Effect of intravenous lidocaine on chronic postoperative pain in patients undergoing breast cancer surgery: a prospective, double-blind, randomized, placebo-controlled clinical trial

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Contributions: (I) Conception and design: M Xia, H Jiang; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Q Wei, Q Zhang; (V) Data analysis and interpretation: M Xia, Q Wei, Q Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Chronic postoperative pain (CPSP) is one of the common complications of breast cancer patients, which can seriously affect the quality of life and long-term prognosis of patients. The purpose of this study was to investigate whether perioperative intravenous lidocaine infusion could reduce the incidence of CPSP in patients with breast cancer.

Methods: Female patients undergoing radical breast cancer surgery were randomly assigned to the 2% lidocaine group (L) and the control group (S). group L received an intravenous infusion of 1.5 mg/kg lidocaine 10 minutes prior to induction, followed by a continuous infusion of 2 mg/kg/h until the end of surgery. The control group received an equal amount of saline. The primary outcome was the incidence of CPSP at 3 months. Secondary outcomes included VAS pain scores and frequency of remedial analgesia within 24 hours postoperatively; incidence of CPSP at 1 and 6 months; and scores on the Brief Pain Inventory (BPI), Simplified McGill Pain Questionnaire (SF-MPQ), and Neuropathic Pain Score (DN-4) at 1, 3, and 6 months postoperatively.

Results: Eighty-two patients participated in this study. A total of 78 patients completed the 3-month postoperative follow-up (39 in group S and 39 in group L). At 3 months, the incidence of CPSP was significantly lower in the L group than in the S group (33.3% in the S group and 12.8% in the L group, P=0.032). Pain scores at rest and during exercise were significantly lower in the L group than in the S group at different time points ($P \leq 0.001$ and $P<0.001$). The need for remedial analgesia at 24 hours postoperatively also differed significantly between the two groups (P=0.036). At 6 months, the incidence of CPSP was also lower in the L group than in the S group (29.7% in the S group and 10.5% in the L group, P=0.038). The differences in SF-MPQ scores were statistically significant at both 3 and 6 months postoperatively (P=0.022, P=0.037).

Conclusions: Intravenous infusion of lidocaine reduces the incidence of CPSP in breast cancer patients at 3 and 6 months and is effective in relieving acute postoperative pain.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100050445.

Keywords: Lidocaine; breast cancer; chronic postoperative pain (CPSP)

Submitted Jun 30, 2022. Accepted for publication Jul 20, 2022.

doi: 10.21037/atm-22-3522

View this article at: https://dx.doi.org/10.21037/atm-22-3522

Introduction

In recent years, breast cancer has become the most common malignancy affecting women worldwide, and its incidence is increasing annually. According to the Global Cancer Observatory (GLOBOCAN) 2020 published by the International Agency for Research on Cancer of the World Health Organization, female breast cancer is the cancer with the highest number of new cases worldwide (1). Many studies have been reported on breast cancer treatment options, but few studies have addressed the incidence of chronic postoperative pain (CPSP) after mastectomy. Surgery is an important treatment for breast cancer. However, even minimally invasive procedures, such as lumpectomy or lymph node biopsy, may produce CPSP (2). Approximately 25–60% of women develop CPSP after breast cancer surgery, which severely affects their quality of life, emotions, and psychological state (3). The occurrence of CPSP is influenced by many factors, including psychosocial issues, type of breast cancer, perioperative chemotherapy or radiotherapy, the presence of preoperative pain, perioperative medication management (especially for pain), and tumor recurrence (2).

