ABSTRACT

Introduction Postoperative pain remains incompletely controlled for decades. Recently, multimodal analgesia is emerging as a potential approach in the management of postoperative pain. Therein, S(+) -ketamine is appealing as an adjuvant drug in multimodal analgesia due to its unique pharmacological advantages. This pragmatic clinical trial (SAFE-SK-A trial) is designed to investigate the analgesic effect and safety of S(+)-ketamine for acute postoperative pain in adults and explore the optimal strategy of perioperative intravenous S(+)-ketamine in a real-world setting.

Methods and analysis This multicentre, randomised, open-label, positive-controlled, pragmatic clinical trial (SAFE-SK-A study) is planned to conduct in 80 centres from China and recruit a total of 12,000 adult participants undergoing a surgical procedure under general anaesthesia. Patient recruitment started in June 2021 and will end in June 2022. Participants will be randomised in a ratio of 2:1 to either receive perioperative intravenous S(+) -ketamine plus conventional anaesthesia or conventional anaesthesia only. Given the pragmatic nature of the study, no specific restriction as to the administration dosage, route, time, synergistic regimen or basic analgesics. Primary endpoints are the area under the broken line of Numerical Rating Scale (NRS) scores for pain intensity and the total opioid consumption within 48 hours postoperative. Secondary endpoints are postoperative NRS scores, the anaesthesia recovery time, time of first rescue analgesia, the incidence of rescue analgesia, the incidence of postoperative delirium, patient questionnaire for effect, changes from baseline in cognitive function and anxiety and depression, as well as the adverse events and pharmacoeconomic outcomes. The general linear model will be used for the primary endpoint, and appropriate methods will be used for the secondary endpoints.

Ethics and dissemination This trial has been approved by the local Institutional Review Board (S2021-026-02) and conducted following the Declaration of Helsinki. Results of this trial will be publicly disclosed and published in scientific journals.

Trial registration number NCT04837170; Pre-results.

INTRODUCTION

Postoperative pain remains a significant clinical problem following inpatient and outpatient surgeries. Unfortunately, despite remarkable improvements in the knowledge of the mechanisms and treatment of pain, postoperative pain is still inadequately relieved and controlled for decades. The undertreatment of acute postoperative pain after surgery increased the risk of postoperative complications, as well as results in harmful chronic effects such as delayed rehabilitation and chronic postsurgical pain, which adversely affects the quality of life. At present, several studies overwhelmingly support the concept of pre-emptive

Strengths and limitations of this study

► This large-scale, multicentre, real-world study will thoroughly evaluate the risk–benefit of perioperative S(+)-ketamine with high external validity.

► Cost-effectiveness analysis in this trial will provide found evidence to relevant decision-makers.

► The lack of blinding is a limitation of the trial, but the lack of blinding assessment could reduce the bias risk.

To close to the clinical practice, there is no restriction to the dose, route, time, synergistic regimen of S(+)-ketamine and no fixed analgesic regimen required, which will increase the risk of confounding bias.
algesia for postoperative analgesia. Nevertheless, the evidence from clinical trials is equivocal. Accordingly, there has been considerable interest and controversy around the management of postoperative pain for several years.

Opioid analgesics as one cornerstone option for the treatment of postoperative pain remain the most effective. However, opioid analgesics may cause well-recognised side effects, such as respiratory depression, vomiting, nausea, ileus, hyperalgesia and deterioration of consciousness, which limit their use in clinical application. Because of this, the judicious addition of adjuvant non-opioid analgesics, such as ketamine, clonidine and so on, might improve postoperative analgesia and potentially reduce analgesic-related side effects. Several studies have established exciting evidence that multimodal analgesia approaches improved outcomes, or even potentially reduced incidence of chronic postsurgical pain and side effects. Among them, ketamine has been suggested as an effective adjuvant drug in opioid analgesia due to its lack of respiratory depression and potential prevention of hyperalgesia and central sensitisation. It could provide profound analgesia and immediately reduce the need for opioid analgesics. Moreover, S-ketamine is supposed to have fewer side effects and a shorter sedation time than racemic ketamine, thereby, it is appealing as an adjuvant drug in multimodal analgesia.

