Study Protocol

Title

Acupuncture for Post-hemorrhoidectomy Pain Control with Acute Anti-inflammatory Effects: A Randomized Controlled Trial

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1. Background

Hemorrhoidal disease is a common condition and frequently presents with anal pain, bleeding and prolapse. Conventional hemorrhoidectomy (CH) is the standard surgical treatment for symptomatic high grade hemorrhoids. Post-operative pain control remains a major concern and is crucial to early patient recovery. Various perioperative strategies have been reported to enhance pain management including mode of anesthesia, surgical techniques, medications and topical treatment for wound care [1]. An effective multimodal pain management program is essential to expedite post-operative functional recovery.

Acupuncture is a widely adopted and safe technique for pain relief in Traditional Chinese Medicine (TCM). It has been applied as an adjunct for post-operative pain control in various surgical procedures including but not limited to abdominal, pelvic, obstetric and gynecological operations [2]. A handful of trials have been reported in the Chinese literature regarding its use after surgical treatment for hemorrhoids [3]. The benefits and effectiveness of electroacupuncture [4, 5] and manual acupuncture [6] in alleviating post-hemorrhoidectomy pain have been proven by multiple controlled trials. However, the efficacy remains for further validation in a larger sample size, more rigorously designed trial. Meanwhile, the acupuncture protocol, in particular acupoints used, modes, frequency, and duration should be generated and standardized.

It is well evidenced that analgesic effects of acupuncture are associated with its modulation of automatic nervous system-mediated anti-inflammatory and parasympathetic actions which promote anal sphincter relaxation [7]. Such anti-inflammatory effects may be more apparent in alleviating short-term anal pain [6, 8].

Combination of acupuncture into post-hemorrhoidectomy analgesic pathway is a novel approach which is supported by preliminary data published in the Chinese literature. This study aims at investigating the effectiveness and safety profile of acupuncture as an adjunctive therapy for pain control after CH compared with a placebo intervention and standard care.

2. Objective

The objectives of this trial are: (i) to evaluate efficacy and safety of generated acupuncture regime in post-operative pain management after conventional hemorrhoidectomy; and (ii) to correlate acute analgesic effects with changes in peripheral inflammatory biomarkers.

3. Trial Design

3.1. Design

This is a prospective, single-center, double-blinded, randomized controlled trial. Patients will be randomized into intervention group (Fully active acupuncture group) and control group (minimum acupuncture stimulation group) in 1:1 ratio.

3.2. Patient recruitment

All patients scheduled for elective conventional hemorrhoidectomy in Tung Wah Hospital are recruited. The recruitment period is 1 year.

3.3. Hypothesis

Compared to control group, fully active acupuncture intervention can improve post-hemorrhoidectomy pain control in terms of a significant reduction in maximal pain score in numeric rating scale. With a better analgesic regime, the overall patient satisfaction and quality of recovery can be improved.

3.4. Primary Outcome

The primary outcome is the maximal pain intensity expressed by patients using the 0-10 numerical rating scale (NRS) on post-operative day 1.

3.5. Secondary Outcome

Secondary outcomes include maximal and resting NRS pain scores on post-operative days 0, 2 to 7 and day 14 as well as resting NRS pain score on postoperative day 1.

Other secondary outcomes include requirement of opioids, length of hospital stay, time of absence from work, return of defecatory and urinary function, adverse effect from acupuncture and analgesic medication, quality of recovery (QoR-15) and serum C-reactive protein level.

