

Opioid-Free General Anesthesia with Dexmedetomidine-Esketamine-Lidocaine Versus Opioid-Based General Anesthesia with Sufentanil-Remifentanil for Breast Benign Patients Undergoing Lumpectomy

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Abstract

Background: Opioid-free anesthesia (OFA) is being implemented in breast benign lumpectomy due to increased awareness of opioid adverse effects and the national opioid crisis. The objective of this study was to examine the effect of Dexmedetomidine-Esketamine-Lidocaine OFA technique in breast benign lumpectomy and assess its impact on subjective pain, intraoperative hemodynamic parameters, adverse events versus standard opioid-based technique (OA).

Methods: In this prospective, randomized study, sixty breast benign patients, aging from 20 to 60 years with American Society of Anesthesiologists physical status I or II, were scheduled to undergo lumpectomy. The patients were randomized to receive either OFA (OFA group) or opioid-based (OA group) anesthesia. Dexmedetomidine-Esketamine-Lidocaine or Sufentanil-Remifentanil was administered for induction and maintenance in OFA group or OA group, respectively. Intravenous flurbiprofen axate 50 mg was administered 10 minutes before the end of surgery, and dezocine 5 mg was given to patient showing visual analog scale (VAS) pain score ≥ 4 at any point of time for postoperative rescue analgesia in both groups. Intraoperative hemodynamic parameters at the time points of entering operating room (T_0), immediately after induction of anesthesia (T_1), immediately after intubation (T_2), 1 minute after surgical incision (T_3), 5 minutes after surgical incision (T_4), and 10 minutes after surgical incision (T_5), number of vasoactive drugs required, awakening time and recovery time of orientation, postoperative pain VAS at 2 h, 12 h, and 24 h after recovery, number of postoperative rescue dezocine analgesia required, and incidence of adverse events were recorded.

Results: The mean arterial pressure and heart rate at T_1 , T_2 , T_3 , T_4 , T_5 were significantly lower in OA group than OFA group. The incidences of application of rescue ephedrine (1 of 30 [3.3%] versus 12 of 30 [40%], $P=0.001$) and rescue atropine (2 of 30 [6.7%] versus 6 of 30 [20%], $P=0.038$) were significantly lower in OFA group compared with OA group. The pain VAS scores at 2 h, 12 h, and 24 h after surgery and number of rescuing dezocine analgesia required (0 of 30 [0%] versus 0 of 30 [0%]) had no statistically significant difference between the two groups. Postoperative nausea and vomiting (3 of 30 [10%] versus 16 of 30 [53%], $P=0.001$) and application of rescue ondansetron (1 of 30 [3.3%] versus 10 of 30 [33%], $P=0.003$) were both less in the OFA group compared to those in OA group. However, compared with OA group, patients in OFA group had more delayed awakening time ($[7.27 \pm 2.85]$ min versus $[4.47 \pm 1.11]$ min, $P=0.000$) and prolonged recovery time of orientation. ($[11.97 \pm 3.19]$ min versus $[6.93 \pm 1.17]$ min, $P=0.000$).

Conclusions: The combination of Dexmedetomidine-Esketamine-Lidocaine OFA technique may be an alternative anesthesia for breast benign lumpectomy as better hemodynamic stability, lower incidence of postoperative nausea and vomiting, and adequate postoperative analgesia compared with OA, although longer awakening time and longer recovery time of orientation.

Trial registration number: ChiCTR2100044230 (<http://www.chictr.org.cn/>)

1 Introduction

Nowadays, opioids have been widely used in general anesthesia since they have low stress responses, stabilize the circulatory system and alleviate the pain of the cancer patients ^[1]. However, they are associated with severe side effects. Some of these side effects such as respiratory depression, postoperative nausea and vomiting (PONV) are obvious; some are of a more clandestine nature. For example, hyperalgesia caused by opioids are of concern yet often go unnoticed ^[2] ^[3]. Furthermore, the opioid epidemic and chronic long-term opioid usage have been attributed, in part, to the use of opioids in the perioperative period ^[4].

