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Protocol for a double-blinded randomised controlled trial investigating the use of adjunct bicarbonate in carpal tunnel release: a single-centre study

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ABSTRACT

Introduction This study aims to compare the effectiveness of buffered and non-buffered long-acting local anaesthetics in pain relief during and after carpal tunnel release (CTR) surgery. Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome. Surgical treatment of CTS, CTR, is the most common hand surgical operation. CTR is usually performed under local anaesthesia, the application of which is often the most painful event during the procedure. One important aspect of patient satisfaction is adequate pain management during and after CTR. Long-acting local anaesthetics provide good postoperative pain control. Adjunct bicarbonate has been shown to reduce pain during injection of local anaesthetic and to prolong its analgesic effect. To date, no published randomised controlled trial has compared buffered to non-buffered long-acting local anaesthetic during CTR.

Methods and analysis The study will randomly assign 116 patients with CTS to receive buffered or non-buffered mixtures of lidocaine and bupivacaine with epinephrine before CTR. The primary outcome is overall pain experienced during the injection of local anaesthetic, assessed with the Visual Analogue Scale. The secondary outcomes are pain intensity from the injection and during CTR, use of painkillers and pain intensity every 4 hours until third postoperative night, symptom severity and functional status preoperatively and at 3 months after surgery, and patient-rated outcome measures at 3 months after surgery.

Ethics and dissemination This protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District (2311/2021). The study will be performed according to the principles of good clinical practice and the Declaration of Helsinki. The results are expected to be presented in an international hand surgical conference and the manuscript to be sent to a hand surgery-orientated peer-reviewed journal during 2024.

Trial registration number This study is registered to clinicaltrials.gov, study ID NCT05328180.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blinded randomised controlled trial.
⇒ Large representative sample.
⇒ Outcome variables designed to measure subjective patient satisfaction.
⇒ Individual pain tolerance will be accounted for
⇒ Primary data collection method after operation is via internet, and this might create challenges of follow-up data completion rate, especially with elderly population.

INTRODUCTION

Background

Carpal tunnel syndrome (CTS) is worldwide, the most common peripheral nerve entrapment syndrome.[1] The prevalence of clinically and electrophysiologically diagnosed CTS is 2.7% in the general population, and it is more common in women.[2] There are multiple risk factors for CTS. Diabetes,[3] hypothyroidism,[4] overweight,[5] and physical work load factors, such as use of vibrating tools and high handgrip force,[6] have been linked to elevated risk of CTS.

Surgery has been reported to provide longer relief from symptoms, with better functional improvement than non-operative treatment.[1] Traditional carpal tunnel release (CTR) performed under general, regional or local anaesthesia with a tourniquet has lately largely been replaced with Wide Awake Local Anaesthesia No Tourniquet (WALANT). It has been shown that WALANT results in better perioperative and postoperative pain control,[7 8] at least in terms of good patient satisfaction,[9] equal functional results[8 9] and improved cost-efficiency.[10] Usually the most painful event during WALANT is the infiltration of the

local anaesthetic,[11] which was reported to cause a burning sensation.[12]

Rationale of the study

Multiple different methods have been used to reduce pain caused by injection of local anaesthetic, including topical anaesthetic creams,[13] smaller gauge needles[14 15] and slow infiltration of anaesthetic.[16] Pain can also be reduced by buffering the anaesthetic solution closer to neutral pH.[17] All of these aforementioned methods[13 14 16 17] have also been used in CTR.

Buffering lengthens the duration of analgesia and results in lower perceived pain levels at least 6 hours after CTR.[18] Buffering lidocaine with sodium bicarbonate reduces pain associated with the local anaesthetic injection before CTR.[19 20] Preliminary evidence also suggests that buffering of local anaesthetics could decrease postoperative painkiller consumption.[18]

There are no studies comparing the injection pain of long-acting local anaesthetics with and without a buffer in WALANT CTR surgery. Second, individual pain tolerance has not been accounted for in other studies assessing the possible pain reducing effect of buffered local anaesthetics in CTR.