The effect of perioperative S(+)-ketamine on acute pain has been investigated in several studies, but these studies were all randomised controlled trials with small samples and restricted to a specific dose and surgical type. In fact, previous reports have revealed that both analgesic and adverse effects of S-ketamine are dose-related. High doses of S-ketamine might induce reversible neuropsychiatric side effects, such as hallucinations, nightmares, delirium and blurred vision; on the contrary, these side effects of low S-ketamine doses are well tolerated, reversible and low incidence. However, the optimal dose or route of administration has still not been thoroughly analysed. Therefore, a large-scale investigation of its analgesic properties and safety in a real-world setting is an urgent need.

In order to investigate the optimal management strategy of postoperative pain in the Chinese population, we plan to conduct a pragmatic clinical trial (PCT) in 80 centres from China. For this purpose, the primary aim of the present study is to evaluate the analgesic effect of perioperative administration of S(+)-ketamine for acute postoperative pain in adults. Secondary aims are to investigate its effects on postoperative depression, anxiety, cognitive function and delirium, as well as its safety. In addition, this PCT is designed to explore the optimal strategy of perioperative intravenous S(+)-ketamine, particularly the effects of administration dose, administration time, drug compatibility and operation type on clinical endpoints.

### Main inclusion and exclusion criteria

**Inclusion criteria**
- Male or female, aged ≥18 years old;
- Scheduled for the elective surgical procedure under general anaesthesia, including digestive tract surgery, gynaecological surgery, urological surgery, thoracic surgery, orthopaedic limb surgery, orthopaedic spine surgery or body surface surgery (thyroid surgery or breast surgery), head and neck surgery;
- American Society of Anesthesiologists class I–III;
- Signed informed consent for trial participation.

**Exclusion criteria**
- The expected length of hospital stay of the patient is less than 48 hours;
- Patients expected to be admitted to the intensive care unit after surgery;
- Patients expected to return to the ward with a tracheal catheter after surgery;
- Be allergic to S(+)-ketamine or any of their formulation ingredients;
- Patients with severe disorder of consciousness or mental system diseases (schizophrenia, mania, bipolar disorder, psychosis, etc) or cognitive dysfunction;
- Patients with a history of severe cardiovascular disease (onset of congestive heart failure or severe angina attack; unstable angina or myocardial infarction within previous 6 months);
- Patients during pregnancy or lactation;
- Participants with Mini–Mental State Examination score <18 points.
- Patients with any of the following contraindications of S(+)-ketamine:
  - Patients with a high risk of elevated blood pressure or intracranial pressure;
  - Patients with high intraocular pressure (glaucoma) or penetrating ocular trauma;
  - Patients with poorly controlled or untreated hypertension (resting systolic blood pressure greater than 180 mm Hg, or resting diastolic blood pressure greater than 100 mm Hg);
  - Patients with untreated or undertreated hyperthyroidism.

*The assessment at 72 hours postoperatively (visit 4) applies to patients who have not been discharged.

### METHODS AND ANALYSIS

**Study design**
SAFE-SK-A is a multicentre, randomised, open-label, positive-controlled, practical clinical trial in adult patients undergoing a surgical procedure under general anaesthesia. The study is planned to include 12000 patients at 80 centres from China. Eligible patients are randomly allocated to receive S(+)-ketamine (n=8000) or positive control drug (n=4000) in a ratio of 2:1. The first patient was enrolled in June 2021, and recruitment is ongoing at the time of submission. The end of the study is defined as the last follow-up of the last enrolled patient, and the study is expected to end around June 2022. The trial has been registered on ClinicalTrials.gov.

