

The use of 5% lidocaine medicated plaster for acute postoperative pain after gynecological surgery

A pilot randomized controlled feasibility trial

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Abstract

Objectives: To examine the feasibility and potential efficacy of 5% lidocaine medicated plaster for acute postoperative pain in a parallel, blinded, randomized controlled pilot trial.

Methods: Twenty-eight women undergoing elective gynecological surgery with midline incisions were randomly allocated 5% lidocaine medicated patch (Lignopad) or placebo plasters. Postoperative pain at rest and on movement at 24 hours were the primary study endpoints, with secondary endpoints of postoperative pain within the first 48 hours, cumulative morphine consumption (mg), predicted peak flow rate (PFR) (%) and adverse effects. We assessed pain scores at rest and on movement using the visual analogue scale (0–100).

Results: The lidocaine patch group had lower postoperative pain scores at rest at 24 hours (mean difference [MD] –15.1, 95% confidence interval [95% CI] –28.3 to –2.0; $P = .024$) but not on movement at 24 hours (MD –6.4, 95% CI –22.7 to 9.9; $P = .445$). Compared to placebo, lidocaine may slightly lower cumulative morphine consumption (mg) over time (MD –3.4, 95% CI –6.9 to 0.2; group*time interaction $P = .065$). The difference in improvement in the PFR over time after surgery between groups appeared small (group*time $P = .0980$). No adverse effects occurred.

Conclusions: Lidocaine patch may provide a clinically important reduction in postoperative pain intensity. A larger trial to confirm the efficacy and safety of lidocaine patch is feasible after modifying the inclusion criteria and collecting patient-centered outcomes, such as quality of recovery and patient satisfaction.

Abbreviations: 95% CI = 95% confidence interval, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IQR = interquartile range, IVPCA = intravenous patient controlled analgesia, MD = mean difference, PACU = post-anesthesia care unit, PFR = predicted peak flow rate, VAS = visual analogue scale.

Keywords: local anesthetics, pain management, transdermal patch

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The authors have no conflicts of interest to disclose.

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1. Introduction

Severe postoperative pain often occurs in patients undergoing laparotomies with midline incisions.^[1,2] Inadequate postoperative analgesia is associated with delayed recovery, poor patient wellbeing, pulmonary complications and deep vein thrombosis.^[3,4]

Current modalities for managing acute postoperative pain after abdominal surgery have limitations. Regional techniques, such as thoracic epidural analgesia and rectus sheath blocks may fail, are sometimes contraindicated and occasionally associated with rare but severe complications.^[5,6] With local anesthesia infiltration, the effect is short-lasting, and wound infection and delayed wound healing may occur.^[7] On Q pump providing continuous local anesthesia infusion may be associated with systemic local anesthesia toxicity and delay wound healing.^[8] Most patients with intravenous patient-controlled analgesia (IVPCA) have effective pain control but are at higher risk of pruritus as well as other opioid-related complications.^[9] Therefore, new methods of postoperative pain management are still sought after.

Topical 5% w/w lidocaine medicated patch is a 10 cm × 14 cm white hydrogel plaster, containing 700 mg lidocaine, which diffuses continuously into the applied skin, providing a local analgesic effect without producing local anesthesia.^[10,11] Lidocaine plaster is a non-invasive adjunct to pain management that is not limited by oral intake or adverse opioid-related effects, such as nausea, vomiting and respiratory depression. In patients with post-herpetic neuralgia and neuropathic pain syndrome, lidocaine is effective and well tolerated with mild skin irritation.^[12] However, the few studies of lidocaine plaster for acute postoperative pain management show inconsistent results.^[11,13,14]

Therefore, we examined the feasibility and potential efficacy of 5% lidocaine medicated patch (Lignopad, Mundipharma, Hong Kong) for acute postoperative pain in women undergoing elective gynecological surgery with midline incisions. The primary objective was to describe the postoperative pain intensity up to 72 hours and compare these patients in a way to guide future, well-designed randomized controlled trials. The secondary objective was to examine the cumulative morphine consumption, spirometry results and adverse effects. Our preliminary hypothesis was that lidocaine patch would reduce postoperative pain intensity without adverse effects.

