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STUDY PROTOCOL

The Opioid-Sparing Effect of Acupuncture After Abdominal Surgery: A Systematic Review and Meta-Analysis Protocol

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Purpose: Routine overprescribing of postoperative opioid analgesics may induce side effects and correlate with chronic opioid use following surgery. This review aims to evaluate the effectiveness and safety of acupuncture for opioid-sparing effects in patients who underwent abdominal surgery.

Methods: Eleven databases in different languages, including English (Ovid MEDLINE, CENTRAL, EMBASE, CINAHL), Chinese, Korean, and Japanese, will be searched. Randomized controlled trials using acupuncture for postoperative pain control in adult patients undergoing abdominal surgery will be screened. All randomized controlled trials comparing acupuncture with no treatment, sham acupuncture, and conventional treatments will be included. The Cochrane risk of bias tool will be used to assess the risk of bias. The primary outcome will consist of a cumulative opioid consumption. Additionally, the number of cumulative opioid analgesic demands/requests, the time to initial opioid analgesic usage, postoperative pain, opioid-related side effects, and adverse events of acupuncture will be assessed. The mean differences or risk ratios with a 95% confidence interval will be calculated to estimate the pooled effect of acupuncture when it is possible to conduct a meta-analysis.

Results: This study could confirm the effect of opioid-sparing on acupuncture after abdominal surgery.

Conclusion: This study would evaluate the evidence on the effectiveness of acupuncture after abdominal surgery with a focus on opioid intake. It provides evidence to support decision-making on applying acupuncture for postoperative management.

Registration Number: CRD42022311155.

Keywords: acupuncture, abdominal surgery, opioid-sparing effect, systematic review, meta-analysis, protocol

Introduction

Opioid analgesics are pharmacological agents used for managing moderate to severe pain in postoperative, cancer, and trauma patients.[1,2] Opioids are commonly administered intravenously via patient-controlled analgesia or orally to manage postoperative pain.[3] Appropriate postoperative pain management is required for persistent pain control and better surgical outcomes.[4] However, routine administration of opioids for postoperative pain management can occasionally trigger opioid-related side effects and affect opioid use after the acute postoperative phase.[5] Recent reviews indicate opioid use in the postoperative phase may contribute to prolong opioid use after surgery. In particular, high-dose opioid prescription at discharge[6–8] and routine opioid use during the acute postoperative phase[9] could be the cause of long-term use of opioids continuously prescribed over 90 days.[10]

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Reducing a chance of being over-exposed to opioids is important for patients under pain management in the current opioid endemic.[11] The opioid-sparing effect is based on the current need to decrease opioid requirements with equivalent analgesic effects and simultaneously fewer side effects of opioids. Conventional analgesic medications, including non-opioid medications (eg, dexmedetomidine, gabapentinoids, ketamine, and lidocaine), and regional anesthesia medications (eg, dexamethasone, and clonidine) could be an optional adjuvant for pain management with opioid-sparing effect.[12] However, some contradictory evidence and limited use with side effects make it hard to draw a strong conclusion. In addition to perioperative pain relief, there are currently increased efforts on patients' postoperative comprehensive recovery. Enhanced recovery after surgery (ERAS) program is an evidence-based multimodal management approach to optimize patient's postoperative condition[13] and may decrease postoperative opioid use with the opioid-sparing effect.[14]

Acupuncture, a nonpharmacological intervention, has been used for pain-related disorders, such as osteoarthritis, labor, cancer, and postoperative pain.[15–17] It has reduced opioid dosage for postoperative pain management when used as an adjunct to conventional analgesics.[18–21] Furthermore, acupuncture is also known as a safe technique with its perioperative use.[22]

Previous systematic reviews have investigated the effect of acupuncture in lowering cumulative opioid consumption for 24 hours following surgery,[20,21,23] and suggested acupuncture can reduce opioid consumption after various surgeries, including spinal surgery, thoracotomy, hip arthroplasty, hemorrhoidectomy, and abdominal surgery. The mechanism of pain reduction using acupuncture were explained via local analgesic effects mediated by adenosine A1 receptors[24] or inactivation of the myofascial trigger point[25] and general analgesic effects through descending inhibitory pain control by serotonin and noradrenaline.[26,27]

However, the mechanisms underlying the opioid-sparing effect of acupuncture have not yet been clearly elucidated. This might be related to secretion of various endogenous opioid peptides (β-endorphin, enkephalin, and dynorphin), increasing μ-opioid binding ability, and descending pain pathway.[28–30] Previous reviews on postoperative acupuncture have focused on managing pain as an alternative to analgesics, rather than opioid dosage. Moreover, these reviews have reported large heterogeneities due to the synthesis of diverse types of surgeries. Thus, conflicting results regarding the opioid-sparing effect of acupuncture exist.[31,32]

Therefore, a systematic review and meta-analysis will be performed focusing on the opioid-sparing effect of acupuncture after abdominal surgery, one of the most common surgical procedures with moderate postoperative opioid consumption, which is a risk factor for continued opioid use.[7,33,34] The present study aims to determine the effectiveness and safety of acupuncture for the opioid-sparing effect compared with no treatment, sham acupuncture, and conventional treatment in patients who underwent abdominal surgery.