**Eligibility criteria**

Patients are eligible for enrolment if they fulfil the inclusion criteria at screening and are not allowed to have any of the exclusion criteria (Box 1). Additionally, patients are allowed to withdraw from the trial at any time if they withdraw informed consent, loss to follow-up, do not report the efficacy and safety data or are required by
investigators (such as unexpected indication for endotracheal tube in the ward).

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Randomisation and blinding**

The randomisation schedule is generated by a computerised centralised randomisation system and held centrally. Stratified block randomisation based on operation types is used to assign participants to S(+)-ketamine arm or control arm in a ratio of 2:1. The surgeons and pharmacists will not be blinded, but the outcome assessors will not inform the treatment assignment throughout the study.

**Intervention**

The study outline is presented in figure 1. Patients will be randomly allocated to either perioperative intravenous S(+)-ketamine plus conventional anaesthesia (intervention group) or conventional anaesthesia only (control group). As for the intervention group, no specific dosage of administration, route, time or synergistic regimen of S(+)-ketamine will be restricted. However, recommended dosages of S(+)-ketamine based on a meta-analysis have been provided for doctors, which are lower than the prescribed dose in the medicine specification. The intervention group are recommended to receive a single preoperative intravenous injection of 0.1–0.5 mg/kg S(+)-ketamine before incision, a postoperative continuous infusion of 0.02–0.1 mg/kg/hour for 24–48 hours or a single preoperative injection (0.1–0.25 mg/kg) followed by an intraoperative continuous infusion (0.1–0.25 mg/kg/hour). This decision of specific protocol is fully at the discretion of the investigator. Since the excessive secretions or mental adverse events that may be caused by S(+)-ketamine could be prevented by atropine or benzodiazepines, atropine or benzodiazepines will be considered in combination based on the clinical course and treatment guidelines. As for the control group, patients will receive the conventional anaesthesia except for other N-methyl-d-aspartate (NMDA) receptor antagonists (ie, dextromethorphan, amantadine) based on the clinical guideline, without specific restriction as to the drugs, dosage and synergistic regimen. Anaesthetic protocol for each patient will be fully decided by the investigator based on existing experience, expertise and clinical practice guidelines. The decision of postoperative analgesic protocol will be fully at the discretion of the investigator. In case the nerve block, intrathecal block or routine analgesic administration are used for postoperative analgesia, these analgesic schemes will be registered in detail. Electronic analgesia pumps will be required to record the dosage and total amount of analgesic drugs accurately.

**Assessments**

In this study, the pain intensity, cognitive function, delirium, anxiety and depression will be assessed using standardised and validated questionnaires.

At the selection and inclusion visits (visit 0), informed consent will be obtained for study-related procedures in the study (online supplemental file 1). Baseline assessments are performed at the baseline visit, including the verification of inclusion and exclusion criteria, demographic characteristics (age, height, weight, medical history, concomitant treatments, American Society of Anesthesiologists class, etc), physical examination (blood pressure, heart rate, respiratory rate), laboratory examination (urinalysis, haematology and blood chemistry) and the assessment of pain intensity measured with Numerical Rating Scale (NRS), anxiety and depression measured with Hospital Anxiety and Depression Scale (HADS), as well as the cognitive function measured with Mini-Mental State Examination (MMSE).

On the day of surgery (visit 1), details of the surgery, including the operation type, durations of surgery, side of surgery, incision number, incision length, amount of bleeding and blood transfusion volume, are recorded. Meanwhile, details of the anaesthesia process are also recorded at preoperative and intraoperative, measuring
the heart rate, oxygen saturation, blood pressure every 15 min; recording the anaesthesia methods, airway management anaesthesia methods, dose and route of drug administration; also recording the timeline of anaesthesia and surgical procedures.

At the second visit (24 hours postoperative), NRS score, delirium measured by 3-Minute Diagnostic Interview for CAM-Defined Delirium (3D-CAM), details of postoperative analgesics (types, administration time, doses and cost) or other concomitant drugs will be collected. Besides, laboratory examination or auxiliary examination (electrocardiograph) will be recorded if it is available.