There was no clear definition of CPSP after breast surgery (CPBS) until 2019, when the International Association for the Study of Pain (IASP) clearly defined CPBS as "pain that develops or worsens after surgery in the breast region (anterolateral chest wall and, in some cases, the ipsilateral axillary region) and persists for 3 months after surgery". The mechanism by which CPSP occurs has not yet been fully understood. There are several pathophysiological theories regarding chronic pain after surgery, including traumatic nerve injury, inflammation, and peripheral and central sensitization. A Cochrane systematic review and meta-analysis published in 2013 (4) showed that, in addition to regional anesthetic techniques, only 1 systemically applied drug, intravenous ketamine, reduced the incidence of CPSP at 6 months; however, that meta-analysis did not include lidocaine-related studies. Lidocaine, similar to ketamine, reverses antagonism of human N-methyl D-aspartate (NMDA) receptor expression in *in vitro* models, and is significant in the range of plasma concentrations used in clinical applications (5). Where NMDA receptors in the dorsal horn of the spinal cord play a key role in neuroinflammation and nociceptive hypersensitivity (6), lidocaine also shows potent anti-inflammatory effects in both *in vitro* and *in vivo* models (7). Nociceptive hypersensitivity and neuroinflammation are precisely the key mechanisms by which chronic pain occurs. In a prospective study of 36 breast cancer surgery patients, it was found that intravenous lidocaine 1.5 mg/kg before induction of general anesthesia followed by a continuous infusion of lidocaine 1.5 mg/kg/h was effective in reducing the incidence and severity of CPSP after breast cancer surgery. At 3 months postoperatively, there were 2 patients (11.8%) in the lidocaine group and 9 patients (47.4%) in the control group, P=0.031 (8). However, the sample size of the study was small and only the McGill Pain Questionnaire was used in the study, which did not assess the occurrence of neuropathic rational pain after breast cancer surgery. Since then, researchers have increasingly explored this role of amide local anesthetics in surgical patients, as it modulates many pathophysiological processes associated with the development of CPSP. High-quality clinical evidence is needed to demonstrate the long-term effects of intravenous lidocaine. The purpose of this study was to explore whether perioperative intravenous lidocaine infusion could reduce the incidence of CPSP and improve outcomes related to CPSP in breast cancer patients. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3522/rc).

Methods

This is a double-blind, prospective, randomized controlled trial for which approval was granted by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (No. XYFY2021-KL273-01). Written informed consent was provided by all patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants

All female patients undergoing elective breast cancer surgery at Affiliated Hospital of Xuzhou Medical University between September 2020 and June 2021 were evaluated for eligibility. Participants who met all of the following criteria were included: American Society of Anesthesiologists (ASA) physical status I–III, age between 18 and 85 years, and planned to undergo breast cancer surgery under general anesthesia prior to registration. Only female patients were enrolled. Patients who were experiencing pain for any reason or were taking pain medication were excluded from this clinical trial. In addition, patients with a body mass index (BMI) >30 kg/m^2 or weight <40 kg, severe cardiac, renal, or hepatic disease, severe arrhythmias,

congestive heart failure, psychiatric or neurological disorders, emergency surgery, visual dysfunction, and contraindications or allergy to lidocaine were excluded from participation. The exclusion criteria were as follows: those who interrupted the infusion due to subjective or objective reasons; patients who were uncooperative, for whom we were unable to determine the efficacy, or whose data were incomplete and affected the determination of efficacy.

Randomization, blinding, and allocation concealment

A simple randomization method was used to randomly group the participants at the ratio of 1:1 using random numbers generated by a computer probabilistic system. The preparation of the intravenous infusion drug for patients in both groups was performed independently by an anesthesia nurse who did not participate in this study. The syringes containing the preparation were labeled with the patient's name, date of preparation, and route of administration, hence the blinding staff could not determine whether the preparation belonged to the control group or test group based on the appearance of the preparation. Emergency envelopes were prepared at the same time as drug blinding, and an opaque emergency envelope was set up for each blind number containing the case medication number and drug name so that individual cases could be unblinded and resuscitated in case of emergency. After the unblinding, the corresponding case would be treated as a shedding case. The emergency envelope was sent to the researcher along with the already-blinded drugs. This was a double-blind trial, all the patients and their families, anesthesiologists, surgeons, study recorders, and evaluators were unaware of the grouping and the composition of the drugs dispensed. A supervisor dedicated to coordinating and overseeing the entire study supervised the implementation of the blinding method, ensuring participant safety and the reliability of the results. This supervisor was responsible for distributing emergency envelopes, maintaining the blind codes, and opening the blind aspects at the end of the trial.

Anesthesia and post-anesthesia management

All patients were routinely requested to fast from solid food and liquids before surgery. The data collector visited the patients 1 day before surgery, explained the meaning and use of visual analogue scale (VAS) to the patients. After admission, all patients were monitored for non-invasive blood pressure (NIBP), electrocardiogram (ECG), and pulse oxygen saturation (SpO_2). The upper limb venous access was opened and intravenous infusion of compound electrolytes of 8 mL/kg was administered.

The bispectral index (BIS) was monitored by a brain state index monitor. General anesthesia was induced by intravenous administration of midazolam 0.05 mg/kg, sufentanil of 0.05 μg/kg, rocuronium 0.9 mg/kg, and etomidate 0.4 mg/kg, and the laryngeal mask was inserted when the patient's neck muscles were relaxed and the BIS value had decreased to 40–60. The respiratory parameters were set as follows: adjust the total flow of fresh gas to 2 L/min (FiO_2 0.5), tidal volume to 6–8 m/kg, and respiratory rate to 12–14 times/min. Intraoperative respiratory parameters were adjusted according to the situation, maintaining patient end-tidal carbon dioxide ($P_{ET}CO_2$) at 35–45 mmHg (1 mmHg =0.133 kPa). All participants were given 4 mg of tropisetron intravenously before skin excision to prevent postoperative nausea and vomiting.