Materials and Methods

Study Registration

This present study was registered online at PROSPERO (CRD42022311155) on March 3, 2022. The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist is presented in Supplement 1.

Inclusion Criteria for Study Selection

Types of Studies

Prospective randomized controlled trials will be included with no language limitations. Qualitative, observational, and non-randomized controlled trials will be excluded.

Types of Participants

Studies, including patients ≥18 years, who have undergone abdominal surgeries (ie, hysterectomy, appendectomy, prostatectomy, laparotomy, laparoscopy, and open surgery) and have received postoperative pain management via all routes of opioid medication administration without a history of long-term opioid use prescribed over 90 days and taking assisted medication for opioid dependency will be eligible for screening.

Types of Interventions

Interventions will be eligible for any type of acupuncture in the form of penetrating skin or applying electrical stimulation on acupuncture point, such as manual acupuncture, electroacupuncture, transcutaneous electrical acupoint stimulation (TEAS), transcutaneous electrical nerve stimulation (TENS) on acupuncture points, pharmaco-acupuncture, auricular acupuncture, and dry needling. However, studies with herbal medicine, moxibustion, cupping therapy, capsicum plaster, and acupressure will be excluded.

Studies will be included with control groups who received sham acupuncture, no treatment, and conventional treatments for opioid sparing, such as nonopioid medications, regional anesthesia, or neuraxial blocks.[12]

Types of Outcome Measures

Primary Outcome

The primary outcome of the study will be postoperative period cumulative opioid consumption. Postoperative cumulative opioid consumption is defined as the total amount of opioids used for postoperative pain control. According to previous studies,[20,23,35,36] it will be evaluated at 8, 24, and 72 h after surgery. The opioid dosage will be calculated and converted to morphine milligram equivalent (MME).[37]

Secondary Outcomes

The secondary outcomes will include the number of cumulative opioid analgesic demands/requests by patients, time to initial opioid analgesic usage during the postoperative period, pain intensity measured using the visual analog scale (VAS), opioid-related side effects, such as nausea, vomiting, dizziness, and pruritus, and adverse events related to acupuncture. These adverse events usually appear as minor symptoms, such as bleeding, needle site pain, and other local reactions rather than serious adverse events.[38]

Search Methods for Identification of Studies

Electronic Searches

The following eleven databases will be searched from inception to November 28, 2021: four English-language databases [Ovid MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)], one Chinese database [China National Knowledge Infrastructure (CNKI)], five Korean databases [KoreaMed, Research Information Service System (RISS), Korean Studies Information Service System (KISS), Database Periodical Information Academic (DBpia), and Oriental Medicine Advanced Searching Integrated System (OASIS)], and one Japanese database [Japan Science and Technology Information Aggregator Electronic (J-STAGE)].

Search for Other Resources

The World Health Organization International Clinical Trials Registry Platform will be searched to identify ongoing and recently completed studies. Reference lists in the relevant publications will be manually checked for additional eligible trials.

Search Strategy

The search terms will consist of three parts: abdominal surgery (including hysterectomy, appendectomy, and laparoscopy), opioid medication consumption (including opioids, narcotics, and morphine), and acupuncture (including acupuncture, electroacupuncture, auricular acupuncture, TENS, and TEAS). Detailed search strategies for Ovid MEDLINE, EMBASE, CENTRAL, CINAHL, and CNKI are presented in Supplement 2.

Data Collection and Analysis

Selection of Studies

The titles and abstracts of the studies will be independently reviewed with predefined form with reasons for exclusion by two authors. Disagreements between authors will be resolved by the third author. The retrieved studies will be imported in Endnote X9.

Data Extraction and Management

Two authors will extract the data independently using a predefined standard data extract form. The data will include basic information of the study (title, author, and publication year), participants (sample size, age, type of surgery, and the American society of anesthesiologists physical status classification), intervention (timing of acupuncture, acupuncture type, and location and duration of acupuncture treatment), control type, conventional treatments (eg, nonopioid medications, regional anesthesia, or neuraxial blocks), and outcomes (postoperative opioid consumption, cumulative opioid consumption timing, and secondary outcome). Disagreements during the data extraction process will be resolved through debate, and if it remained unsolved, the third reviewer will address the issue.

Assessment of Risk of Bias

The Cochrane risk of bias tool will be used to analyze the risk of bias among the included studies.[39] The risk of bias will be assessed at three levels (ie, low, high, and unclear) for each of the following seven domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Two authors will independently analyze the studies using the Cochrane risk of bias tool, and disagreements will be resolved through discussion.

Measurers of Treatment Effect

The extracted treatment effect data will be synthesized and analyzed statistically by using the RevMan software (version 5.4). The mean difference (MD) with 95% confidence intervals (CIs) will be used for analyzing continuous data. If the measures of outcomes differ among studies, the standard mean difference (SMD) will be used. The risk ratio (RR) will be used for analyzing dichotomous data.