At the third visit (48 hours postoperative), the NRS score and the questionnaires for patient efficacy (International Pain Outcome Questionnaire (IPOQ)), delirium (3D-CAM), cognitive function (MMSE) and anxiety and depression (HAD) will be performed. Meanwhile, details of postoperative analgesics and other concomitant drugs during 24–48 hours postoperative will be recorded. Laboratory examination and electrocardiograph will also be collected when available.

At the fourth visit (72 hours postoperative), the NRS score, 3D-CAM, details of postoperative analgesics and other concomitant drugs will be recorded. Notably, these assessments at visit four only apply to patients who have not been discharged.

Safety assessment is performed throughout the study. Safety will be evaluated through adverse events and vital signs at intraoperative and postoperative. During the operation, adverse events such as drug-induced cough, laryngospasm, respiratory depression, hypotension, hypertension, bradycardia, tachycardia, oxygen desaturation and so on will be registered in detail. After the operation, nausea, vomiting, dizziness, oversedation, infection, nightmares, diarrhoea, delirium, blurred vision, nystagmus, hallucinations and other adverse events will be registered in detail.

Endpoints

This ongoing study has two primary endpoints: the area under the broken line of NRS for self-report of pain intensity at 2, 4, 24, 48 hours after surgery, and the total opioid consumption within 48 hours postoperative.

Secondary endpoints include the following:

- NRS scores measured at 2, 4, 24 and 48 hours postoperative;
- Time of first rescue analgesia, defined as the time from the end of the operation to the first request of rescue analgesia postoperatively;
- The incidence of rescue analgesia within 48 hours postoperative;
- Time to anaesthesia recovery, defined as the time from the end of the operation to recovery;
- Pain efficacy outcomes measured by IPOQ at 48 hours postoperative;
- The incidence of postoperative delirium, which assessed at 24, 48 and 72 (for undischarged patients) hours postoperative;
- The change from baseline in cognitive function assessed by MMSE at 48 hours postoperative;
- The change from baseline in anxiety and depression evaluated by HADS at 48 hours postoperative;
- The incidence of unexpected intraoperative events, including intraoperative cough, laryngeal spasm, body movement, tachycardia, decreased oxygen saturation, respiratory depression, bradycardia, hypertension and hypotension;
- The incidence of postoperative adverse events from the end of the operation to 48 or 72 (for undischarged patients) hours postoperative, including nausea, vomiting, increased secretions, dizziness, oversedation, infection, anaesthetic awareness, nightmares, restlessness, pruritus, disorientation, delirium, respiratory depression, diplopia, diarrhoea, intestinal obstruction, urinary retention, gastro-oesophageal reflux, constipation, chills, hallucinations and so on;
- Pharmacoeconomic outcomes (calculating incremental cost-effectiveness ratio based on cost-effectiveness analysis).

Adverse events

Any adverse events reported spontaneously by patients or observed by investigators will be registered. In this study, serious adverse events are defined as any of the following conditions: death, a life-threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity or organ damages, a congenital anomaly/birth defect or a significant medical event that require intervention. The relationship of adverse events to intervention was determined and summarised by the investigators. All serious adverse events will be registered and reported to the local medical ethical committee within 24 hours.

Statistical considerations

Statistical methodology

Efficacy assessment was based on the intention-to-treat (ITT) population, defined as all randomised patients. Safety analyses will be performed in the safety evaluation set, a subset of all patients exposed to at least one dose of study medication. Data will be expressed as means (SD), frequency (percentage) and median (IQR) as appropriate. For baseline data, the Student’s t-test or Wilcoxon rank-sum test (continuous variables), and Pearson χ² or Fisher’s exact test (categorical variables) will be used, when appropriate. In the primary analysis, the general linear model will be used to test for statistical differences between the groups, taking operation types into account. Other risk factors will be also considered to be taken into account in the sensitivity analysis. Multiplicity caused by the two primary endpoints will be adjusted by using the Bonferroni method by setting a two-sided α-level of 2.5% for each endpoint. Secondary endpoints will be analysed according to the data type.