To begin addressing these issues, opioids-free technique is receiving increasing attention in anesthesiologists ^[5], which has been reported widely in orthopedic surgery, breast surgery and gastrointestinal surgery ^[6] ^[7] ^[8]. There are multiple regimens to achieve an opioid-free perioperative analgesic management. Multimodal analgesia involves the use of sympatholytic drugs and non-opioid analgesics. These drugs can reduce or avoid the use of opioids in the postoperative period. Common non-opioid analgesics, which can be given intravenously in the intra-operative period, include alpha-2 agonists (clonidine and dexmedetomidine), beta blockers (esmolol), gabapentinoids (gabapentine and pregabalin), lidocaine (lidocaine hydrochloride), magnesium (magnesium sulfate), N-methyl D-aspartate (NMDA) receptors (ketamine, esketamine) and dexamethasone (dexamethasone) ^[9]. It has been shown that all these drugs with their analgesic effect if given together are changing the pathophysiologic process that is involved in nociception.

There is no consensus about how to achieve OFA in the literatures and between centers. The combination of Dexmedetomidine-Esketamine-Lidocaine has never been reported in OFA and clinicians uncertain about whether it is beneficial or harmful. Thus, the objective of this study is to examine the use of a OFA protocol which consisted with Dexmedetomidine-Esketamine-Lidocaine in breast benign lumpectomy and assess its impact on subjective pain, intraoperative hemodynamic parameters and adverse events. Further, we raise awareness for our novel OFA protocol to improve safety and quality of care for our patients.

2. Materials And Methods

This prospective, randomized trial was approved by the Institutional Ethics Committee (2020KY071) and was registered at the Chinese Clinical Trial Registry (ChiCTR2100044230). A written informed consent was obtained from all patients enrolled in the study.

Patients with American Society of Anesthesiologists (ASA) physical status classes I or II, aged 20–60 years and scheduled for breast benign lumpectomy between December 2020 and July 2021 were considered eligible to participate in this prospective, randomized clinical trial. Major exclusion criteria were: hypertension; ischemic heart disease; psychiatric disorders; a history of significant hepatic, renal, or cardiac disease; preoperative heart rate (HR) less than 50 beats/min with/without cardiac conduction or

rhythm abnormalities; chronic pain treatment or chronic steroid therapy; allergy to the study drugs; refusal to participate in the study; and inability to comprehend VAS. Those who were transferred to a mastectomy because of the malignant pathology were subsequently excluded from the study. Patients were randomized using computer-generated random numbers to received OFA group or OA group anesthesia (n = 30, each group).

Before the study procedure, all the patients were instructed on using a 10 cm visual analog scale (VAS; with "0" mark corresponding to no pain and "10" mark representing the worst imaginable pain). Investigator assessing the postoperative parameters, and the data analyst were blinded to the study. The anesthetist providing anesthesia was not blinded to the study drugs administered.

OFA was defined as the administration of no opioids either pre- or intraoperatively until wound closure, and rescue opioids were only given when the patients were fully awake and had been administered nonopioid analgesics previously. OA was defined as the administration of any opioid during the pre- or intraoperative period. Postoperative opioids (after OFA or OA) were defined as the administration of opioid from the time of wound closure until discharge from the hospital.

All patients received total intravenous anesthesia (TIVA) without inhalation. A bispectral index (BIS) of 40–60 was maintained for monitoring the depth of anesthesia. The method by which OFA was administered consisting of combining Dexmedetomidine-Esketamine-Lidocaine. Dexmedetomidine was administered $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ over 10 min before induction, $0.1 \mu\text{g}\cdot\text{kg}^{-1}$ at induction, and an infusion of $0.1 \sim 0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance. Lidocaine was administered as $1.5 \text{mg}\cdot\text{kg}^{-1}$ at induction, followed by an infusion of $1 \sim 1.5 \text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance. Esketamine was administered as $0.1 \text{mg}\cdot\text{kg}^{-1}$ at induction, $0.25 \text{mg}\cdot\text{kg}^{-1}$ (maximum 25 mg) before incision, and an infusion of $0.1 \sim 0.2 \text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance.

Sufentanil was administered in the OA group at a dose of $0.2 \sim 0.4 \mu\text{g}\cdot\text{kg}^{-1}$ at induction, $0.4 \mu\text{g}\cdot\text{kg}^{-1}$ before incision. Remifentanil was followed by a continuous infusion of $0.1 \sim 0.3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance. Midazolam was administered $0.03 \sim 0.04 \text{mg}\cdot\text{kg}^{-1}$ at induction, propofol was administered $1.5 \sim 2.0 \text{mg}\cdot\text{kg}^{-1}$ at induction, cisatracurium was administered $0.2 \sim 0.3 \text{mg}\cdot\text{kg}^{-1}$ at induction in both groups. Propofol was followed by a continuous infusion of $4 \sim 6 \text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance in both groups.