2. Methods

We conducted a pilot parallel-group, 1:1 allocation ratio, superiority, blinded randomized controlled trial at the Prince of Wales Hospital, Hong Kong. This study was approved by the Institutional Review Board (CREC-2015.364-T) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at <http://www.chictr.org.cn> (ChiCTR-IOR-16007868, Principal investigator: Lydia Lau, Date of registration: January 29, 2016). After trial commencement, we shortened the postoperative assessment period from 72 hours to 48 hours as most patients had achieved adequate pain relief, did not require IVPCA or further follow-up for acute postoperative pain, and some were discharged home between 48 and 72 hours after surgery.

2.1. Participants

We recruited women from 18 to 60 years (American Society of Anesthesiologist [ASA] I or II) undergoing elective major non-oncological gynecological surgeries via planned midline incisions

between February 2016 and October 2017. We excluded those who refused either IVPCA or lidocaine patch, had hypersensitivity to local anesthetics of the amide type, inflamed or injured skin peri-surgical site, allergy or tolerance to opioids, planned transverse or oblique incisional approach, and extensive existing midline abdominal scarring.

Patients with decreased uterus mobility or uterus size ≥ 20 weeks on clinical examination by surgeons were likely to have midline incisions during surgery. The first author recruited the patients on the morning of the operation in the ambulatory gynecological ward after screening the elective gynecological team's surgical list posted on the day before surgery. Midline incisions were classified as "above umbilicus" or "sub-umbilical".

2.2. Pain management

All patients received standard general anesthetics. Fentanyl, propofol and atracurium were administered on induction and patients were intubated with controlled ventilation. For intra-operative pain management, fentanyl and morphine were used but regional anesthetic techniques (e.g. local anesthesia wound infiltration, thoracic epidural analgesia, transversus abdominis plane and rectus sheath blocks), ketamine and remifentanyl were avoided as per our institutional practice. An intravenous morphine patient-controlled analgesia (PCA) (setting: bolus dose 1 mg, lockout time 5–6 minutes, 4-hour limit 20–25 mg) and oral analgesic adjunct (paracetamol 1 g every 6 h) were prescribed for all patients for postoperative pain management. In case of insufficient analgesia, oral tramadol 50 mg every 6 hours could be given when necessary.

2.3. Intervention

Patients were randomized (unrestricted) to either lidocaine patch (Lignopad) or placebo plaster in the post-anesthesia care unit (PACU). Sequence generation was from a computer-generated random binary number list performed by an anesthesiologist not involved in the study. A sealed opaque envelope was used for allocation concealment. The patients, Acute Pain Team staff, study personnel and the data analyst were blinded to treatment allocation.

For patients randomized to the lidocaine patch group, 1 lidocaine patch covered with Omnifix (latex-free dressing retention tape, Hartmann, Sydney) was cut in half and applied along both sides of the midline wound before returning to the ward. In the placebo group, the lidocaine patch was replaced by a placebo plaster of the same size, which was made of dressing tape (Omnifix) sandwiching sterile gauzes. The active and placebo plasters were prepared by third-party anesthesiologists, stored in identical packaging within identical bags labelled 0 and 1. The plasters were applied by an Acute Pain Service nurse in the PACU, for 12 hours and removed. After a subsequent 12 hours plaster-free interval, a new set of plasters was applied. To maintain blinding, the plaster applications and removal were performed by nurses who were not part of the study team.

2.4. Outcomes

The primary outcomes were visual analogue scale (VAS) pain scores at rest and on movement (100 mm scale, 0 = no pain, 100 = worst possible pain) at 24 hours; these are recommended endpoints for clinical trials assessing patient comfort and pain

after surgery.^[15] Secondary study endpoints were pain at rest and on movement within the first 48 hours after surgery, cumulative IVPCA morphine consumption up to 48 hours after extubation, spirometry readings (predicted peak flow rate [PFR], forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC]) before surgery, at 24 h and 48 h after surgery, and adverse effects arising from active or placebo plasters.

The spirometry readings in patients were performed by the first author at the bedside using a digital spirometer (Micro Medical Microloop II Spirometer model serial #3356, Kent). The Acute Pain Team staff collected the other primary and secondary outcomes in the postoperative period.