General anesthesia was maintained with propofol (4–6 mg/kg/h) and remifentanil to maintain BIS values of 40–60. The infusion volume of remifentanil was adjusted as needed to maintain the mean arterial pressure (MAP) within ±20% of baseline values. Hypotension was defined as exceeding or decreasing 20% of the baseline MAP, or MAP <65 mmHg for more than 30 seconds.

In the case of hypotension, 20 μg of phenylephrine was administered. The intraoperative heart rate (HR) was maintained at 60–100 beats/min. When bradycardia (HR <50 beats/min) was present, 0.5 mg of atropine was administered. A convective warming blanket was used to maintain the patient's intraoperative body temperature at 36–37 ℃. Anesthetics were stopped during skin suturing; 0.04 mg/kg of neostigmine, 0.02 mg/kg of atropine, and 0.5 mg of flumazenil was injected intravenously, and the patient was sent to the post-anesthesia care unit (PACU). When the patient was awake with spontaneous breathing restored, laryngeal reflex and cough reflex restored, and tidal volume and minute respiratory normalized, the laryngeal mask could be removed and oxygen was administered with a face mask at 3 L/min. After observation in the PACU for about 1 hour, the patient could return to the ward. All participants were given standard postoperative analgesic analgesia. If the postoperative VAS score exceeded 4 points, 50 mg flurbiprofen axetil was injected intravenously. If it still exceeded 4 points, 0.1 mg of fentanyl was injected intravenously.

Intervention

In addition to the standard intraoperative management described above, a loading dose of 2% lidocaine of 1.5 mg/kg was pumped intravenously into Group L participants 10 minutes before induction of anesthesia, followed by induction of anesthesia using mask ventilation for oxygen denitrogenation. After the induction of anesthesia, this drug was continued at a pumping rate of 2.0 mg/kg/h using a micropump until the end of surgery. In Group S, a loading dose of normal saline with pumping was applied in an equal volume.

Outcomes and data collection

General and baseline data were collected and recorded by the preoperative visitors, including age, height, weight, comorbidities, marital status, history of surgery, history of smoking and drinking, education level, childbearing period, chronic pain, and pathological pain. Literacy was divided into 3 levels according to illiteracy, primary and high school, university and master's degree and above. Fertility was classified according to the "Stages of reproductive aging workshop +10 (STRAW+10)" staging system published in 2012, which divided the female reproductive aging process into 3 stages: the reproductive stage, the transitional stage of menopause, and the late stage of menopause (9), and each stage was further divided into early and late stages, which were represented by the Arabic numerals –5 to +2. The "–5 to –3a" was classified as the reproductive phase, "–2 to +1a" as the perimenopausal phase, and "+1b to +2" as the late menopausal phase. The presence of CPSP (defined as pain lasting at least 3 months prior to surgery), the presence of neuropathic pain [assessed by the Neuropathic Pain Score (DN-4) scale, with a DN-4 score ≥4 considered present], and the clinical significance, extent, nature, and treatment effect of pain and the physical and emotional impact of pain [Brief Pain Questionnaire (BPI), Simplified McGill Pain Questionnaire (SF-MPQ)] were used. During the study period, all study personnel were trained to comply with the study protocol and to use the above scales according to instructions or user guidelines.

The following intraoperative data were collected by the anesthesiologist: duration of anesthesia, type and dose of anesthetic drugs, type of procedure, and fluid balance. Any adverse event that occurred from the start of anesthesia until 24 hours after surgery that required or did not require intervention was recorded as an adverse event.

Acute pain: a numerical score of 0 to 10 (VAS) was used to rate the intensity of pain during the patient's stay in the PACU and ward at 30 minutes (t1), 1 hour (t2), 4 hours (t3), 8 hours (t4), 12 hours (t5), and 24 hours (t6) postoperatively at rest and during activity (ipsilateral arm elevation to 90° abduction position), respectively. Higher scores indicated higher levels of pain. Participants' complaints other than pain and medication use were observed and recorded by trained ward nurses.