3.6. Inclusion criteria

1. Age 18-90
2. Symptomatic grade III or IV hemorrhoids undergoing CH

3.7. Exclusion criteria

1. Patients scheduled for stapled hemorrhoidopexy
2. Concomitant surgery other than CH
3. Bleeding tendency, thrombocytopenia (platelet count < 100 x 10^9/L)
4. Immunocompromised status or use of chemotherapy

5. Active dermatitis
6. Patients with pacemaker or automated implantable cardioverter-defibrillator
7. Pregnant patients
8. Known allergy to opioids, local anaesthetic drugs, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) including COX-2 inhibitors
9. History of chronic pain (duration for 3 months or more)
10. Daily use of strong opioids (e.g. morphine, fentanyl, hydromorphone, methadone, oxycodone, or meperidine)
11. Alcohol or drug abuse
12. Psychiatric illness
13. Impaired renal function (preoperative serum creatinine level > 120 μmol/L)
14. Recent acupuncture treatment for other medical conditions

3.8. Subject withdrawal

Acupuncture will be stopped in case:

1. Patient refuses to continue in study
2. Patient develops adverse reaction to acupuncture

Patient withdrawal from study will be respected and standard post-operative management will be applied accordingly.

3.9. Randomization and blinding

Patients scheduled for elective CH in Tung Wah Hospital are attended by surgeon during preoperative assessment clinic at 1 week before operation. The detailed study protocol is explained to eligible patients and informed consent is obtained. Patients are admitted on the same day of operation. Randomization is performed immediately before operation using a computer-generated list of variable block size. Patients, operating surgeons and assessors are blinded. Allocation concealment is ensured using the sealed envelope method.

3.10. Sample Size Calculation

46 patients per group were estimated to be sufficient to show a significant difference of the maximal NRS pain score on post-operative day 1 with an absolute mean difference of 1.3 and standard deviation of 2.2, at a significance level of 0.05 and power of 0.8 in a two-sample t-test. To account for an expected dropout rate of 10%, the estimated sample size in each group is 50 patients (total = 100 patients). [6]

4. Treatment

4.1. Surgery

Conventional hemorrhoidectomy is performed with Ferguson approach in prone jackknife position. Glycerol enema was given 2 hours before surgery. All procedures are performed by colorectal specialists or general surgeons under supervision by colorectal specialists. No routine antibiotics prophylaxis is given. Local anesthesia with 10mL 2% lignocaine in 1:200,000 adrenaline is administered into the intersphincteric space. Grading of hemorrhoids in terms of Goligher's classification and length of mucosal incision is documented. Grade III and IV hemorrhoids are excised with standard Ferguson technique using monopolar diathermy. Ultrasonic or bipolar energy devices are not routinely used. Mucocutaneous defect is closed with continuous absorbable sutures. Pedicles of grade II internal hemorrhoids are transfixed. Hemostatic sponge is placed in anal canal upon completion of operation. Weight of the excised specimen is measured.
Normal diet is resumed at 4 hours after surgery. Stool softener and flavonoids are given for the first two weeks after surgery and patients are advised to have potassium permanganate sitz bath.

4.2. Anaesthesia and analgesic management

Patients from both groups will be anaesthetized according to the following protocol:

On arrival to the operation theatre, a 20 or 22 gauge intravenous cannula will be inserted. Standard monitoring with pulse oximeter, non-invasive blood pressure, and three lead electrocardiogram will be applied prior to induction. Non-invasive blood pressure will be checked at least every 5 minutes throughout the operation.

Spinal anaesthesia

All patients will undergo spinal anaesthesia. A saddle block will be performed using aseptic technique and patients will be placed in a sitting position for the block. A 25G Whitacare spinal needle will be used. Heavy Bupivacaine (0.5%) at a volume of between 1.6-2ml will be administrated into the intrathecal space at the L3/4 or L4/5 level. Patients will be kept in the sitting position for between 3-10 minutes after injection.

Analgesic modalities

Paracetamol 1g and Celecoxib 200mg will be given orally one hour prior to surgery.

In the PACU, 2mg intravenous morphine sulphate will be given every 5 minutes until the NRS is less than 4/10.

When the patient resumes diet on postoperative day 0, regular oral celecoxib 200mg BD and oral paracetamol 1g tds will be given for 3 days (postoperative day 0-2). Oral tramadol 50mg up to a maximum of four times a day will be prescribed as needed. Patients can request for oral tramadol if their NRS pain score is equal or above 4/10. Breakthrough pain while in hospital will be treated by intramuscular morphine 0.1mg/kg every 4 hours as needed.

