A randomized controlled study to compare analgesic efficacy of sublingual buprenorphine and intravenous tramadol in patients undergoing mastectomy

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Abstract

Sublingual (SL) buprenorphine is approved for managing acute postoperative pain, characterized by easy administration, good pain relief and good patient compliance. We hypothesized that SL buprenorphine would be a better perioperative analgesic compared to intravenous (IV) opioids like tramadol in patients undergoing mastectomy surgery for breast cancer. After institutional ethics committee approval, we randomized 60 patients with breast cancer into 2 groups. In buprenorphine group, patients received 200 µg of SL buprenorphine thrice daily and in tramadol group patients received 100 mg of IV tramadol thrice daily. The analgesic efficacy of SL buprenorphine was comparable to that of IV tramadol. Visual Analogue Scale scores had no significant difference between the two groups at various time frames (0, 1, 3, 6, 12, 18 and 24 hours) at rest and movement except at 0 and 3 hours during movement when the score was lower in the tramadol group than the buprenorphine group. Four patients in the buprenorphine group received rescue analgesic (IV morphine 3 mg). Analgesic efficacy of SL buprenorphine appears comparable to IV tramadol for managing postoperative pain after mastectomy. SL buprenorphine can be administered sublingually, which is an advantage.

Key words: acute pain; analgesia; anesthesia; buprenorphine; mastectomy; opioids; perioperative care; postoperative pain; sublingual; tramadol

INTRODUCTION

Postmastectomy pain syndrome (PMPS) is a chronic neuropathic pain observed in women who undergo breast surgery.[1] The causes for PMPS are multifactorial and not understood completely.[2] However once developed, it is very difficult to treat. The incidence of PMPS is 25–60%.[3] Poorly managed postoperative pain after breast surgery is one of the important causes of PMPS.[4]

Buprenorphine is a semisynthetic derivative of thebaine that is in use for more than 30 years. It is 25 to 50 times more potent than morphine in terms of analgesia. The analgesic efficacy of 300 µg of intravenous (IV) buprenorphine is equal to 10 mg of IV morphine.[5] Although classified as a partial µ-opioid receptor agonist, buprenorphine acts on mu, delta, and opioid-like receptors and antagonist kappa-receptor.[6] The use of buprenorphine has been suggested for moderate to severe acute postoperative pain.[7] Buprenorphine is available in an injected form that has been used IV, intrathecally, epidurally as an adjunct in peripheral nerve block.[8,9]

Although transdermal buprenorphine patch is approved for use in chronic pain, researchers have used it successfully in managing acute postoperative pain.[10] Buprenorphine is available for clinical use in the form of sublingual (SL) tablets which have been successfully used in managing acute postoperative pain without major adverse events.[11] In a systematic review and meta-analysis of randomized control trials comparing IV/intramuscular morphine with SL buprenorphine, White et al.[12] concluded that SL buprenorphine provides analgesic efficacy comparable to morphine but has the advantage of the ease of administration and lesser incidence of pruritus.

We hypothesized that SL buprenorphine used in a dose of 200 µg every 8 hours in patients undergoing modified radical mastectomy provides better postoperative analgesia compared to IV tramadol 100 mg every 8 hours that is an established practice in our department.

SUBJECTS AND METHODS

Design

An approval was obtained from the Institutional Ethics Committee at Basavatarakam Indo-American Cancer Hospital and Research Institute (IEC/2019/66, dated May 13, 2019), Hyderabad, Telangana State, India) for this prospective, randomized, single-blinded study. The study was performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement[13] (**Additional file 1**).