CPSP: long-term follow-up by face-to-face or telephone interview at 1, 3, and 6 months after surgery. The definition of CPSP was pain lasting at least 3 months after surgery, not present before surgery or with different characteristics, and other possible causes of pain (e.g., cancer recurrence, infection) were excluded. Assessments were performed using the DN-4 scale, the BPI scale, and the SF-MPQ questionnaire, a self-administered questionnaire assessing pain severity and pain impact (10). Pain severity included 5 items, namely present pain, average pain, worst pain in the last 24 hours, least pain in the last 24 hours, and pain relief; each item was assessed on an 11-point numerical scale, where 0= no pain and 10= worst pain; the mean score was calculated to indicate the severity of pain. Pain impact included 7 items on general activity, mood, ability to walk, normal work, relationships with others, sleep, and enjoyment of life; each item was assessed on an 11-point numerical rating scale, where 0= no impact and 10= worst; mean scores were calculated to indicate the level of impact. The SF-MPQ is a pain self-rating questionnaire (11), consisting only of 11 sensory and 4 affective categories describing pain words as well as the present pain index (PPI) and VAS. Here we did not calculate the scores of PPI and VAS.

The primary outcome was the incidence of CPSP within 3 months after breast cancer surgery. Secondary outcomes included VAS pain score and frequency of remedial analgesia within 24 hours postoperatively; incidence of CPSP at 1 month and 6 months; and incidence of BPI scale, SF-MPQ scores and neuropathic pain at 1, 3, and 6 months postoperatively.

Sample size

Previous study has reported the incidence of CPSP as being from 25% to 60% (3). We hypothesized that lidocaine intervention would reduce the incidence of CPSP from 50% to 20% at 3 months after breast cancer surgery. The sample size required to detect a difference was 72 patients when significance and certainty were set at 0.05 (bilateral) and 80%, respectively. Considering the 20% shedding rate,

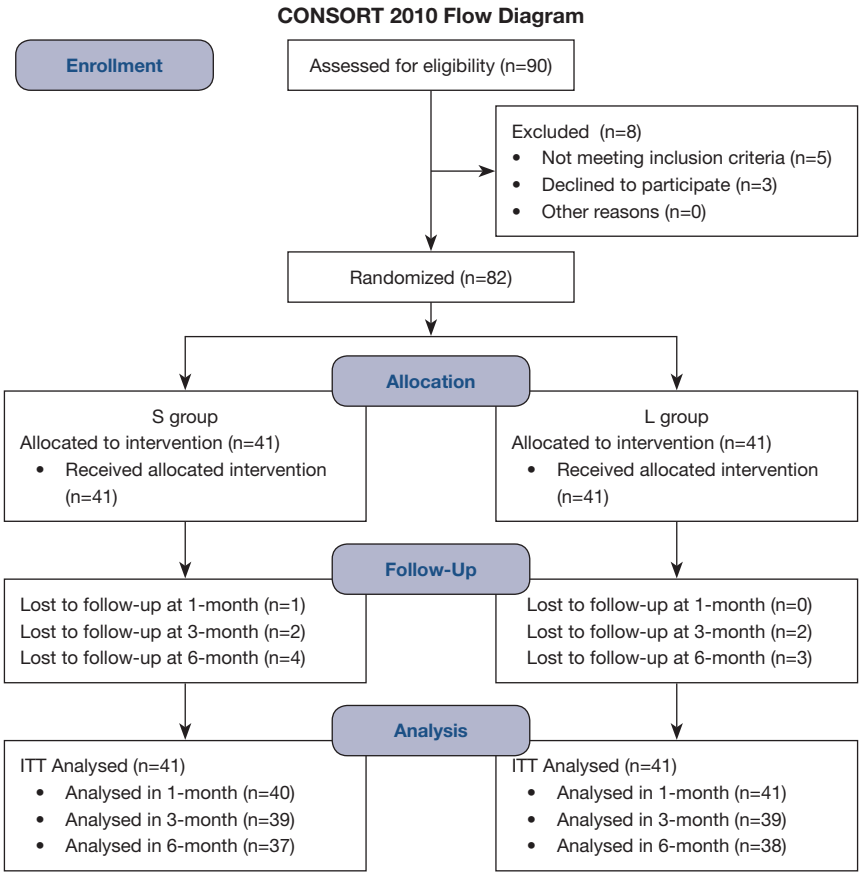

Figure 1 Flowchart of the study. CONSORT, Consolidated Standards or Reporting Trials; S, control; L, lidocaine; ITT, intention-to-treat.

we planned to recruit 90 patients. Sample size calculations were performed using PASS 15.0 software (NCSS, LLC, Kaysville, UT, USA).

Statistical analysis

The primary outcome, the incidence of CPSP at 3 months, was compared by χ^2 test, and differences between groups were expressed as relative risks (RRs; 95% CIs). These factors included age, BMI, education, STRAW+10 stage, history of preoperative pain, surgical approach, lymph node management, and whether or not radiotherapy was administered postoperatively.