2.5. Statistical analysis

Since this was a pilot trial, 15 patients per treatment arm would be large enough to detect a small to medium effect size with a 2-sided Type 1 error rate of 5% and a power of 80%.^[16] A total of 30 patients would identify any issues with study practicalities and recruitment logistics.

Intention-to-treat analysis was used. Descriptive data are reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. A Mann-Whitney *U* test was performed to compare the median postoperative length of stay between groups. A generalized estimating equation (GEE) model with a Gaussian distribution, identity link function,

exchangeable correlation, and robust variance was used to estimate the main effect of treatment, time and group*time interaction on outcomes. We used the recommended minimal clinically important difference for measuring acute postoperative pain; a change of 10 for the 100 mm pain VAS.^[17] The level of significance was set at 2-sided $P < .05$. We interpreted borderline significant results using guidelines from Hackshaw and Kirkwood.^[18] The statistical tests were performed using Stata 15.1 (StataCorp, College Station, TX).

3. Results

Of the 41 patients recruited, 13 patients were excluded (11 transverse incisions, 1 no IVPCA due to allergic reactions and 1 did not proceed to surgery due to pyrexia). Thus, 28 patients were randomized, with 14 in each arm (Fig. 1). The 2 groups were comparable for patient demographics and baseline characteristics (Table 1). No patient required oral tramadol during the follow-up.

3.1. Safety and feasibility

Sixty-eight percent of patients eligible for the trial were recruited over 21 months. All patients received their allocated intervention and none were lost to follow-up. There were no missing data. None of the patients reported any adverse effects with the plasters (0%, 95% CI 0% to 10.1%).