Study aim and hypothesis

Our primary aim is to evaluate how buffering affects overall experienced injection pain during injection of long-acting local anaesthetic during surgical WALANT CTR. Our hypothesis is that buffering long-acting local anaesthetic with sodium bicarbonate decreases injection pain significantly.

METHODS AND ANALYSIS

Study design

DELICATE (aDjunct bicarbonatE in Local anaesthesIa for CarpAl Tunnel rElease) is a single-centre double-blinded randomised controlled superiority trial. The participants will be randomised in a 1:1 ratio into two groups.

Study setting

This study is conducted at the Kuopio University Hospital in Finland. Due to the centralised nature of the Finnish public healthcare system, most cases of CTS in the Northern Savo Hospital District are expected to be seen at Kuopio University Hospital. To be eligible to perform CTR, the surgeon must have already performed more than 30 CTR operations. All participating surgeons will be trained to inject the local anaesthetic and to perform CTR in a standardised way.

Participants (criteria)

The patients will be enlisted from referrals to the Kuopio University Hospital hand surgery outpatient clinic. 116 patients aged 18 or older with clinically and electrophysiologically diagnosed CTS who are scheduled for CTR will be included. Patients who have an associated disease or condition, including injuries to the median nerve, cervical radiculopathy, cubital tunnel syndrome, other peripheral neuropathy, previous carpal tunnel surgery on the same hand (reoperation), allergies to any component of the used anaesthetic solution, rheumatoid arthritis, chronic renal failure or profound cognitive impairment or pregnancy, will be excluded.

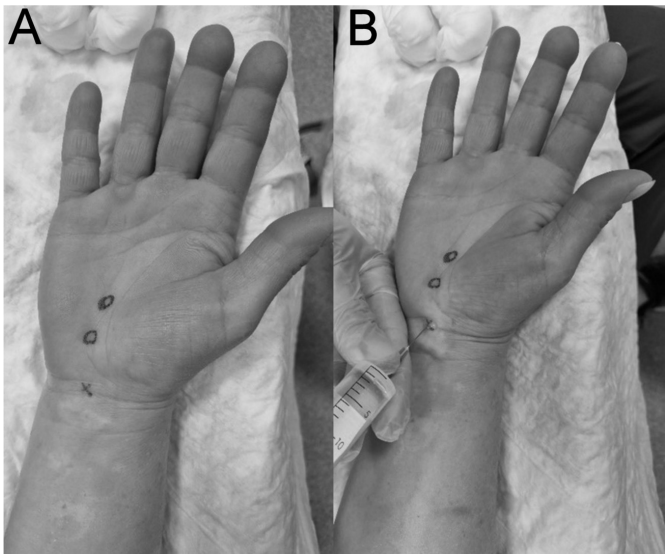

Figure 1 (A) Injection sites; X = mandatory infiltration site, O = optional infiltration site. (B) Infiltration of local anaesthetic to the carpal tunnel.

Interventions

The first group will receive a buffered local anaesthetic with epinephrine, while the second group will receive a non-buffered local anaesthetic with epinephrine. The buffered anaesthetic solution consists of 4.5 mL lidocaine with 1% epinephrine, 4.5 mL bupivacaine with 0.5% epinephrine and 1 mL 7.5% sodium bicarbonate. The non-buffered anaesthetic consists of 5 mL lidocaine with 1% epinephrine and 5 mL bupivacaine with 0.5% epinephrine. The purpose of buffering the anaesthetic is to raise its pH to closer neutral. All the surgeons will receive a written guide on how to perform anaesthesia, showing injection sites (figure 1A), and participate in a training session. A 10 mL of the anaesthetic solution is injected to the operative field (figure 1B). Injection lasts a minimum of 4 min. Additional local anaesthetic solution may be administered up to a maximum of 20 mL if required. A 24-gauge needle and a 10 mL syringe is used, and a wait of ≥5 min takes place before the skin incision. CTR is performed under WALANT. The skin incision is made on top of the carpal tunnel. Bleeding is controlled with bipolar coagulation forceps and the flexor retinaculum is released under direct vision. Neurolysis is not performed. The skin is closed either with absorbable or non-absorbable sutures. A wound dressing is applied. Paracetamol and ibuprofen are prescribed to the patients for postoperative pain management. If there are contraindications for either drug, only one will be prescribed.