Unit of Analysis Issues

In the case of crossover studies, the first-period data will be used to avoid a carry-over effect. Cluster randomized trials will not be included in this study.

Addressing Missing Data

The author of included studies will be contacted and requested for the missing data. The potential impact of the missing data will be addressed in the discussion section. If missing data could not be obtained, the available data will be analyzed.

Assessment of Heterogeneity

Heterogeneity will be assessed using RevMan software (version 5.4). It will be measured with the I^2 statistic, which quantifies the inconsistencies among included studies, and will be identified using the chi-squared distribution with a significance level of $P<0.1$ according to the Cochrane handbook.[40] Additionally, the I^2 statistic will be assessed to quantify the inconsistencies among the studies, with a value of more than 50% indicating significant heterogeneity. The I^2 value of 0%–40%, 30%–60%, 50%–90%, and 75–100% is considered to represent unimportant, moderate, substantial, and considerable heterogeneity, respectively.

Assessment of Reporting Biases

Reporting biases will be evaluated using a funnel plot if more than ten studies reporting the primary outcome are included.

Data Synthesis

The meta-analysis will be performed with RevMan software (version 5.4). The pooled estimate will be calculated with a weighted average, and a random-effect model will be used owing to the potential heterogeneity among the included studies. If there is significant heterogeneity of included studies, quantitative analysis will not be performed.

Subgroup Analysis and Investigation of Heterogeneity

A subgroup analysis will be performed to identify the heterogeneity of the studies based on the type of surgery (eg, laparoscopic vs open surgery), the timing of acupuncture administration (eg, preoperative, intraoperative, postoperative,

and perioperative), and the type of acupuncture stimulation (eg, electrical vs manual stimulation and penetration vs non-penetration).

Sensitivity Analysis

A sensitivity analysis will be performed to test the robustness of the primary analyses, based on the statistical method (eg, random-effect model vs fixed-effect model) and study quality (eg, all studies vs studies with low risk of allocation bias).[41]

Summary of Evidence

Our findings will be evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[42] The quality of evidence will be presented with summary of the findings and certainty of the evidence. The GRADE assessment of certainty is determined by considering five domains: risk of bias, consistency of effect, imprecision, indirectness and publication bias.

Patient and Public Involvement

Patients and/or the general public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics and Dissemination

Written informed consent and ethical approval will not be required because this study is a systematic review. The main results of this review will be distributed through posters, newspapers, conference presentations, and peer-review journals.

Discussion

This protocol of a systematic review will assess acupuncture as an effective and safe treatment for opioid-sparing effects after abdominal surgery.

Some pharmacological interventions, such as gabapentin, ketamine, block agents, non-steroidal anti-inflammatory drugs, and α-2 agonists, have been used to reduce opioid analgesic consumption and minimize opioid-related side effects.[35,36,43–45] Gabapentin, in particular, has significant opioid-sparing effects with minimal opioid-related adverse effects compared with other adjuvant analgesics.[46] However, owing to the limitation of pharmacological agents and the possibility of another abuse, such as "gabapentinoids abuse",[47] a recent review suggests the multimodal combinations of nonpharmacological interventions with conventional analgesic medications not only for analgesia but also for reducing opioid consumption.[48]

The opioid-sparing mechanism of non-opioid medications is based on synergistic pain modulation pathways at central and peripheral sites, consequently reducing opioid consumption and enhancing analgesia.[12] In a similar way, the analgesic effects of acupuncture acting through different sites of action with presynaptic and postsynaptic pathways may decrease opioid requirements.[24,27,49] In analgesia, cannabinoid systems are known to share mechanisms with opioid systems and synergistically enhance opioid-sparing effect.[50] Acupuncture simultaneously affects opioid and cannabinoid systems by releasing opioid receptor ligands. Collectively, acupuncture may share similar mechanisms to cannabinoids regarding the opioid-sparing effect.[51]

The ERAS program consists of a multidisciplinary approach from the behavioral preparation of patients to a perioperative strategy of physicians for better clinical outcomes of patients after surgery.[52] As acupuncture can relieve pain, improve surgical stress, and prevent complications in the perioperative state,[53,54] it could be a possible treatment option for the ERAS program after abdominal surgery. If acupuncture treatment could reduce opioid consumption and opioid-related adverse events with low risk in this review, it could be applied more widely in further ERAS programs of abdominal surgery.

Therefore, this study will evaluate the evidence for the effectiveness and safety of acupuncture for opioid-sparing effects after abdominal surgery. These findings will provide recommendations to physicians, health care policymakers, and patients on the use of acupuncture to reduce opioid consumption after abdominal surgery. Moreover, the results of this review will be used as basic data for further clinical studies.

Abbreviations

CIs, confidence intervals; ERAS, enhanced recovery after surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; MME, morphine milligram equivalent; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol; RR, risk ratio; SMD, standard mean difference; TEAS, transcutaneous electrical acupoint stimulation; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

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Disclosure

The authors report no conflicts of interest in this work.

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