After induction of anesthesia, laryngeal mask airway was placed in all patients. Intravenous flurbiprofen axate 50 mg for multimodal analgesia and ondansetron 4 mg for preventing postoperative nausea and vomiting were administered 10 minutes before the end of surgery in both groups. Dexmedetomidine, esketamine, lidocaine, remifentanil, and propofol were stopped at the end of the surgery. Atropine $10 \mu\text{g}\cdot\text{kg}^{-1}$ and neostigmine $50 \mu\text{g}\cdot\text{kg}^{-1}$ were administered to reverse muscle relaxation. Laryngeal mask airway extubation was performed once the patient was conscious and spontaneous ventilation of the patient was adequate, and the patients were transferred to the postanesthesia care unit (PACU).

Non-invasive blood pressure was assessed at least at 3 min of interval during anesthesia. Hypotension (MAP < 60 mmHg) was treated with ephedrine 6 mg intravenously and bradycardia (heart rate < 45 bpm) was treated with atropine 0.5 ~ 1 mg intravenously. Hypertension (MAP > 120mmHg) was treated with urapidil 5 ~ 10 mg intravenously. Any patient showing VAS \geq 4 at any point of time was administered intravenous dezocine 5 mg slowly for postoperative rescue analgesia.

The following demographic data were recorded: age, BMI, duration of surgery, amount of bleeding, current or recent motion sickness, or previous PONV. Noninvasive blood pressure and heart rate were recorded at the time points of entering operating room (T_0), immediately after induction of anesthesia (T_1), immediately after intubation (T_2), 1 minute after surgical incision (T_3), 5 minutes after surgical incision (T_4), and 10 minutes after surgical incision (T_5). The cases of receiving ephedrine, urapidil, and atropine were recorded. The time of awakening, recovery time of orientation, cases of increased oral secretion were recorded while patients in PACU. Postoperative pain was assessed at 2 h, 12 h, and 24 h postoperatively using the VAS score. The incidence of adverse events during the first 24 h postoperatively, such as postoperative nausea and vomiting and the number of antiemetics administered after PONV, were also recorded.

We calculated that a sample size of 36 patients per group would maintain 90% power at 5% significance level (two-sided) to detect a difference of 0.35 in the postoperative pain VAS at 2 h after recovery between the two groups, with a SD of 0.43 and an estimated 10% dropout.

Statistical analysis was performed with SPSS V.26.0 (IBM Corp, Armonk, New York, USA) for Windows and GraphPad Prism 8 (GraphPad Software, La Jolla, California, USA) for Windows. Continuous data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data which were presented as mean \pm SD were compared using Student's T test. Nonnormally distributed data which were presented as median [interquartile range] were compared using the Mann-Whitney U test. Categorical data which were presented as n (%) were compared using the χ^2 test or Fisher's exact test, as appropriate. Two-tailed $P < 0.05$ value was considered to be statistically significant.

3. Results

Seventy-two patients undergoing breast benign lumpectomy were identified. Four of them were cancelled of scheduled surgery, three declined to participated, five changed to a mastectomy, and the remaining sixty patients were equally randomized to either OFA group (n = 30) or OA group (n = 30) [Figure 1].

The demographic profile of the two study groups were summarized in Table 1. Statistical analysis revealed nonsignificant differences between the two study groups as regards age, height, weight, the duration of surgery, the amount of bleeding, current or recent motion sickness and previous PONV ($P > 0.05$).

Table 1
Demographic profiles

Characteristics	OFA group (n = 30)	OA group (n = 30)	P
Age (years)	38.97 ± 11.38	39.67 ± 9.19	0.794
Height (cm)	161.83 ± 4.86	159.73 ± 5.41	0.119
Weight (kg)	58.13 ± 8.91	58.00 ± 7.44	0.950
Duration of surgery (min)	33.67 ± 7.66	34.67 ± 9.26	0.650
amount of bleeding (ml)	8.20 ± 3.32	9.17 ± 3.37	0.267
Motion sickness n (%)	2(6.7)	3(10)	1.000
previous PONV n (%)	4(13.3)	3(10)	1.000
Data are presented as mean ± SD or number (%).			

As regards changes in the mean arterial blood pressure and heart rate, they were significantly lower in OA group compared to those in OFA group [Figures 2 and 3].

Compared with OFA group, the incidences of application of rescue ephedrine, atropine were statistically higher in OA group, whereas the incidence of rescue urapidil showed no significant difference between the two studied groups [Table 2].