For other outcomes, the Kolmogorov-Smirnov test was used to determine whether continuous-type data obeyed a normal distribution, and the Levene test was used to assess the chi-squareness. Normally distributed measures were expressed as mean ± standard deviation (mean ± SD), and 2 independent samples *t*-test was used for comparison between groups; non-normally distributed measures were expressed as median (M) interquartile range (IQR), and the Mann-Whitney U test was used for comparison between groups; the count data were expressed as the number of cases and percentages (%). The χ^2 test or Fisher's exact probability test were used for comparison between groups for count data. Differences between medians [95% confidence intervals (CIs)] were calculated using the Hodges-Lehmann estimator. Repeated measures data were analyzed using generalized estimating equations. Missing data are filled in using Last Observation Carried Forward (LOCF) as a replacement. Statistical analyses were in agreement with the intention-to-treat (ITT) principle. A 2-sided test was used, and differences were considered statistically significant when $P<0.05$. All statistical analyses were conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA).

Results

The CONSORT flow chart for this study is shown in *Figure 1*. Of the 90 patients who agreed to participate in

our study, 8 patients were excluded. Finally, 82 patients who underwent breast cancer surgery from September 2020 to June 2021 were included in this study. During the study period, 1 participant was lost at month 1 follow-up, 4 were lost at month 3 follow-up, and 7 were lost at month 6 follow-up. As a result, 82 patients were included in the intention-to-treat analysis; 81, 78, and 75 patients were included in the 1-month, 3-month, and 6-month analyses, respectively.

Patient demographics and baseline characteristics were well balanced between the 2 groups (*Table 1*). Intraoperative characteristics were as expected, with intraoperative remifentanil consumption (P=0.015) and the need for rescue analgesia within 24 hours postoperatively (P=0.036) significantly lower in the L group than in the S group. The time to extubation was also significantly shorter in the L group than in the S group (P=0.002). Other perioperative variables were not significantly different between the 2 groups (*Table 2*).

The incidence of CPSP was lower in the L group than in the S group at 3 months, with a statistically significant difference [33.3% (13/39) in the L group and 12.8% (5/39) in the S group, RR (95% CI): 0.600 (0.399 to 0.902), P=0.032] (*Table 3*). The incidence of CPSP at 1 month was not significantly different between the 2 groups (P=0.194), and the incidence of CPSP at 6 months was lower in the L group than in the S group, with a statistically significant difference (P=0.038). There was also no significant difference in neuropathic pain at 1, 3, and 6 months postoperatively. Other parameters were not significantly different between the 2 groups (*Table 3*).

The differences in VAS scores between the 2 groups were statistically significant (P<0.05) at 24 hours postoperatively, whether in the quiet or exercise state. The differences in VAS scores between the 2 groups were not statistically significant at 30 minutes, 12 hours, and 24 hours after extubation (P>0.05), and the VAS scores at 1, 4, and 8 hours postoperatively in the quiet state were 2.10 (0.8), 2.30 (1.0), and 2.50 (0.8) in group L and 2.70 (1.2), 3.30 (0.9), and 2.80 (0.9) in group S. The VAS scores of the L group were significantly lower than S group (P<0.001, P<0.001, P=0.038) both at rest and during activities, and the VAS scores at 1 hour and 4 hours postoperatively under exercise were 2.70 (1.0) and 2.60 (1.4) in the L group and 3.35 (1.2) and 3.80 (1.1) in the S group, which were significantly lower in L group (P<0.001), but at 8 hours postoperatively, they were 3.30 (1.7) and 3.70 (1.3) in group S. The difference between the 2 groups was not statistically significant (P=0.149) (*Figure 2* and *Table 4*).

Discussion

This study shows that intraoperative intravenous lidocaine infusion reduces the incidence of CPSP in patients undergoing mastectomy for breast cancer. It also yielded a significant improvement in postoperative acute pain intensity and intraoperative opioid requirements.

The continuous intravenous infusion of lidocaine is based on basic research. Although the pathophysiological mechanisms of CPSP are very complex, the current view is that the establishment and maintenance of central sensitization of nociceptive neurons in the dorsal horn of the spinal cord is its predominant pathophysiological process, with intense, repetitive, painful stimulation of peripheral neurons leading to central sensitization, and glial cell-mediated neuroinflammation is involved in maintaining this sensitized state (12). This thus leads to pain being perceived by patients in the presence of both painful stimuli (nociceptive hypersensitivity) and even non-painful stimuli (nociceptive hypersensitivity).