We recruited 60 female patients aged 18 to 65 years belonging to the American Society of Anesthesiologists-physical status class I and II,[14] scheduled for elective, unilateral modified radical mastectomy surgery for breast cancer in the study. Patients who were unable or unwilling to give informed consent; a history of addiction, current usage of opioids or known allergy to opioids, severe respiratory, renal, hepatic, or cardiac issues, hemodynamically unstable, pregnant, history of exces-

sive nausea/vomiting during chemotherapy or previous history of postoperative nausea/vomiting (PONV) and weighing less than 50 kg were excluded from the study. All the patients were fully informed of the study process, advantages, disadvantages, and side effects, and informed consent (Additional file 1) was taken from each patient. Computer-generated block randomization (www.random.org) was used for the two groups of 30 each. Patients were randomized to receive either SL buprenorphine (buprenorphine group) or IV tramadol (tramadol group) postoperatively. The demography data were collected after randomization and entered into a form.

Preoperative phase

A pre-anesthesia check-up was done to evaluate for surgical fitness. Routine investigations like complete blood picture, blood group, serum creatinine and viral markers were ordered for all patients. Patients who received anthracycline based chemotherapy or trastuzumab were advised a 12-lead electrocardiogram and two-dimensional echocardiography. Once declared fit for surgery and after confirming nil by mouth status of 6 hours for solids and 2 hours for clear liquids, patients were shifted to the operating room.

Intraoperative phase

An appropriately sized IV line was secured on the non-operative side upper limb. Lidocaine (1.5 mg/kg, up to 100 mg; 2%; Xylocard®, Astra Zeneca, Bangalore, India) and midazolam (0.03 mg/kg; Mezolam®, Neon Pharmaceuticals, New Delhi, India) were administered IV for premedication followed by IV fentanyl (2 µg/kg, max 150 µg; Fenstud®, Rusan Pharmaceuticals, Dehra Dun, India) was given. Patients were preoxygenated with 100% oxygen and induced with IV propofol (2–2.5 mg/kg; Profol Spiva, Baxter Pharmaceuticals India Private Ltd., Ahmedabad, India). An appropriately sized supraglottic airway (Ambu® AuraGain™, Xiamen, China) was used to secure the airway. IV atracurium (Atrapure®, Samarth Pharmaceuticals, Mumbai, India) 0.5 mg/kg was administered to achieve neuromuscular blockade approximately 5 minutes prior to incision. Maintenance of general anaesthesia was with oxygen, medical air, and isoflurane (minimal alveolar concentration of 1.0; Aerrane, Baxter Healthcare Corporation, Guayama, Puerto Rico, USA) using volume-controlled ventilation.

Intraoperatively monitoring was done as per standard American Society of Anesthesiologists monitoring guidelines15 with electrocardiogram (lead II, V5), non-invasive blood pressure, oxygen saturation, end-tidal carbon dioxide, and end-tidal isoflurane. Ranitidine (50 mg; Rantac®, J.B. Chemicals and Pharmaceutical Ltd., Mumbai, India), dexamethasone (0.1 mg/kg; Dexona®, Zydus Alidac, Vadodara, India) and cefuroxime (1.5 g; Fervay®, Biocon Pharma, Vadodara, India) were administered IV to all patients after securing airway. During surgery with an increase in heart rate and blood pressure by at least 20% above baseline, fentanyl 0.5 µg/kg was given. Intraoperative fentanyl consumption was noted between both groups for comparison. All patients received IV paracetamol (Paraprime®, Intas Pharmaceutical, Ahmedabad, India) 1 g over 15 minutes during skin closure. Supraglottic airway was removed at the end of the surgery after reversing neuromuscular blockade with

neostigmine (Myostigmine®, Neon Laboratories) 0.05 mg/kg and glycopyrrolate (Licolate®, Samarth Pharmaceuticals) 0.01 mg/kg. Patients were shifted to high dependency unit from operation theatre. To assess pain postoperatively, the visual analogue scale (VAS) was used. It consists of a 100 mm scale with marks 1–10, 10 mm apart, from left to right. The left end denotes "no pain" and the right extreme at 10 is the worst experienced pain. Patients were given either SL buprenorphine 200 µg (ADDNOK®, Rusan Pharmaceuticals) or IV tramadol (Tramazac®, Zydus Healthcare, Ahmedabad, India) 1.5 mg/kg (max 100 mg) slowly in the immediate postoperative period (after 30 minutes of getting shifted to recovery room) as per computer-generated randomization and thereafter every 8 hours for 24 hours. IV paracetamol 1 g was continued every 6 hours from the time intraoperative dose was given for the postoperative period of 24 hours. IV morphine (3 mg; Rumorf®, Rusan Pharmaceuticals) was administered as a rescue analgesic if VAS score was 4 or above.