We will consider performing a predefined subgroup analysis on primary endpoints according to the age,
operation types, intervention and drug combination regimens. Missing data will not be imputed. In addition, the analysis of primary endpoints will also be conducted in the per-protocol set and compared with the ITT analysis as a sensitivity analysis. There are no interim analyses planned.

Sample size calculations
Power calculations were performed using Power Analysis and Sample Size Software (PASS 2019). We calculated power for primary outcomes (NRS for pain intensity and opioid consumption within 48 hours after surgery) based on an ITT analysis. Considering no reference data, we calculated the estimated sample size for different effect size scenarios, presuming a power of 80% and a two-sided α-level of 2.5%. We assume a 2:1 ratio of intervention to control patients. A sample size of 357 (control) and 714 (intervention) achieve 80% power to detect an effect size of 0.2. Given the pragmatic nature of the study and more than 10 different operation types used in this study, we plan to enrol a total of 12 000 patients (control, 4000; intervention, 8000), allowing for a dropout rate of 10%.

Data handling and record-keeping
To improve data completeness, the SAFE-SKA study will use a mobile device-based electronic data capture (mEDC) system to support data capture, monitoring and project management. The mEDC consists of two primary components: a server-based clinical trial database and an application installed in mobile phones. The personal information for each participant will be collected and stored digitally in a database on mEDC system, which can be accessed by the researchers per participating centre. Data management and monitoring are conducted by data managers to check the abnormal value or missing data. The database was locked post reconciliation of all data. To ensure the completeness and accuracy of the data, the locked database will be provided to the statisticians who were independent of the study team and conduct the independent statistical analyses. Data will be stored under lock and key for 5 years.

Ethical considerations, amendments and dissemination
This trial is conducted in accordance with the Declaration of Helsinki. The informed consent and assent process is in line with the Good Clinical Practice guideline. This trial has been approved by the Institutional Review Board of Chinese PLA General Hospital. Any significant modifications to the study protocol or significant modifications in other study documents which may affect the study, potential benefit or safety of patients, including the changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will be submitted for approval to the local medical ethical committee, and meanwhile require a formal amendment to the protocol. All study participants will be notified, and informed consent will be requested again when necessary. The amendment will be updated on the Trial register website to ensure transparency. Results of this trial will be publicly disclosed, published in scientific journals or presented at scientific conferences, regardless of the outcome.

Trial status
The SAFE-SKA study protocol was approved on 20 February 2021. The trial started recruiting patients in June 2021 in Chinese PLA General Hospital. Recruitment in other centres will follow when ethical approval becomes available.

DISCUSSION
Multimodal analgesia is advocated for pain management to reduce opioid consumption, therein achieving adequate postoperative pain relief, fewer side effects and reduced surgical stress response.\(^\text{18}\) With the theoretical basis of preventing central sensitisation, S(+)\text{-}ketamine has been widely used as an adjuvant drug.\(^\text{19}\) However, some key questions remained unanswered: What are the optimal dose, route of administration and drug compatibility recommended in clinical? How effective would S(+)\text{-}ketamine be when widely used in the Chinese population? And whether it is well tolerated in real-world clinical practice? S(+)\text{-}ketamine is the first S-ketamine biosimilar developed in China. The phase III study in China has shown that S(+)\text{-}ketamine presented potential clinical advantages with a shorter recovery time and orientation recovery time compared with racemate ketamine.\(^\text{20}\) Despite its pharmacokinetics and safety have been reported preliminarily,\(^\text{20, 21}\) the data were only from small-scale studies, and safety analysis in a clinical setting is also generally limited. Therefore, we have chosen the PCT trial in a large scale population to explore the efficacy and safety of S(+)\text{-}ketamine, aiming to provide more high-level evidence for the clinical application of S(+)\text{-}ketamine, as well as the risk management and control of medical institutions.