Lidocaine blocks sodium channels in nerve cell membranes, which may play a blocking role in the onset and transmission of inflammatory pain and neuropathic pain (13-15). It is now clear that lidocaine has anti-inflammatory effects: it prevents neutrophils from aggregating at the site of injury and reduces the release of inflammatory mediators (16). Lidocaine has shown antinociceptive effects in both the peripheral and central nervous systems. The use of lidocaine prior to surgical incision reduces nerve conduction from damaged peripheral nerves, thereby inhibiting pain onset and the development of secondary nociceptive hypersensitivity through peripheral and central mechanisms, respectively (17). Lidocaine has been used successfully in the treatment of central and peripheral neuropathic pain, complex regional pain syndromes, and fibromyalgia (18).

The optimal dose and duration of systemic application of lidocaine to reduce CPSP is currently unclear. In a meta-analysis of perioperative lidocaine to reduce acute pain, infusion doses of 2 mg/kg/h or more appeared to be effective, while lower doses were ineffective (19). Due to the apparent association between acute and CPSP (20) and the fact that patients with lidocaine infusion can be significantly relieved when plasma concentrations reach 2–3 μg/mL, the high-dose lidocaine regimen in the study CPSP trial is worth further investigation. Mechanistic studies of lidocaine ameliorating the pathophysiology of CPSP also suggest that

Table 1 Demographic and baseline characteristics

Characteristics	S group	L group	P value
Age, years	51.49±9.18	51.56±12.48	0.976
Body mass index, kg/m^2	24.73±2.08	23.89±2.77	0.125
Comorbidities			
Hypertension	22 (53.7)	23 (56.1)	0.824
Diabetes mellitus	11 (26.8)	12 (29.3)	0.806
Coronary heart disease	5 (12.2)	5 (12.2)	1.000
Pulmonary disease	3 (7.3)	3 (7.3)	1.000
ASA class			0.191
I	14 (34.1)	10 (24.4)	
II	25 (61.0)	31 (75.6)	
III	2 (4.9)	0 (0)	
Education			0.807
Illiteracy	24 (58.5)	22 (53.7)	
Primary junior high school	13 (31.7)	14 (34.1)	
University or master's degree	4 (9.8)	5 (12.2)	
History of nonthoracic surgery	9 (22.0)	8 (19.5)	0.785
Married	41 (100.0)	40 (97.6)	1.000
STRAW+10 stage			0.184
Growth Period	13 (31.7)	17 (41.5)	
Perimenopausal	13 (31.7)	6 (14.6)	
Postmenopausal	15 (36.6)	18 (43.9)	
Tobacco use	2 (4.9)	2 (4.9)	1.000
Alcohol use	7 (17.1)	4 (9.8)	0.331
CPSP*	5 (12.2)	4 (9.8)	0.724
Neuropathy pain**	1 (2.4)	2 (4.9)	0.556
SF-MPQ scores (0–45)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.857
SF-MPQ-S scores (0–33)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.957
SF-MPQ-A scores (0–12)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.943
Pain severity†	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.986
Pain interference‡	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.723

Data are mean ± SD, number (%), or median (interquartile range). *, defined as persistent pain for at least 3 months; **, defined as a score of ≥4 on the DN-4 scale; †, scores of pain severity on the Brief Pain Inventory-Short Form; ‡, scores of pain interference on the Brief Pain Inventory-Short Form. S, control; L, lidocaine; ASA, America Society of Anesthesiologists; STRAW+10 stage, stages of reproductive aging workshop +10; CPSP, chronic postoperative pain; SF-MPQ, short-form McGill pain questionnaire; SF-MPQ-S, short-form McGill pain questionnaire-sensitive; SF-MPQ-A, short-form McGill pain questionnaire-affective; SD, standard deviation; DN-4, Neuropathic Pain Score.