Table 1 Data collection time points

	Baseline	Before LA	After LA	After CTR	3 Months follow-up
Primary outcome					
Total pain (VAS)			X		
Key secondary outcomes					
Pressure pain (VAS)			X		
Burning pain (VAS)			X		
Needle sting pain (VAS)			X		
Pain during CTR				X	
Symptom severity and functional status (BCTQ)	X				X
Patient satisfaction					X
Exploratory secondary outcomes					
Expected pain (VAS)		X			
No. of needle stings			X		
Analgesia duration					X
Consumption of pain killers					X

BCTQ, Boston Carpal Tunnel Questionnaire; CTR, carpal tunnel release; LA, local anaesthetic; VAS, Visual Analogue Scale.

Primary outcome

Our primary outcome for the study is overall pain experienced by the patient during injection of the local anaesthetic (table 1). Data will be collected immediately after injection of local anaesthetic.

Secondary outcomes

Our key secondary outcomes are different types of pain during injection of local anaesthetic, maximum pain during CTR, symptom severity and functional status and patient satisfaction at 3 months after CTR (table 1).

Our exploratory secondary outcomes are expected pain, number of needle stings, painkiller consumption and postoperative pain levels (table 1).

Primary and secondary outcomes and the data collecting time points are shown in table 1.

Participant timeline and recruitment

The first patient was recruited on 5 October 2022 and all the patients are assumed to be recruited during 2024. The cover letter, trial notice and trial consent regarding the research will be sent to patients with the invitation letter to CTR and the official recruitment will take place on the day the patient comes to surgery. The patient will be informed in person of the study and will complete a trial consent form. The recruiter helps the patient to fill the preoperative questionnaires. The patient completes postoperative questionnaires via an internet form at the 3 months follow-up time point (table 1).

The recruiter collects the following baseline data from the participants: age, gender, chronic diseases or conditions, continuous pain medication, smoking history, symptom severity and functional status, expected pain during injection of local anaesthetic and Pain Catastrophising Scale (PCS) Score. The patient recruitment process and initial data collection are depicted in figure 2.

Sample size

Sample size is calculated by the power of 90% and the risk for type 1 error is assumed to be 5%. A group difference of 15 mm is assumed, which is the smallest difference that is preferred to be detected. Minimal clinically important difference for Visual Analogue Scale (VAS) has been defined to be 13 mm on a 100 mm scale.[21 22] A common SD of 25 is assumed. With these values the sample size is 58 patients per group. All the patients are expected to remain in the trial, because there is no need for long follow-up. Hence, the final total sample size is 116 patients.

Allocation and blinding

Trialist AR will prepare randomisation lists. The groups will be coded as 1 and 2. AR will not participate in the treatment of patients and will not know which anaesthetic mixture each group (1 or 2) will receive. A research assistant (RA) prepares the anaesthetic solutions and gives them the assigned number (1 or 2). RA will decide which anaesthetic solution will be used in groups 1 and 2. RA will document the group identifications and the information will be kept unknown from the surgeons, caregivers, patients, researchers and data analysts until the unblinding is effected. The recruiter (study nurse or one of the researchers) has identification lists which contain the patient identification number. RA receives the identification number from the recruiter by phone and gives the recruiter the randomly allocated anaesthetic solution number (1 or 2) for the patient. The recruiter informs caregivers which numbered anaesthetic solution will be