4.3. Acupuncture treatment

Fully active acupuncture (FAA) and minimum acupuncture stimulation (MAS) as control will be performed and acupoints used are listed as follows:

FAA: Local acupoints: Yao-Shu (DU2, 腰俞), Ci-Liao (BL32, 次髎), Bai-Huan-Shu (BL30, 白環俞), Da-Chang-Shu (BL25, 大腸俞), and specific points that are located at the 1, 3, 5, 7, 9, and 11 o'clock positions, 4 cm away surrounding the anus. Distance points: Er-Bai (EX-UE2, 二白), Zhi-Gou (SJ6, 支溝), and Cheng-Shan (BL57, 承山).

MAS: Local points: Guan-Yuan-Shu (BL26 關元俞), Distance points: Shou-San-Li (LI11 手三裡) and Fu-Yang (BL59 跗陽).

Patients will be required to lay in prone position. For FAA, disposable acupuncture needles (0.30 mm in diameter and 25–40 mm in length) will be inserted at a depth of 10-50 mm perpendicularly or obliquely into acupoints, upon the location of acupoints. Manual manipulation will be carried out for all acupoints to evoke needling sensation. Electrical stimulation will be delivered on 4 pairs of local acupoints surrounding the anus. The output peak current and voltage of the machine (model: ITO ES-360) are 6 V and 48 mA, respectively, with constant wave at frequency of 10 Hz and phase duration of 100 μs for 30 min. The stimulation intensity will be adjusted to a level at which patients felt most comfortable. For MAS, electrical stimulation will be only performed on bilateral Guan-Yuan-Shu (BL26 关元俞) and the parameters are the same as above, but the intensity will be adjusted to a level at which patients just start feeling stimulation. The design of MAS control regimen is based on the following two principals: (1) The acupoints used are unrelated or less related to the treated syndromes according to traditional Chinese medicine (TCM) theory; and (2) the number of acupoints used and the intensity of electrical stimulation are kept to a minimum level at which patients are aware of receiving active acupuncture treatment.

There will be a total of 7 sessions of treatment over the course of the trial. Each treatment session will last for 45 minutes. The first session will be conducted 4 hours after the completion of the surgery, and then repeated in evening on the same operative day. The procedure is repeated again in the morning and afternoon on post-operative day 1 before patient discharge, then once

daily on day 2 to day 4 in the ambulatory TCM center. Acupuncture procedure will be performed by TCM practitioner who have at least 5 years of experience in acupuncture practice.

4.4. Follow-up

Patients are interviewed by phone on post-operative day 7. Pain scores, use of opioid analgesics, time to return to work, presence of adverse effects from surgery, medication and acupuncture are recorded. First out-patient surgical clinic visit is scheduled on day 14. Perineal wound is examined and any presence of post-operative complication is documented. Questionnaire on patient satisfaction is collected. Weekly follow-up visits are arranged subsequently until the perineal wound is completely healed.

5. Data collection and outcome measurement

5.1. Data collected at randomization before operation

- Eligibility criteria fulfilled
- Randomising surgeon
- Hospital number
- Patient gender
- Date of birth
- Body mass index
- Occupation
- Medical history
- American Society of Anesthesiologists (ASA) status
- Grading, number and location of hemorrhoids
- Previous intervention to hemorrhoids
- Blood test for preoperative serum inflammatory markers (C-reactive protein)
- Hemorrhoidal Disease Symptom Score (HDSS) [9]
- Short Health Scale-Hemorrhoidal Disease (SHS-HD) [9]

5.2. Data collected during operation

- Code of surgeon
- Date of surgery
- Operative duration
- Number and location of hemorrhoidectomy
- Length of wound
- Use of transfixive ligation
- Weight of excised specimen
- Mode of anesthesia