Table 2
Rescue vasoactive agents

Variable	OFA group (n = 30)	OA group (n = 30)	P
Number of rescue ephedrine required n (%)	1(3)	12(40) *	0.001
Number of rescue atropine required n (%)	2(6)	8(27) *	0.038
Number of rescue urapidil required n (%)	0(0)	0(0)	NS
Data represented as number (percentage). NS: No significant difference. $P < 0.05$ was considered statistically significant. *Significant to the OFA group.			

As regards pain VAS scores at 2 h, 12 h, and 24 h after recovery, and number of rescue dezocine analgesia required, there were no statistically significant difference between the two studied groups ($P > 0.05$) [Table 3].

Table 3

Postoperative pain VAS at different timings and number of rescue dezocine analgesia required

Variable	OFA group (n = 30)	OA group (n = 30)	<i>P</i>
Postoperative pain VAS at different timings, median (IQR)			
2 h after recovery	1[0.25,2]	1[0,1]	0.078
12 h after recovery	2[0,1]	1[0,1]	0.358
24 h after recovery	1[1,1]	0[0,1]	0.085
Number of rescue dezocine analgesia required, n (%)	0(0)	0(0)	NS
Data represented as median [IQR], number (percentage). IQR: interquartile range. NS: No significant difference.			

Awakening time and recovery time of orientation at the end of surgery were significantly longer in patients of OFA group than those in OA group ($P < 0.01$) [Table 4].

Table 4
Postoperative data

Variable	OFA group (n = 30)	OA group (n = 30)	<i>P</i>
Awakening time	7.27 ± 2.85	4.47 ± 1.11 *	0.000
Recovery time of orientation	11.97 ± 3.19	6.93 ± 1.17 *	0.000
Values are presented as mean ± SD. $P < 0.05$ was considered statistically significant.*Significant to the OFA group.			

The incidences of nausea and vomiting, application of rescue ondansetron, were statistically higher in OA group than those in OFA group, whereas the incidences of increased oral secretion and dizziness showed no significant difference between the two studied groups [Table 5].

Table 5
Incidences of adverse events

Variable	OFA group	OA group	P
Nausea and vomiting, n (%)	3(10)	16(53) *	0.001
Application of rescue ondansetron, n (%)	1(3)	10(33) *	0.003
Increased oral secretion, n (%)	7(23)	1(3)	0.052
Dizziness, n (%)	10(33)	4(13)	0.067
Values are present as n (%). <i>P</i> < 0.05 was considered statistically significant. *Significant to the OFA group.			

4. Discussion

This prospective randomized study exploring the use of an OFA regime in women undergoing breast benign lumpectomy demonstrated similar clinical outcomes to conventional OA when comparing pain scores, as well as postoperative rescue analgesic required. In fact, this study demonstrated that not only can patients achieve equivalent outcomes without intraoperative opioids, but also can achieve better hemodynamic stability and lower incidences of postoperative nausea and vomiting.

OFA is based on the use of drugs that do not interact significantly with opioid receptors μ , κ and δ . N-methyl-D-aspartate antagonists such as ketamine and esketamine, α_2 agonists such as clonidine, dexmedetomidine, and acetaminophen, nonsteroidal anti-inflammatory flurbiprofen axate and local anaesthetics lidocaine are the major medicines used [9][10]. Dexmedetomidine is a highly selective α_2 -adrenergic agonist that blocks sympathetic nervous system activity by directly acting on spinal preganglionic sympathetic neurons. It is widely used for sedation, anxiolysis, and analgesia to reduce the requirement of anesthetics during general anesthesia [11][12]. Ketamine and esketamine act on N-methyl-Daspartate receptors to provide superior analgesia and prevent opioid induced hyperalgesia [13][14][15]. Lidocaine is known to have anti-inflammatory and immunomodulatory effects in patients undergoing abdominal surgery, which can reduce postoperative ileus, nausea, and vomiting and improve the rate of recovery of bowel function, thereby shortening the hospital stay [16]. Previous studies had shown that the combination of dexmedetomidine-ketamine-lidocaine in OFA reduced intraoperative stress, postoperative pain, and opioid-related complications [17][18], but the total intravenous anesthesia composed of dexmedetomidine-ketamine-lidocaine for OFA in lumpectomy had rarely been reported. Esketamine is an optical isomer of ketamine. Its pharmacological characteristics are similar to racemic ketamine, but it has more advantages in clinical application. The hypnotic and analgesic effect is twice than that of ketamine. Beyond that, it has higher bioavailability, shorter elimination half-life, and fewer side effects [19][20]. Taking together, we chose the combination of dexmedetomidine-esketamine-lidocaine for OFA in breast benign lumpectomy.