Postoperative phase

All patients were monitored for pain (VAS), respiratory depression, sedation, hypotension, dizziness, nausea, vomiting from right in the recovery room and thereafter at regular intervals for 24 hours. The primary outcome was to compare the analgesic efficacy of SL buprenorphine with IV tramadol. Comparison of PONV, sedation, and the number of rescue analgesic used in 24 hours were the secondary outcomes.

Analgesic efficacy was assessed by VAS score.[16] Sedation was assessed by Ramsay Sedation Scale.[17] 1: Awake and alert, 2: awake but tranquil, 3: asleep and moves on conversation, 4: asleep and responds to light glabellar tap, 5: asleep and responds to strong glabellar tap, 6: Asleep and responds to painful stimuli, 7: asleep with no purposeful response, and 8: unresponsive to external stimuli including pain.

The evaluator was blind to grouping information.

Statistical analysis

The sample size for this study was derived from the study by Desai et al.[18] in which authors compared transdermal buprenorphine with oral tramadol for the treatment of postoperative pain following surgery for fracture neck of femur. The authors recruited 25 patients in each group for α-error of 0.05 and 80% power. We recruited 30 patients in each group to address possible exclusions and attrition rate. We used an online software (https://clincalc.com/stats/samplesize.aspx) to calculate the sample size.

Data were collected and entered into Microsoft Excel (2016 version) sheet for analysis. Continuous data (age, body mass, body mass index, fentanyl consumption, sedation scores) are expressed as mean ± standard deviation (SD). Categorical data (American Society of Anesthesiologists-physical status, side of surgery, PONV) are expressed as absolute numbers. The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. Unpaired *t*-test was used for analysis for continuous data (age, body mass, body mass index, fentanyl consumption, sedation scores). The chi-square test was used to compare qualitative variables (American Society of Anesthesiologists-physical status, side of surgery, PONV). Statistical analysis was performed using GraphPad

Prism 5 for Windows (GraphPad Software, La Jolla, CA, USA). A P value < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by ASN, the corresponding author of this paper.

RESULTS

A total of 60 patients were recruited with 30 patients in each group. The study was conducted from July 2019 to June 2020. Two patients in the tramadol group were excluded as they underwent re-exploration for bleeding in less than 24 hours of surgery. Finally, we analyzed 58 patients, including 30 patients in buprenorphine group and 28 patients in tramadol group. The CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram is depicted in **Figure 1**.

Figure 1: CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram.
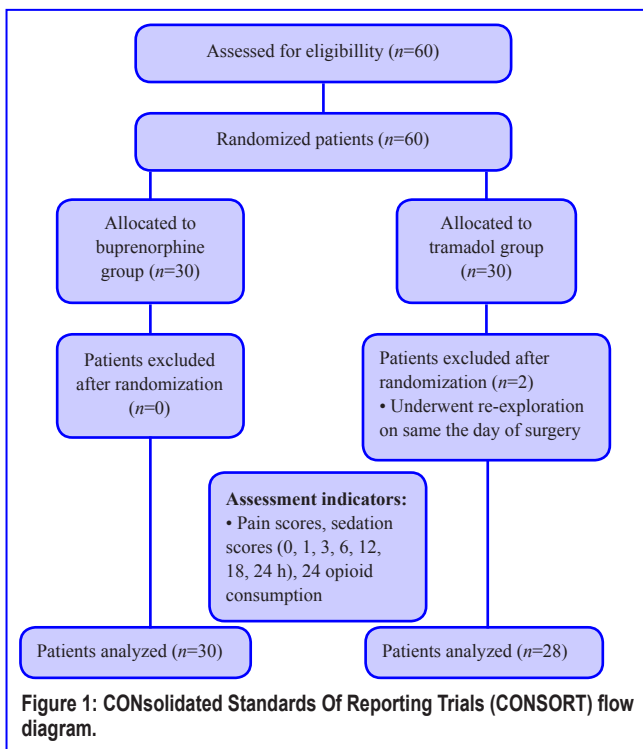
Demographic data (body mass, age, body mass index) and other variables like American Society of Anesthesiologists-physical status, side of surgery were comparable in both groups. Intraoperative fentanyl consumption in buprenorphine and tramadol groups was not significant statistically (**Table 1**). VAS scores at various time frames (0, 1, 3, 6, 12, 18 and 24 hours) postoperatively were comparable between the two groups both at rest and movement, except at 0- and 3-hour during movement which was lesser in tramadol group (P = 0.029 and 0.0133 respectively) (**Table 2**). PONV and Ramsay Sedation Scale showed no significant difference between the two groups (**Table 3**). Four patients in the buprenorphine group received rescue analgesic (IV morphine 3 mg) which was not significantly different from 5 mg IV morphine (P = 0.1129).