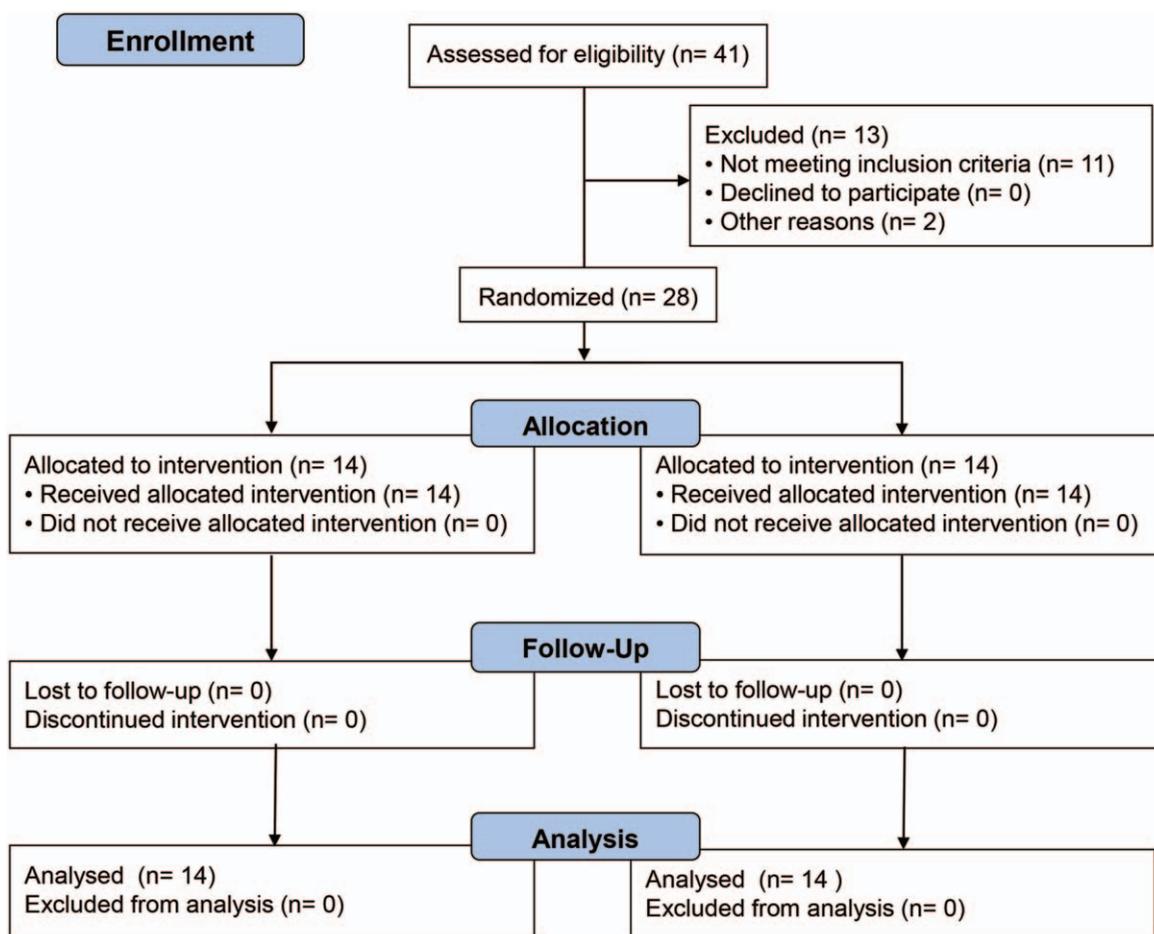


Figure 1. Flow diagram of participants.

Table 1**Patient demographics and baseline characteristics by treatment arm.**

Characteristic	Lidocaine patch Group (n=14)	Placebo plaster Group (n=14)
Median (IQR) Age, years	46 (43.8–48.5)	46 (40.0–50.5)
Mean (SD) BMI, kg/m ²	26.4 (5.7)	25.3 (3.5)
ASA Physical Status I: II, n	10: 4	8: 6
Incision above umbilicus, n	4	6
Median (IQR) uterus size on palpation, weeks	24 (20–24)	20 (20–24)
Median (IQR) duration of surgery, mins	135 (114–151)	135 (110–160)
Median (IQR) blood loss, ml	350 (238–850)	550 (88–1313)
Mean (SD) Preoperative spirometry		
Peak flow rate (%)	72.7 (16.8)	82.4 (16.0)
FEV1 (%)	95.9 (19.7)	102.2 (14.6)
FVC (%)	84.6 (15.4)	89.6 (13.3)
Mean (SD) Baseline VAS in PACU (mm)		
At rest	68.7 (22.5)	69.6 (24.8)
On movement	78.0 (17.9)	76.9 (24.0)

ASA = American Society of Anesthesiologist, BMI = body mass index, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity over time, IQR = interquartile range, PACU = postanesthesia care unit, SD = standard deviation, VAS = visual analogue scale.

3.2. Clinical outcomes

For the primary outcomes, the lidocaine patch group had lower postoperative pain scores at rest at 24 h (mean difference [MD] -15.1 , 95% CI -28.3 to -2.0 ; $P = .024$) but not on movement at 24 h (MD -6.4 , 95% CI -22.7 to 9.9 ; $P = .445$) [Fig. 2A and Fig. 2B].

During the follow-up, the mean postoperative pain intensity scores at rest and on movement decreased significantly in a time-dependent manner (both $P < .001$). The overall reductions in postoperative pain intensity at rest or on movement over 48 hours were not greater in patients given lidocaine patches than those given placebo plaster (group*time interactions $P = .397$ and $P = .758$ respectively) [Fig. 2A and Fig. 2B]. The overall mean reduction in postoperative pain intensity (mm) at rest from the lidocaine patches (31.6, 95% CI 25.6–37.6) compared to placebo plaster (39.8, 95% CI 32.2–47.4) was probably small (MD -8.2 , 95% CI -17.9 to 1.5 ; $P = .098$) [Fig. 2A]. For the overall mean postoperative pain intensity (mm) on movement, there was no difference between lidocaine (55.3, 95% CI 49.3–61.3) and placebo (58.1, 95% CI 48.4–67.8) groups (MD -2.8 , 95% CI -14.2 to 8.6 ; $P = .632$) [Fig. 2B].

Compared to placebo, the lidocaine patch may slightly lower cumulative morphine consumption (mg) over time (MD -3.4 , 95% CI -6.9 to 0.2 ; group*time interaction $P = .065$) [Fig. 2C]. However, there was no overall MD in cumulative morphine consumption (mg) between lidocaine (15.3, 95% CI 9.2–21.3) and placebo (19.6, 95% CI 13.5–25.8) groups (MD -4.4 , 95% CI -13.0 to 4.2 ; $P = .317$).