Table 2 Intra- and post-operative data

Characteristics	S group	L group	P value
Duration of anesthesia, min	108.0 (83.0–145.0)	111.0 (85–152.0)	0.568
Intraoperative medication			
Propofol, mg	888.4 (759.0–1,212.5)	1,032.6 (751.8–1,347.1)	0.368
Remifentanil, μg	1,225.0 (1,015.3–1,463.3)	1,022.4 (757.0–1,370.0)	0.015
Lidocaine, mg	0.0 (0.0–0.0)	340 (226.1–435.6)	0.000
Fluid balance			
Total fluid infusion, mL	1,079.5±365.7	1,128.2±360.8	0.467
Estimated blood loss, mL	58.5±21.1	51.7±19.5	0.143
Duration of surgery, min	128.0 (101.0–160.0)	140.0 (96.0–186.5)	
Type of breast surgery			0.810
Mastectomy	29 (70.7)	28 (68.3)	
Lumpectomy	12 (29.3)	13 (31.7)	
Management of ALNs			0.671
Dissection of ALNs	15 (36.6)	18 (43.9)	
Sentinel node biopsy	23 (56.1)	19 (46.3)	
None	3 (7.3)	4 (9.8)	
Induction			
HR, beats/min	82.5±7.6	81.9±8.8	0.749
MAP, mmHg	93.5±12.4	89.7±10.7	0.138
SPO_2, %	96.4±1.7	96.6±1.7	0.567
Extubation			
HR, beats/min	95.9±6.4	93.3±6.7	0.086
MAP, mmHg	100.2±7.1	99.6±8.5	0.707
SPO_2, %	98.2±1.4	97.9±1.3	0.354
Time, min	8.9±4.2	6.2±3.2	0.002
Frequency of analgesics used within 24 h after surgery	1 (0–2)	0 (0–1)	0.036
Postoperative chemotherapy	29 (70.7)	27 (65.9)	0.635
Postoperative radiotherapy	19 (46.3)	17 (41.5)	0.656
Postoperative hormone therapy	23 (56.1)	22 (53.7)	0.824

Data are median (interquartile range), number (%), or mean ± SD. S, control; L, lidocaine; ALNs, axillary lymph nodes; HR, heart rate; MAP, mean arterial pressure; SPO_2, oxygen saturation; SD, standard deviation.

prolonged lidocaine exposure results in better efficacy (16).

This study was conducted according to the pain survey short form (BPI form) and the McGill Pain Questionnaire recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). Follow-up of patients in both groups (21) assessed not only the presence or absence of chronic pain, but also the clinical significance of pain, the degree of pain at rest and during exercise, the nature of pain and treatment outcome, and the physical and emotional impact of pain. However, this study

Table 3 Effectiveness outcomes

Outcome	S group	L group	RR or median difference (95% CI)	P value
Primary outcome				
CPSP at 3 mo	13 (33.3)	5 (12.8)	0.600 (0.399–0.902)	0.032
Secondary outcomes				
CPSP at 1 mo	7 (17.5)	3 (7.3)	2.687 (0.643–11.235)	0.194
CPSP at 6 mo	11 (29.7)	4 (10.5)	0.591 (0.388–0.900)	0.038
SF-MPQ scores (0–45)				
At 1 mo	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.195
At 3 mo	33.0 (0.0–35.0)	0.0 (0.0–29.0)	0.0 (0.0–0.0)	0.022
At 6 mo	29.0 (0.0–34.0)	0.0 (0.0–28.3)	0.0 (0.0–0.0)	0.037
SF-MPQ-S scores (0–33)				
At 1 mo	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.189
At 3 mo	24.0 (0.0–27.0)	0.0 (0.0–21.0)	0.0 (0.0–0.0)	0.019
At 6 mo	20.0 (0.0–24.0)	0.0 (0.0–21.2)	0.0 (0.0–0.0)	0.039
SF-MPQ-A scores (0–12)				
At 1 mo	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.155
At 3 mo	9.0 (0.0–11.0)	0.0 (0.0–8.0)	0.0 (0.0–0.0)	0.024
At 6 mo	9.0 (0.0–9.2)	0.0 (0.0–7.0)	0.0 (0.0–0.0)	0.021
Neuropathic pain*				
At 1 mo	4 (10.3)	2 (4.9)	2.229 (0.384–12.923)	0.426
At 3 mo	6 (15.8)	4 (10.3)	1.641 (0.424–6.347)	0.470
At 6 mo	4 (11.1)	3 (7.9)	1.458 (0.303–7.023)	0.707
Pain severity†				
At 1 mo	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.397
At 3 mo	0.0 (0.0–2.0)	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.452
At 6 mo	0.0 (0.0–0.3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.622
Pain interference‡				
At 1 mo	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.347
At 3 mo	0.0 (0.0–2.2)	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.358
At 6 mo	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.510

Data are number (%), median (interquartile range), or mean ± SD. *, defined as a score of ≥4 on the DN-4 scale; †, scores of pain severity on the Brief Pain Inventory-Short Form; ‡, scores of pain interference on the Brief Pain Inventory-Short Form. S, control; L, lidocaine; RR, relative risk; CPSP, chronic postoperative pain; SF-MPQ, short-form McGill pain questionnaire; SF-MPQ-S, short-form McGill pain questionnaire-sensitive; SF-MPQ-A, short-form McGill pain questionnaire-affective; DN-4, Neuropathic Pain Score.

did not monitor intraoperative and postoperative patient serum lidocaine concentrations. If we had performed this measurement, we could have determined the effective dose of lidocaine and may have monitored the adverse effects of lidocaine more specifically. The safety of the small dose of lidocaine infusion used in this trial has been demonstrated in other studies. However, higher dose lidocaine infusions as well as more prolonged infusions warrant further study.