DISCUSSION

Based on the results obtained in our study, it appears that the analgesic efficacy of SL buprenorphine is comparable to IV tramadol for the first 24 hours with a comparable PONV and

Table 1: Comparison of demographic data, intra-operative fentanyl, rescue analgesia requirement and postoperative nausea/vomiting of postmastectomy pain syndrome patients treated with buprenorphine or tramadol

Variable	Buprenorphine group (n=30)	Tramadol group (n=28)	P-value
Age (yr)	48.63 ± 9.54	47.96 ± 8.06	0.7748
Body mass (kg)	65.43 ± 9.08	65.39 ± 11.40	0.9881
Body mass index (kg/m^2)	28.01 ± 3.44	28.15 ± 4.64	0.8934
American Society of Anesthesiologists-physical status (I/II)	6/24	3/25	0.329
Operative side (left/right)	16/14	11/17	0.57
Postoperative nausea/vomiting	12/18	8/20	0.36
Intra-operative fentanyl consumption (μg)	140.83 ± 29.25	136.61 ± 30.4	0.591
Rescue analgesic requirement	4/26	0/28	0.1129

Note: Variables like age, body mass, body mass index, intraoperative fentanyl consumption are expressed as the mean ± SD and were analyzed by unpaired t-test. Variables like side of surgery and rescue analgesic requirement are expressed as absolute numbers, and were analyzed by chi-square test.

sedation scores. U.S. Food and Drug Administration has approved the use of buprenorphine for acute pain, chronic pain, and opioid dependence (in combination with naloxone).[19] Buprenorphine is available as an injection for IV/neuraxial and adjuvant use, transdermal patches, buccal films, and SL tablets.[20,21] SL buprenorphine is an easy, non-invasive route of administration of a potent analgesic.[22,23] In the immediate postoperative period, the patients might either find it inconvenient to swallow or are not allowed orally immediately.[24,25] The bioavailability of SL buprenorphine appears to be comparable to that of IV morphine because of equianalgesic efficacy.[26] Jalili et al.[27] compared analgesic efficacy of 400 μg of SL buprenorphine with 5 mg of IV morphine for managing acute pain after a bone fracture. In 89 patients analyzed (44 patients with buprenorphine and 45 patients with morphine), authors concluded that 400 μg of SL buprenorphine is as effective and safe as 5 mg of IV morphine for addressing acute pain after bone fracture. Payandemehr et al.[28] compared the analgesic efficacy of 2 mg of SL buprenorphine and IV placebo with 0.1 mg/kg IV morphine with SL placebo in patients with renal colic. Thirty-seven patients were recruited in the morphine group and thirty-two in the buprenorphine group. Analgesic efficacy was comparable in both groups based on numerical rating scale scores. Mozafari et al.[29] compared the efficacy of 2 mg of SL buprenorphine (32 patients) with 30 mg IV ketorolac (31 patients) in patients with acute renal colic. Authors found no difference between SL buprenorphine and IV ketorolac but more adverse effects like vomiting, nausea, and dizziness in the buprenorphine group.