From a design point of view, the PCT trial is more likely to have higher external validity; that is, they will generalise better to wider normal clinical settings. This helps translate research results to clinical care and facilitates decision-making about whether therapies should be used more widely. Thus, this PCT trial could provide direct evidence in clinician practices if S(+)\text{-}ketamine is a potential adjunct in multimodal analgesia. Furthermore, to the best of our knowledge, the SAFE-SKA study is the first and largest-scale trial exploring the optimal approach for perioperative pain management in China to date. Previous evidence of S(+)\text{-}ketamine in the management of postoperative pain are only derived from several small scale randomised trials, as reported by Mendola et al (66 patients),\(^\text{22}\) Spreng et al (77 patients)\(^\text{19}\) and Ithnin et al (90 patients).\(^\text{23}\) Here, we plan to recruit 12 000 patients and stratified according to the operation type, aiming to provide large-scale, randomised evidence for the analgesic effect and safety of S(+)\text{-}ketamine. In addition, the
cost-effectiveness analysis in this trial is another crucial component to enable patients to make informed decisions on value for money.

Despite the careful design of this trial, there are still some limitations. First, we have designed a PCT with the inherent limitation, the potential criticism for increased resources. Second, the lack of blinding is another limitation of the trial. However, our study has been designed to separate the surgeons and pharmacists from the follow-up doctors (outcome assessors), the outcome assessors will not be informed about treatment assignment, which will eliminate the limitation to a large extent. Third, to close to the clinical practice, no restriction to the dose, route, time, synergistic regimen of S(+)-ketamine and no fixed analgesic regimen required, there is a risk of more confounding factors in this trial, influencing the strength of the results. Considering the exploratory and pragmatic nature of the study, we plan to recruit 12000 patients with large sample size and using stratified randomisation to control the confounding bias to the utmost extent. Besides, these questionnaires are mostly subjective in nature, influenced by the patient impression of pain; thereby, they may not directly measure the analgesic effect and lead to subjective bias. Thus, before the initiation of this trial, the investigator and site staff received systemic training for the use of these questionnaires and were certificated to avoid subjective bias as much as possible. Meanwhile, in this trial, objective assessment, including the duration of postoperative analgesia, the incidence of rescue analgesia and time to fully alert, will also be performed to fully assess the analgesic effect.

In summary, this trial is a significant attempt to evaluate the efficacy and safety of S(+)-ketamine in perioperative acute pain management, more crucially, in a large population and a real-world setting, hoping to be fully qualified for selecting the optimal treatment for individual patients.

Author affiliations
1Department of Anesthesiology, The First Medical Center of Chinese PLA General Hospital, Beijing, China
2Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, Guangdong, China
3Department of Anesthesiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
4Department of Anesthesiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China
5Department of Anesthesiology, Jiangsu Province Hospital, Nanjing, Jiangsu, China
6Department of Anesthesiology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China
7Department of Anesthesiology, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi, China
8Department of Anesthesiology, General Hospital of Northern Theater Command, Shenyang, Liaoning, China
9Department of Anesthesiology, Beijing Hospital, Beijing, China
10Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Contributors W-DM and P-YC are the initiators of the study and were in charge of coordination. HW and C-YD wrote the manuscript protocol. All authors collaborated in writing and designing the study protocol. W-QH, PZ, L-ZY, Y-HL, C-ML, H-CC, QW, Y-GD, ZH and Q-TM are responsible for data acquisition. HL and X-YZ made amendments and participated in designing the trial protocol. HW and C-YD wrote the manuscript and all authors read and approved the manuscript.