- Dosage of local anesthetics used

5.3. Data collected during post-operative period and follow-up visit

- Maximal and resting NRS pain score on post-operative day 0, 1, 2, 3, 4, 7 and 14
- Opioid analgesic requirement (oral tramadol and parenteral morphine)
- Quality of recovery (QoR-15) [10]
- Patient satisfaction (0-10, 0 represents least satisfaction and 10 represents the most satisfaction)
- Blood test for preoperative serum inflammatory markers (C-reactive protein) on day 0 and day 1
- Length of hospital stay
- Date of return to work
- Time to first urination
- Time to first bowel motion
- Frequency of bowel motion
- Time to wound healing
- Presence of post-operative complications, e.g. acute retention of urine, per-rectal bleeding
- Readmission
- HDSS and SHS-HD scores at post-operative 3 months

5.4. Handling and Storage of Personal Data and Study Data

All personal and study data will be handled by the investigator and the confidentiality will be strictly maintained. Data will be locked in encrypted file in a password protected computer. Only the investigators will have access to the personal and study data. The principal investigator will be responsible for safekeeping of the personal and study data. All study data will be kept for 5 years and erased after completion of the storage period.

6. Statistical analysis

Baseline demographic data are described in means with standard deviation. Categorical data are displayed in number with percentages. Matched analysis is performed with grading of hemorrhoids, number of hemorrhoidectomy, number of transfixive ligation and size of incision being adjusted. Comparative analysis is conducted on intention-to-treat basis. Post-operative pain scores in NRS and other secondary outcomes are analyzed with Mann-Whitney U test. Paired sample t-test is used to compare individual changes in pain severity before and after acupuncture.

7. Ethical consideration and confidentiality

This study has been approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 25-302). This study is conducted in accordance with the Declaration of Helsinki. No major ethical issue is anticipated. Only the investigator and co-investigators are allowed to access the source of data. The Hospital Authority and other related monitoring boards including auditor, Institutional Review Board and Independent Ethics Committee officers are allowed to access the data and documents for inspection and monitoring. This study is conducted in compliance with the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines.

8. Financial disclosure

No commercial funding is received for this study.

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Patient Information Sheet and Consent Form

Study Title

Acupuncture for Post-hemorrhoidectomy Pain Control with Acute Anti-inflammatory Effects: A Randomized Controlled Trial

Background information

Conventional hemorrhoidectomy (CH) is the standard surgical treatment for symptomatic high grade hemorrhoids. Post-operative pain control remains a major concern and is crucial to early patient recovery.

Acupuncture is a widely adopted and safe technique for pain relief in Traditional Chinese Medicine (TCM). It has been applied as an adjunct for post-operative pain control in various surgical procedures including but not limited to abdominal, pelvic, obstetric and gynecological operations [1]. Various trials have been reported in the Chinese literature regarding its use after surgical treatment for hemorrhoids [2]. The benefits and effectiveness of electroacupuncture [3, 4] and manual acupuncture [5] in alleviating post-hemorrhoidectomy pain have been proven by multiple controlled trials.

We believe that this study will help to validate a standardized acupuncture protocol in combination with post-hemorrhoidectomy analgesic regime and increase our current understanding of biomarkers in the field of pain management.

Purpose of study

The aims of this trial are: (i) to evaluate efficacy and safety of generated acupuncture regime in post-operative pain management after CH; and (ii) to correlate acute analgesic effects with changes in peripheral inflammatory biomarkers.

Why have you been chosen for the study?

You are invited to take part in this clinical study because you are scheduled to undergo conventional hemorrhoidectomy for symptomatic hemorrhoids. Participation is voluntary and a written consent is sought. Before you decide whether you wish to participate, you will be given a clear explanation by your surgeon-in-charge about what the study involves. Please read this information sheet carefully. You may also discuss it with your partner, friends or family. If you have any questions, please do not hesitate to ask. You have at least 72 hours to decide if you want to take part in this study.

Method of study

In order to investigate whether acupuncture is beneficial for post-operative pain control after CH, the participating patients will be randomly allocated into two groups by computer programme in 1 to 1 ratio. The surgical and anesthetic procedure will be the same for both groups and also for patients not participating in this study. An additional blood sample (10ml) will be collected during the perioperative period for the study of inflammatory markers.