Sumanth et al.[30] investigated the safety and efficacy of SL buprenorphine in 10 patients undergoing mastectomy. They observed that none of the patients received rescue analgesia (IV morphine) in the first 24 hours. Soltani et al.[31] random-

Table 2: Comparison of visual analogue scale score in postmastectomy pain syndrome patients treated with buprenorphine or tramadol at rest and movement during 24 hours after surgery

Time point	Buprenorphine group (*n*=30)	Tramadol group (*n*=28)	*P*-value
0 h (immediately after surgery)			
Rest	1	1.07 ± 0.26	0.141
Movement	1.60 ± 0.56	1.89 ± 0.42	0.029
1 h			
Rest	1.20 ± 0.66	1.04 ± 0.19	0.212
Movement	1.70 ± 1.02	1.64 ± 0.56	0.794
3 h			
Rest	1.10 ± 0.31	1	0.087
Movement	1.33 ± 0.48	1.68 ± 0.55	0.013
6 h			
Rest	1.03 ± 0.18	1	0.338
Movement	1.30 ± 0.47	1.43 ± 0.5	0.317
12 h			
Rest	1.13 ± 0.35	1.14 ± 0.36	0.918
Movement	1.20 ± 0.41	1.36 ± 0.49	0.187
18 h			
Rest	1.1 ± 0.55	1	0.338
Movement	1.27 ± 0.78	1.25 ± 0.44	0.921
24 h			
Rest	1.07 ± 0.25	1.11 ± 0.31	0.59
Movement	1.10 ± 0.31	1.04 ± 0.19	0.343

Note: Data are expressed as the mean ± SD and were analyzed by unpaired *t*-test.

Table 3: Comparison of Ramsay Sedation Scale scores in postmastectomy pain syndrome patients treated with buprenorphine or tramadol during 24 hours after surgery

Time point (h)	Buprenorphine group (*n*=30)	Tramadol group (*n*=28)	*P*-value
0	3	2.93±0.26	0.1411
1	2.43±0.57	2.39±0.50	0.7746
3	2.23±0.43	2.36±0.56	0.3465
6	2.30±0.47	2.50±0.51	0.1240
12	2.77±0.43	2.82±0.39	0.6144
18	2.23±0.43	2.25±0.44	0.8847
24	2.03±0.18	2.04±0.19	0.9409

Note: Data are expressed as the mean ± SD and were analyzed by unpaired *t*-test.

ized 90 patients with fractures requiring closed orthopedic reduction into two groups. One group received 4.5 µg/kg buprenorphine and another received 0.2 mg/kg IV morphine. They concluded that SL buprenorphine offered better analgesia than IV morphine and recommended buprenorphine in such situations due to simple usage and longer postoperative sedation. In our study, analgesic efficacy of SL buprenorphine was comparable to tramadol group. Although four patients in the buprenorphine group received rescue analgesic, it was not statistically significant.

Our study has several limitations. Pain scores were monitored and compared for the first 24 hours. There were logistics involved for calling the study off after 24 hours. We monitored all patients in the high dependency unit so that monitoring and documentation were foolproof. Moreover, several patients get discharged on the second postoperative day thereby making data collection difficult for us. We did not include other breast cancer surgeries such as breast conservation surgery, mastectomy with sentinel lymph node biopsy, and breast surgeries undergoing reconstruction for the sake of standardization of methodology. Another limitation is that we did not assess the absorption of SL buprenorphine by confirming plasma levels. To conclude, the analgesic efficacy of SL buprenorphine appears comparable to IV tramadol at rest and movement for the first 24 hours after a mastectomy. However, SL buprenorphine scores over tramadol in terms of ease of administration. SL buprenorphine can be considered as part of multimodal analgesia for acute postoperative pain after breast surgeries.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	3,4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	5
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	5
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4,5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4,5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	3
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5

Results

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7

Discussion

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8,9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8,9

Other information

Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	9

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.