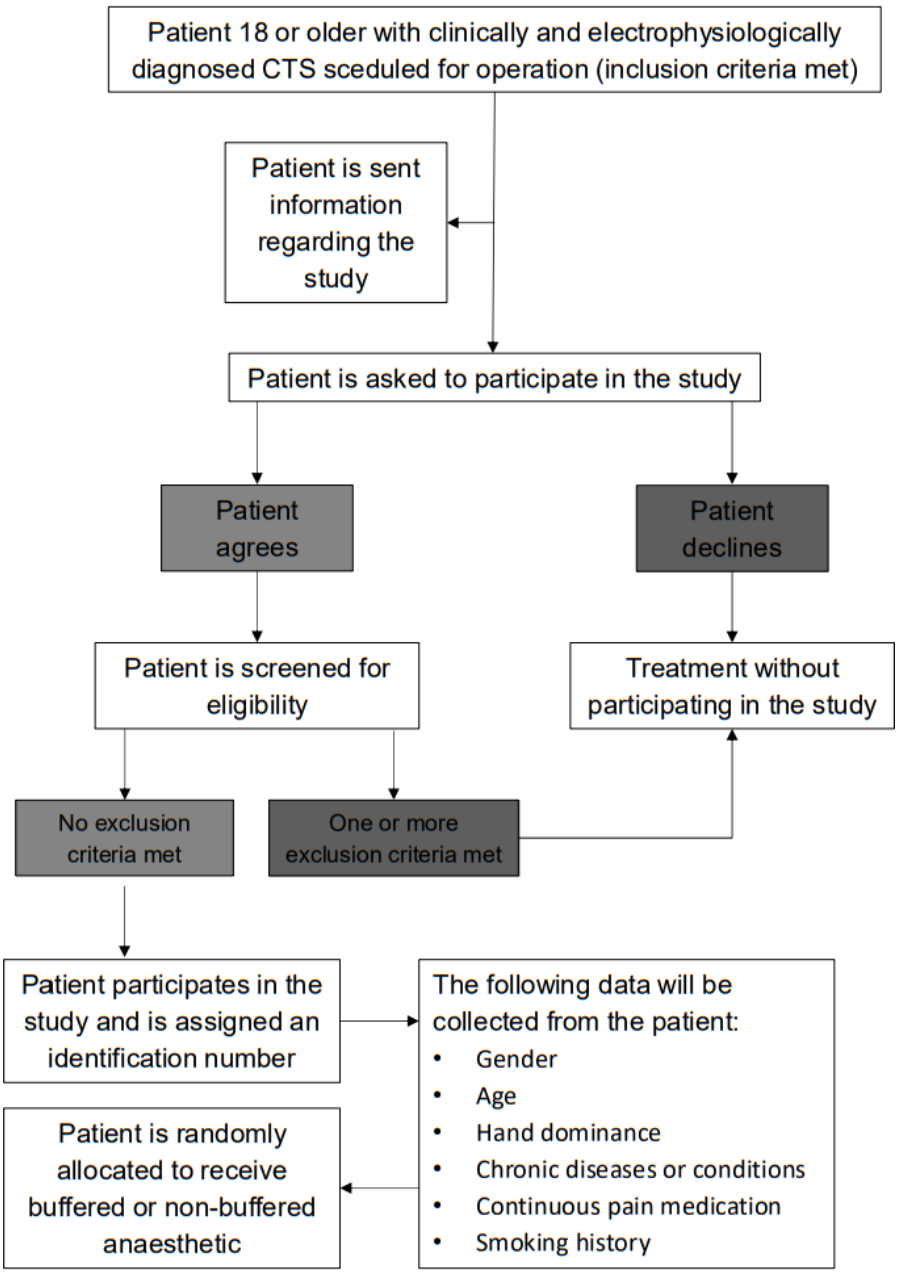

Figure 2 Patient recruitment path on the day of surgery. CTS, carpal tunnel syndrome.

used. After the results have been analysed, the randomisation is unblinded.