Funding This study was supported by the National Key Research and Development Program of China (Grant number. 2018YFC2001900)

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs Hong Wang http://orcid.org/0000-0002-5348-362X
Wei-Dong Mi http://orcid.org/0000-0001-9814-2450

REFERENCES
1 Mitra S, Carlyle D, Kodumudi G, et al. New advances in acute postoperative pain management. *Curr Pain Headache Rep* 2018;22:35.
2 Inaw N. Current issues in postoperative pain management. *Eur J Anaesthesiol* 2016;33:160–71.
3 Wu CL, Raja SN. Treatment of acute postoperative pain. *Lancet* 2011;377:2215–25.
4 Hurley RW, CLW S. Acute postoperative pain. Miller’s *Anaesthesia* 2010;7:2757–87.
5 Kissin I, Weiskopf Richard B. Preemptive analgesia. *Anesthesiology* 2000;93:1138–43.
6 Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res* 2017;10:2287–98.
7 Khademi H, Kamangar F, Brennan P, et al. Opioid therapy and its side effects: a review. *Arch Iran Med* 2016;19:870–6.
8 Thiruvkenkatarajan V, Wood R, Watts R, et al. The intraoperative use of non-opioid adjuvant analgesic agents: a survey of anaesthetists in Australia and New Zealand. *BMC Anesthesiol* 2019;19:188.
9 Helander EM, Menard BL, Harmon CM, et al. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep* 2017;21:3.
10 Imani F, Varrasisi G. Ketamine as adjuvant for acute pain management. *Anesth Pain Med* 2019;9:e100178.
11 Richards JR, Rockford RE. Low-Dose ketamine analgesia: patient and physician experience in the ED. *Am J Emerg Med* 2013;31:390–4.
12 Marland S, Ellerton J, Andolfatto G, et al. Ketamine: use in anesthesia. *CNS Neurosci Ther* 2013;19:381–9.
13 Peltoniemi MA, Hagelberg NM, Oikkola KT, et al. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet* 2016;55:1059–77.
14 Wang X, Lin C, Lan L, et al. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth* 2021;68:110071.
15 Brinck EC, Tippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2018;12:CD012033.
16 Rybakowski JK, Permodak-Nisip A, Bartkowska-Sniatkowska A. Ketamine: Its Safety, Tolerability, and Impact on Neurocognition. In: Mathew SJ, Zarate JCA, eds. Ketamine for treatment-resistant depression: the first decade of progress. Cham: Springer International Publishing, 2016: 57–71.
17 Sloekers JCT, Bois M, Hoogland G, et al. Assessing the effectiveness of perioperative s-ketamine on new-onset headache after resective
epilepsy surgery (ESPAIN-trial): protocol for a randomised, double-blind, placebo-controlled trial. *BMJ Open* 2019;9:e030580.

18 Ho K-Y, Tay W, Yeo M-C, et al. Duloxetine reduces morphine requirements after knee replacement surgery. *Br J Anaesth* 2010;105:371–6.

19 Spreng UJ, Dahl V, Raeder J. Effects of perioperative S (+) ketamine infusion added to multimodal analgesia in patients undergoing ambulatory haemorrhoidectomy. *Scand J Pain* 2010;1:100–5.

20 Wang J, Huang J, Yang S, et al. Pharmacokinetics and safety of esketamine in Chinese patients undergoing painless gastroscopy in comparison with ketamine: a randomized, open-label clinical study. *Drug Des Devel Ther* 2019;13:10.2147/DDDT.S224553:4135–44.

21 Liu P, Li P, Li Q, et al. Effect of pretreatment of S-Ketamine on postoperative depression for breast cancer patients. *J Invest Surg* 2021;34:1–6.

22 Mendola C, Cammarota G, Netto R, et al. S(+)-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. *Minerva Anestesiol* 2012;78:22441361:757–66.

23 Ithnin FB, Tan DJA, Xu XL, et al. Low-Dose S+ ketamine in target-controlled intravenous anaesthesia with remifentanil and propofol for open gynaecological surgery: a randomised controlled trial. *Indian J Anaesth* 2019;63:10.4103/ija.IJA_605_18:126–33.