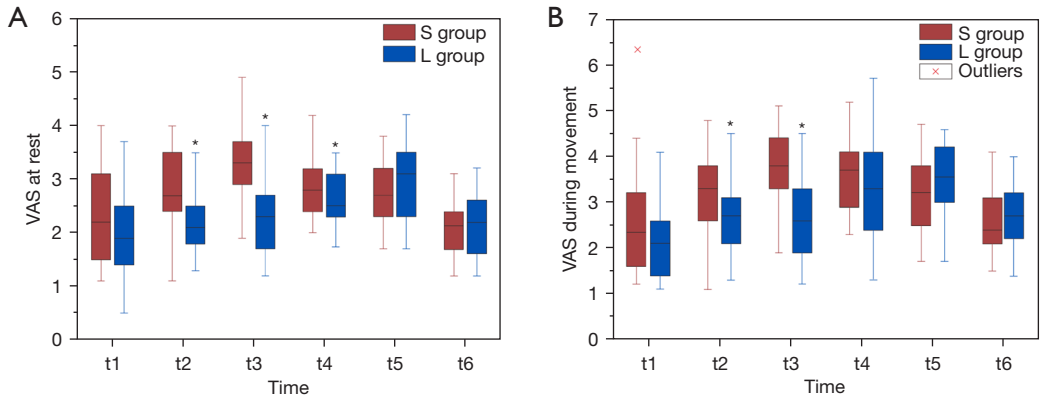

Figure 2 VAS pain scores at rest and during movement after surgery. Pain scores at rest and with movement at different time points were significantly lower in the L group than in the S group (P≤0.001 and P<0.001). Data were analyzed using generalized estimate equation. The box plots show medians and interquartile ranges, and individual points are mild outliers. *, P<0.05 compared with group S at the same time point; t1, 30 min after extubation; t2, 2 h after surgery; t3, 4 h after surgery; t4, 8 h after surgery; t5, 12 h after surgery; t6, 24 h after surgery; VAS, visual analogue scale (an 11-point scale where 0= no pain and 10= the worst pain); L, lidocaine; S, control.

Table 4 Comparison of VAS scores between the two groups at different time points

	Groups	M (IQR)	Wald χ^2	P value
Comparison among groups	S group	2.69 (0.07)	11.474	≤0.001
	L group	2.35 (0.08)		
Compare within groups	t1	2.14 (0.11)	101.873	<0.001
	t2	2.47 (0.85)		
	t3	2.74 (0.97)		
	t4	2.86 (0.83)		
	t5	2.82 (0.90)		
	t6	2.11 (0.07)		

The data does not conform to the normal distribution and is analyzed using a generalized linear model to estimate equations. VAS, visual analogue scale; IQR, interquartile range; t1, 30 min after extubation; t2, 2 h after surgery; t3, 4 h after surgery; t4, 8 h after surgery; t5, 12 h after surgery; t6, 24 h after surgery.

Only patients undergoing surgery for breast cancer were included in this study, but those undergoing excision of benign breast tumor blocks, even very small biopsies, may cause the development of CPSP. However, this study included patients who had pain prior to surgery, which improves the generalizability of the results of this trial. Nonetheless, further studies on a larger scale, in more centers, and with larger sample sizes are still necessary.

Conclusions

In conclusion, this prospective randomized controlled trial found that intraoperative lidocaine infusion reduced the incidence of CPSP in patients undergoing breast cancer surgery.

Acknowledgments

The authors are thankful for the support from the thyroid and breast surgeons and nursing teams of the Affiliated Hospital of Xuzhou Medical University.

Funding: This study was supported by the Talent Construction and Research Start-up Fund of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University

School of Medicine (Ming Xia).

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3522/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3522/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3522/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3522/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (No. XYFY2021-KL273-01). Written informed consent was provided by all patients.

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(English Language Editor: J. Jones)

Cite this article as: Xia M, Wei Q, Zhang Q, Jiang H. Effect of intravenous lidocaine on chronic postoperative pain in patients undergoing breast cancer surgery: a prospective, double-blind, randomized, placebo-controlled clinical trial. Ann Transl Med 2022;10(14):803. doi: 10.21037/atm-22-3522