Randomisation

Patients will be randomised in a 1:1 ratio between intervention groups. Baseline PCS Scores (≥13will be considered high)[23] and hand dominance will be used as stratification variables. A varying block size is used in the randomisation process.

Data collection, management and analysis

The recruiter will obtain the consent form from the patient on the day of surgery. Patient data will be recorded in an identification and enrolment log, and the patient will be assigned an identification number to pseudonymise the data. Baseline data will be collected on the day of the operation. For symptom severity and functional status, the Boston Carpal Tunnel Questionnaire will be used, and for PCS, the PCS-FINv2.0 form will be used. The recruiter will assist the patient in completing paper forms if necessary. The recruiter will accompany the patient to the operating room to collect necessary data regarding pain levels. Preoperative and perioperative data will be collected using paper forms.

Follow-up data will be gathered with Surveymonkey (Momentive, San Mateo, California, USA), which is a General Data Protection Regulation approved survey software. All patients will receive instructions for the follow-up surveys and questionnaires after the operation. Analgesia duration and postoperative painkiller consumption are first recorded by the patient on a paper

form until the third postoperative night. The results are collected via Surveymonkey during follow-up. For evaluation of patient satisfaction, the 11-step Net Promoter Score is used. Adverse effects, such as infection, will be assessed via Surveymonkey in the follow-up survey. If a serious adverse event, such as nerve, artery or deep tendon injury, suspected deep infection or CRPS are noted or suspected, the patient will be referred urgently to the outpatient clinic for assessment. If the patient has not completed the necessary surveys or questionnaires 2 weeks from the follow-up time point, the patient will be contacted by phone. The requisite surveys or questionnaires will be filled out via phone if necessary.

Data of the trial will be exported to the Microsoft excel spreadsheet software (Washington, USA). Paper forms and excel files from the results are stored in a locked cabinet in the study nurse's office.

Statistical plan

Our primary outcome variable is the mean difference of VAS total pain between groups. This is calculated with linear regression. A multivariate analysis is compiled for our main analysis, in which the study group is included as a binary variable and age, gender, hand dominance and PCS will be used as covariates. The regression coefficient for the study group from this model with associated 95% CIs will be interpreted as the treatment effect. The adjusted treatment effect will be estimated by using age and gender as covariates. Adjusting will increase the statistical efficiency and decrease the standard errors. A similar analysis will be made for all other outcome measures, both adjusted for baseline PCS and adjusted for hand dominance, age, gender and baseline PCS.

Since some of the patients could be receiving continuous pain medication, a sensitivity analysis for pain killer consumption will be conducted.

The statistical analysis is performed using the R software environment (R: Core Team (2022); R: A language and environment for statistical computing; R: Foundation for Statistical Computing, Vienna, Austria). If there is missing data, it is expected to be missing at random and will be noted in the analyses.

Patient and public involvement

Patients, caregivers or the public were not involved in the development of the research question or in the planning of the study design. They are not involved in the recruitment or in the execution of the study. Results of the study will be published only in peer-reviewed journals; no other information regarding the study results will be provided to patients or caregivers. Patients or caregivers will not be involved in the assessment of the possible burdens of the study interventions.

ETHICS AND DISSEMINATION

An approval for the trial was acquired from The Research Ethics Committee of the Northern Savo Hospital District (2311/2021), and the consent form was written by the first author. The protocol is registered with clinicaltrials.gov. Personal information (identification code) is kept confidential by storing all confidential files in a locked cabinet in the study nurse's office. Data from the trial will be accessible to the study nurse, researchers and data analysts.

As any serious adverse events that would not be a consequence of routine treatment is not expected, there will be no need for extra harm compensation as a result of the trial. Any possible patient injuries will be compensated by the Finnish patient insurance centre in the usual way.