When you are returned to the surgical ward after the scheduled operation, one group will receive Fully active acupuncture (FAA) while the other group will receive Minimum acupuncture stimulation (MAS) as control. Seven acupuncture sessions will be performed in total over the first 5 post-operative days. The first session will be conducted in 4 hour after the completion of surgery, and then repeated in evening on the same operative day. The procedure is repeated again in the morning and afternoon on post-operative day 1 before discharge, and once daily on day 2 to day 4 at the Academic Building, School of Chinese Medicine, The University of Hong Kong. The acupuncture procedure will be performed by experienced TCM practitioners and each session will last for 45 minutes. In FAA group, acupuncture needles will be inserted to standard acupoints followed by manual manipulation and electrical stimulation at a level at which patients felt most comfortable. In MAS group, a different set of less related acupoints are used and the electrical stimulation intensity will be adjusted to a minimum level at which patients just start feeling stimulation.

The routine follow-up schedule is the same in all patients. You will be given a questionnaire regarding the pain scores and use of oral analgesics in the initial post-operative 2 weeks.

What are the possible advantages and disadvantages in participating in the study?

Possible advantages:

Recent studies have demonstrated potential benefits of acupuncture in alleviating wound pain in the early post-operative period. With a better analgesic regime, early mobilization, return to urinary and defecatory function, reduced use of opioid analgesics and early resumption of work can be facilitated. The primary objective of the study is to improve patient satisfaction and quality of recovery. With a validation of clinical benefit of acupuncture with stronger evidence, it may potentially benefit other patients with similar condition in the future.

Possible disadvantages:

Participants will be receiving additional acupuncture interventions over the first 5 days and questionnaire interview during follow-ups. There may be rare complications arising from acupuncture procedure including bleeding, pain, infection and injury to adjacent viscera. Patients who are allocated to MAS group may not have additional benefit in pain relief except a placebo effect.

Confidentiality

Only the investigators will have access to the medical information. The confidentiality of any personal information will be strictly maintained. The results of the study will be published in a medical journal in an anonymous fashion. When you sign the consent form, you give us your permission to collect, store and access medical and personal data, which will be stored safely for 5 years and erased after completion of study.

You have the rights of access to personal data and publicly available study results, if and when needed. Under the laws of Hong Kong (Personal Data (Privacy) Ordinance, Cap 486), you enjoy the rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of your personal data in this study. For any query, you should consult the Office of the Privacy Commissioner for Personal Data (Tel No.: 2827 2827) as to properly monitor the protection of your personal data so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

By consenting to participate in this study, you expressly authorize:

- the principal investigator and his research team and the ethics committee (Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)) responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process, you have the rights to contact the HKU/HA HKW IRB for any query (Tel No.: 2255 4086) ; and

- the relevant government agencies (e.g. the Hong Kong Department of Health) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

Insurance policy and compensation

Insurance has been applied for patients participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. You will not be charged for the study. The acupuncture intervention is a single one-week course treatment which will not be available after current study period until the service is launched in routine clinical practice.

Contact for enquiry

If you have any questions about this study, you may contact Dr. Patrick Wong at the Division of Colorectal Surgery, Department of Surgery, Queen Mary Hospital (Tel No.: 2255 4389).

Patient Informed Consent Form

Acupuncture for Post-hemorrhoidectomy Pain Control with Acute Anti-inflammatory Effects:

A Randomized Controlled Trial

I understand that the decision to participate in this study is voluntary. If I refuse for any reason or at any time stop to participate in the study, my treatment and care will not be affected in any way. I consent to my data being used for the purpose stated in the information sheet. I understand that the collected blood sample will not be sold for commercial benefits.

I have read and have been informed of the foregoing information, and I have the chance to discuss fully with the investigators about this study. I consent voluntarily to participate as a subject in this study.

Name of patient (in block letters)	Signature of patient	Date
Name of investigator (in block letters)	Signature of investigator	Date
Name of witness (in block letters)	Signature of witness	Date