IP	Not applicable
Clinical Application	Adoption of ketamine–morphine PCA protocol in UMMC Spine Unit

h) Impact Statement (less than 200 words)

Morphine PCA remains the analgesic mainstay after posterior spinal fusion (PSF) in Malaysian adolescents, yet it increases nausea, vomiting, pruritus and delaying mobilisation and discharge. These consequences conflict directly with the Ministry of Health's opioid-stewardship drive and with Enhanced Recovery After Surgery (ERAS) targets that prioritise early ambulation and shorter length of stay. This study will deliver the Malaysian data on a ketamine–morphine PCA regimen, quantifying opioid-reducing, pain control and psychotropic or haemodynamic safety in a uniform adolescent cohort. By establishing local effect sizes and feasibility parameters, the study will supply the critical evidence base required to design a subsequent adequately powered multicentre trial and will provide robust, context-specific figures for forthcoming national guideline revisions on paediatric perioperative care. Demonstrating safe reduction of opioid exposure has clear patient-centred benefits with fewer side-effects and faster recovery in addition to a reduce pharmacy expenditure on anti-emetics. Ultimately, the project advances both national opioid-stewardship goals and ERAS implementation, with potential to shape practice across South-East Asian paediatric spine centres.

i) Risk Assessment

Please provide justification that may cause delays in, or prevent implementation of, the project as proposed above; estimate also the degree of risk.

Major Risks Identified	Level of Risk (Low/ Middle/ High)	Proposed Risk Mitigation Measures
Recruitment < 2 patients / month	*Medium*	*Monthly planning with the surgical team*
Psychotropic adverse event	*Low*	*Dose capped; streamline ward protocol and discontinuation rule*
Drug-supply interruption	*Low*	*Advance purchase 12 month via inpatient pharmacy; secondary vendor letter*

j) Team Narrative (less than 200 words)

Tip: Describe briefly your team's composition of researchers, their relevant area(s) of expertise and their role/contribution to the proposed project

SNY (PI) is a senior lecturer who provide anaesthesia for spine surgery regularly. SNY previously secured a Faculty of Medicine research grant (2020) and has recently published on intravenous lignocaine and neuromonitoring in scoliosis surgery. SNY currently has an on-going carbohydrate-loading study in AIS which further demonstrates trial-management skills. SNY will coordinate all phases of PCA KetaMorph trial, bringing proven expertise in data handling and SPSS analysis.

MSH (scientific advisor) is a senior consultant anaesthetist with > 60 peer-reviewed papers and multiple national and international grants. He will refine the protocol, supervise recruitment targets, safeguard ICH-GCP compliance and interpret interim data.

MFMY (research fellow) is a Clinical Master's trainee who will manage daily screening, consent, data capture and follow-up, while completing GCP certification, strengthening future departmental research capacity.

k) References

1. Lee WS, Tay CG, Lum SH. Textbook of Paediatrics and Child Health. Kuala Lumpur: Universiti Malaya Press; 2020. p. 547-8.

2. Lee JY, Moon SH, Kim HJ, Park M, Suh BK, Nam J, Jung J, Lee HM. The prevalence of idiopathic scoliosis in eleven-year-old Korean adolescents: A 3-year epidemiological study. Yonsei Med J. 2014;55(3):773-8. https://doi.org/10.3349/ymj.2014.55.3.773

3. Deepak AS, Ong JY, Choon D, Lee K, Chiu CK, Chan C, Kwan K. The clinical effectiveness of a school screening programme for idiopathic scoliosis in Malaysia. Malays Orthop J. 2017;11(3):41-6. https://doi.org/10.5704/MOJ.1703.018

4. Seki H, Ideno S, Ishihara T, et al. Postoperative pain management in patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis: a narrative review. Scoliosis. 2018;13:17.

5. Yrjälä T, Helenius I, Rissanen T, Ahonen M, Taittonen M, Helenius L. The extension of surgery predicts acute postoperative pain, while persistent postoperative pain is related to the spinal pathology in adolescents undergoing posterior spinal fusion. Children. 2022;9(11):1729. https://doi.org/10.3390/children9111729

6. Chiu CK, Chong KI, Chan TS, et al. The anatomical locations of postoperative pain and their recovery trajectories following posterior spinal fusion surgery in adolescent idiopathic scoliosis patients. Med J Malaysia. 2020;75(1):12-7.