The difference in improvement in the PFR over time after surgery between groups appeared small (group*time $P = .0980$) [Fig. 2D]. We found no overall MD in predicted PFR (%) between lidocaine (56.4, 95% CI 50.4–62.4) and placebo (58.1, 95% CI 52.2–64.0) groups (MD -1.7 , 95% CI -10.1 to 6.7 ; $P = .689$). The FEV1 and FVC results over time between groups were similar to the predicted PFR results (not shown). The median (IQR) postoperative length of stay (days) in the lidocaine and placebo groups were similar (3.5, 3.0–4.3 versus 3.0, 3.0–4.3, respectively; $P = .701$).

4. Discussion

The results of this pilot randomized controlled trial showed a potential for lidocaine patch to provide acceptable pain control

after gynecological surgery. While all patients experienced severe pain intensities at rest and on movement in the PACU, we found a clinically important reduction in pain scores at rest at 24 hours from using lidocaine patches. A post-hoc analysis of acceptable pain control at rest on the first day after surgery (VAS ≤ 33 mm)^[17] suggests that the lidocaine patch group (12/14) were more likely to respond than the placebo plaster group (7/14) (relative risk 1.71, 95% CI 1.02–3.23). This may partly explain the borderline significance in the group*time interaction result found for cumulative morphine consumption as there was little change in morphine consumption during the 24 to 48 hours interval in the lidocaine group (Fig. 2C). Even though there were no adverse effects throughout the study, the study power was insufficient to confirm the safety of lidocaine patch for acute postoperative pain management in this surgical population.

In a similar randomized controlled trial in 2012, the use of lidocaine patch after laparoscopic gynecological surgery was associated with lower wound pain scores at 1 hour and 6 hours after surgery ($P = .005$ and $P < .005$, respectively).^[19] Like ours, the sample size of this study was also small ($n = 40$) and a borderline significant reduction in the median postoperative pethidine consumption was found ($P = .077$).^[19] In contrast, the results from a systematic review of 5 randomized controlled trials (total 251 participants) of lidocaine patches for acute postoperative pain was difficult to interpret as there was high clinical and statistical heterogeneity among the studies for controls, surgical population (laparoscopic general, orthopedic, urological, and gynecological), level of risk of biases and difference in the timing of postoperative pain scores taken.^[14] Nevertheless, there was no association between lidocaine patches and pain intensity at rest at 24 hours after surgery (MD -9.1 , 95% CI -23.3 to 5.20 ; $P = .21$, $I^2 = 99\%$) or in the duration of hospital stay (MD 0.2 days, 95% CI -0.8 to 0.4 ; $P = .55$, $I^2 = 43\%$).^[14] None of the 5 trials reported the occurrence of wound complications, skin irritation, or systemic side effects, suggesting that lidocaine patches appeared to be safe for acute postoperative pain management.^[14]

Our study identified several issues that need to be addressed when planning for a high quality, larger randomized controlled trial. First, since we restricted the inclusion criteria to women who had benign gynecological surgery with midline incisions to control for clinical heterogeneity, the recruitment rate was disappointingly slow. Broadening the inclusion criteria to either oncological gynecological patients with planned midline incisions