The results of this trial will be published in a hand surgery-oriented peer-reviewed journal. There are no funding-related restrictions on how study results can or will be disseminated.

All the data will be shared in the European Union/European Economic Area if requested. Shared data will be pseudonymised. Data will be stored after the trial for 15 years.

This research has no financial interests.

Time schedule

The recruitment has started in autumn 2022, and all patients are expected to be recruited during 2024. Data analysis should take place in autumn 2024, and the results are to be submitted by the end of 2024.

DISCUSSION

The prevalence of median nerve entrapment symptoms in the general population is up to 14%, and electrophysiologically verified CTS up to 3%.[2] CTS can be effectively treated by CTR,[1] which is increasingly performed under WALANT, due to its acknowledged benefits. WALANT is generally a more positive experience than excepted for the patient, and pain during surgery is comparable to that caused by other anaesthetic methods. Pain during surgery often results in a subjectively unsatisfactory surgery experience. This trial aims to lessen the pain felt during infiltration of the local anaesthetic, which is usually the most unpleasant event during CTR performed under WALANT.

1.0% lidocaine with epinephrine (1:100 000) has a pH of 4.24[24] and 0.5% bupivacaine a pH of 5.5.[25] Bupivacaine and lidocaine with epinephrine solution can be buffered to a more neutral pH using sodium bicarbonate.[26] Raising the pH to more neutral also increases the fraction of the non-ionised form of the anaesthetic,[26] which means that a greater proportion of the drug can enter neurons.[27] Thus, it could reduce injection pain. Buffering also reduces the amount of hydrogen ions in the solution, which could reduce the burning sensation caused by the injection.[26]

Buffering has been reported to be an effective pain reliever in CTR surgery.[18–20 28] Ozer *et al* used sodium bicarbonate to alkalise local anaesthetic, which decreased pain during the first 6 hours after CTR and increased

the duration of analgesia from 2 to 11 hours.[18] Yiannakopoulos[20] reported that addition of sodium bicarbonate to local anaesthetics reduced the infiltration pain during their administration. The authors concluded that sodium bicarbonate reduced especially the sensation of burning pain during the injection.[19] Watts and Mceachan reported that reducing the diameter of the injection needle decreased injection pain,[14] but it has been claimed that needle diameter is not as important in reducing pain as buffering of lidocaine with sodium bicarbonate.[15]

In a meta-analysis concerning local anaesthetics, lidocaine with epinephrine had a 5-hour mean duration of anaesthesia and bupivacaine with epinephrine 16 hours.[29] The mean injection pain of lidocaine with epinephrine on a VAS from 0 to 100 mm was 26 mm, and of bupivacaine with epinephrine 53 mm. Injection pain decreased to 30 mm when bupivacaine was mixed with lidocaine. Therefore, a mixture of bupivacaine with lidocaine should decrease injection pain and increase the duration of analgesia compared with plain lidocaine. Buffering could help to reduce this pain even more.

Better patient satisfaction in healthcare should be our goal. In CTR one of the most important aspects is pain control during and after the surgery. There is evidence that this could be achieved with as neutral as possible anaesthetic solution and long-acting anaesthetics. Hence, there is a clear need for this trial assessing the experienced pain from the injection with long-acting local anaesthetic with and without a buffer.

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Contributors MH: planning, writing and submission of the protocol. YN: planning, reviewing the protocol and steering the primary author. AR: planning and writing the statistical analysis plan. JS: reviewing the protocol and planning the data management and collection. NH and AS: writing the protocol. MPR: planning and writing the protocol; reviewing the protocol and steering the primary author. All authors have participated in revising and planning the article. Their work has been necessary for the submission of the article. All of the authors have approved the submission, and have agreed to be accountable for ensuring that all matters regarding this article will be resolved.

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Competing interests None declared.

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Patient consent for publication Consent obtained directly from patient(s).

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