7. Kwan MK, Chiu CK, Chan TS, Chong KI, Mohamad SM, Hasan MS, Chan CYW. Trajectory of postoperative wound pain within the first 2 weeks following posterior spinal fusion surgery in adolescent idiopathic scoliosis patients. Spine (Phila Pa 1976). 2019;44(18):E1075-E1082.

8. Kaye AD, Urman RD, Rappaport Y, et al. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. J Anaesthesiol Clin Pharmacol. 2019;35(Suppl 1):S40-5.

9. Fletcher D, Stamer UM, Pogatzki-Zahn E, et al. Pain management after surgery: a consensus statement from the ESA. Eur J Anaesthesiol. 2015;32:88-98.

10. Hasan MS, Selvanathan P, Lee ZY, Chiu CK, Chan CYW, Kwan MK, Yunus SN. Perioperative intravenous lidocaine as an analgesic adjunct in adolescent idiopathic scoliosis surgery. Spine (Phila Pa 1976). 2020;45(20):E1261-E1269. doi:10.1097/BRS.0000000000003611

11. Himmelseher S, Duriex ME. Ketamine for perioperative pain management. Anesthesiology.2005;102:211-20.

12. Flood P, Rathmell JP, Shafer SL. Stoelting's Pharmacology and Physiology in Anesthetic Practice. 5th ed. New York: Wolters Kluwer; 2015.

13. Hasan MS, Abdul Razak N, Yip HW, Lee ZY, Chan CYW, Kwan MK, et al. Association between intraoperative remifentanil use and postoperative hyperalgesia in adolescent idiopathic scoliosis surgery: a retrospective study. BMC Anesthesiol. 2023;23:177. doi:10.1186/s12871-023-02127-8

14. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review. Pain. 1999;82:111-25.

15. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative ketamine for analgesia in spine surgery: a meta-analysis of randomized controlled trials. Spine. 2018;43(5):E299-E307.
16. Tornøe AS, Pind AH, Laursen CCW, Andersen C, Maagaard M, Mathiesen O. Ketamine for postoperative pain treatment in spinal surgery: systematic review with meta-analysis and trial sequential analysis. Acta Anaesthesiol Scand. 2023;67(10):1306-21. doi:10.1111/aas.14307
17. Minoshima T, Fukushima S, Yokoyama H, et al. Intra-operative ketamine infusion reduces morphine requirement after adolescent spinal fusion: a randomised trial. Paediatr Anaesth. 2017;27:1064-71.
18. Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomised trials. Br J Anaesth. 2010;104:401-6.
19. Roy JJ, Fortier C, Drolet P, et al. Physical compatibility of ketamine and morphine mixtures in PCA reservoirs. Can J Hosp Pharm. 2000;53:16-21.
20. Hodgman-Korth E, Kenyon NJ. Stability of morphine-ketamine admixtures for patient-controlled analgesia. J Pain Palliat Care Pharmacother. 2009;23:272-6.
21. Sveticic G, Farid R, Lauretti GR, et al. A safety audit of patient-controlled analgesia with ketamine and morphine after major surgery. Acta Anaesthesiol Scand. 2005;49(6):870-875. doi:10.1111/ j.1399-6576.2005.00736.x
22. Sveticic G, Gentilini A, Eichenberger U, Luginbühl M, Curatolo M. Combinations of morphine with ketamine for patient-controlled analgesia: a randomized, double-blind, cross-over study. Anesthesiology. 2003;98(5):1195-1205. doi:10.1097/00000542-200305000-00014
23. Zin CS, Nazar NI, Rahman NSA, et al. Patterns of initial opioid prescription and its association with short-term and long-term use among opioid-naïve patients in Malaysia: a retrospective cohort study. BMJ Open. 2019;9:e027203. doi:10.1136/bmjopen-2018-027203