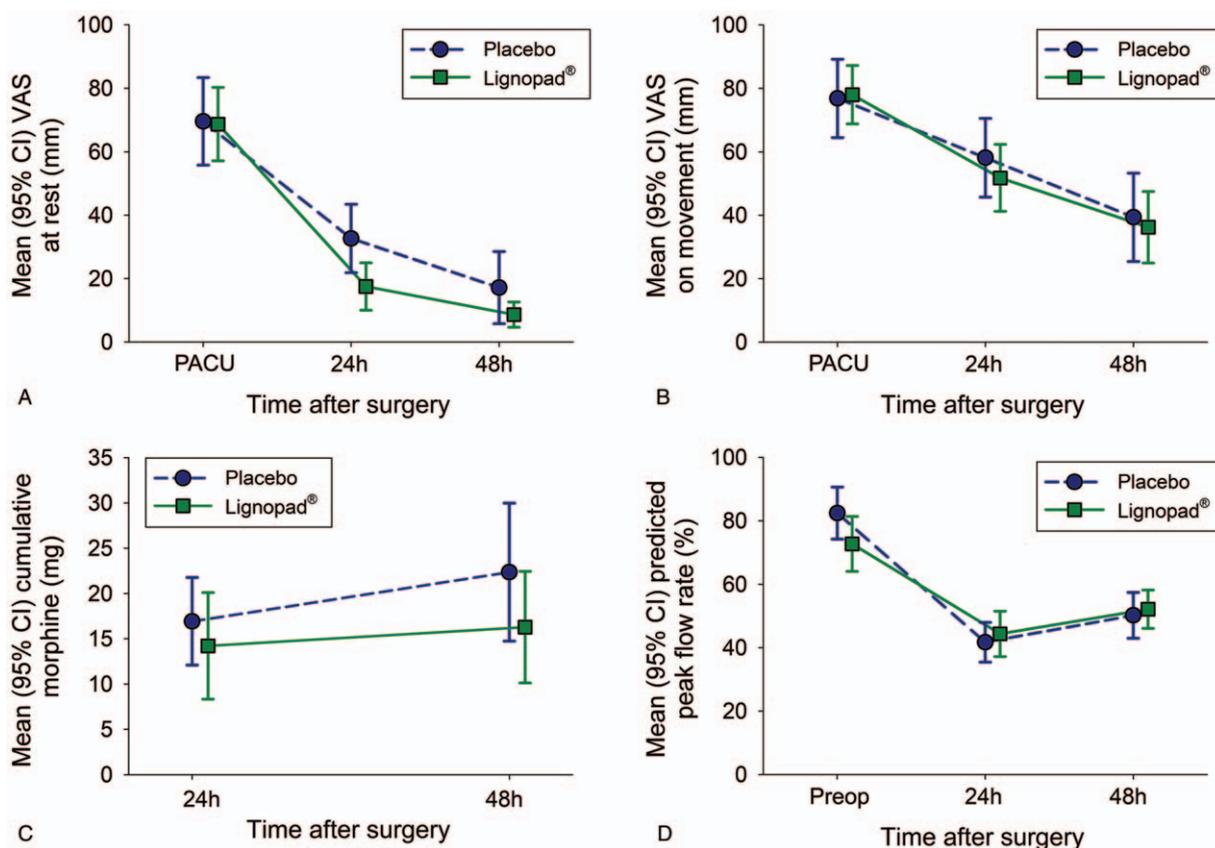


Figure 2. Mean (95% CI) pain intensity scores, intravenous patient-controlled analgesia opioid consumption and spirometry over time by treatment groups (Lidocaine patch n=14, Placebo plaster n=14). (A) pain intensity scores at rest (VAS), (B) pain intensity scores on movement (VAS), (C) cumulative morphine consumption (mg), (D) predicted peak flow rate (%). 95% CI=95% confidence interval, VAS=visual analogue scale.

or patients with transverse incision wounds would increase the recruitment rate and applicability of the results. Second, our production of placebo plasters was tedious, mainly due to the need to dispose of both lidocaine patch and placebo plasters within 2 weeks of the packages being opened. Placebo plasters made by the pharmaceutical company for lidocaine patch are available and should be encouraged in larger scaled studies. In addition, bedside spirometry results to determine respiratory functional improvement may be unreliable as it is mainly patient effort-dependent and performed in suboptimal semi-reclined or sitting positions after surgery. Finally, measuring the quality of recovery using validated questionnaires,^[20] patient satisfaction, days alive and out of hospital in the first month after surgery would be clinically meaningful to assess the full impact of lidocaine patches on 'patient comfort' and 'patient-centered outcomes'.^[15]

In summary, the use of lidocaine patch may provide a reduction in postoperative pain intensity at rest without adverse effects. A larger trial to confirm the efficacy and safety of lidocaine patch is feasible after widening the inclusion criteria and collecting more clinically meaningful patient outcomes.

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sample drug stocks provided by Mundipharma Hong Kong Limited for off-label use in this study.

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