In this study, MAP and HR of OFA group were higher than those of OA group at all time points, confirming that opioids can effectively inhibit various stress responses, but the incidences of hypotension and bradycardia subsequently increased significantly. The intraoperative fluctuation range of MAP and HR in OFA group was smaller than that in OA group, which may be due to the following reasons: (1) dexmedetomidine can active α_2 adrenergic receptor, which leads to a decrease in sympathetic outflow and an increase in vagal activity. Besides, dexmedetomidine may also have a certain peripheral ganglion block effect, which further enhances its antisympathetic effect ^{[11][21]}; (2) The sympathetic excitatory effect of esketamine partly counteracts the cardiovascular inhibitory effect of propofol ^[22].

Previous studies had led to conflicting results regarding the effect of OFA on postoperative analgesia. Indeed, some studies reported a reduction in postoperative analgesia score ^{[23][24]}, whereas others showed a similar postoperative pain score ^{[25][26]}. These discrepancies could be due to the different methods of compound anesthesia and the differences in postoperative multimodal analgesia. A meta-analysis including 1304 patients showed that OFA provide similar analgesia or opioid consumption in the postoperative period ^[27]. In our study, there was no difference in pain scores between the OFA group and the OA group at each time point after surgery, suggesting that both anesthesia methods can provide effective analgesia in breast benign lumpectomy.

Previous studies had shown that compared with pain and other complications, postoperative nausea and vomiting were the last thing patients want to experience ^[28]. Breast benign lumpectomy is common in young women who are at high risk of postoperative nausea and vomiting due to no previous opioid use or smoking history. Up to 50% of patients with traditional OA will experience postoperative nausea and vomiting ^[29]. Ziemann-Gimmel et al found that total intravenous OFA was associated with a large reduction in relative risk of PONV in patients undergoing bariatric operations ^[30]. This was comparable to our finding, which showed a significant reduction in PONV by 43%. However, the comparison of reduction has to be interpreted with caution because of the different patient populations observed.

Awakening time and recovery time of orientation were prolonged in the OFA group in this study. The use of dexmedetomidine might have delayed recovery ^[31]. This finding was consistent with previous research ^[32]. But in that research, patients in OFA experienced high incidences of hypoxemia and bradycardia. The high dosage ($1.2 \pm 2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of dexmedetomidine might be the main reason of causing those side effects. Establishing artificial pneumoperitoneum and the addition of dexmedetomidine in this specific situation contributing to unexpected cardiovascular changes might be another reason for causing those adverse effects. By contrast, the dosage of dexmedetomidine ($0.1 \sim 0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) used in our study was low and our study did not establish artificial pneumoperitoneum, which explaining the low incidences of adverse events.

This study is not without limitations. Firstly, the collection of postoperative nausea and vomiting measures was not standardized, and we did not assess the quality of postoperative recovery. Another limitation is the lack of validated nociception monitor. Finally, our definition of OFA (multimodal

anesthesia including dexmedetomidine, esketamine and lidocaine) is not definitive, and other ways to administer OFA have to be explored [33].

The combination of Dexmedetomidine-Esketamine-Lidocaine OFA technique may be an alternative anesthesia for breast benign lumpectomy. It can provide effective anesthesia, better hemodynamic stability, equivalent postoperative analgesia, lower incidences of postoperative nausea and vomiting compared with OA. It is suitable for special patients with opioid tolerance, high risk of postoperative nausea and vomiting, obesity and other special patients, and also provides more options for clinical anesthesia program. However, it did result in some adverse events, such as longer awakening time and longer recovery time of orientation, so the dosage of combination drug still needs to be further optimized.

Declarations

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Author's contributions

The authors have contributed to this study as follows:

- Substantial contributions to the conception or design of the work: Shanwu Feng (MD, PhD), Xian Wang (MD, PhD), Xiali Qian (MS).
- Statistics: Hongmei Yuan (MS), Yajie Chen (MS), Lin Zhao (MS).
- Writing original draft: Xiali Qian (MS).
- Reviewing and editing the draft: Shanwu Feng (MD, PhD).

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

All authors declare no competing interests.

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Figures

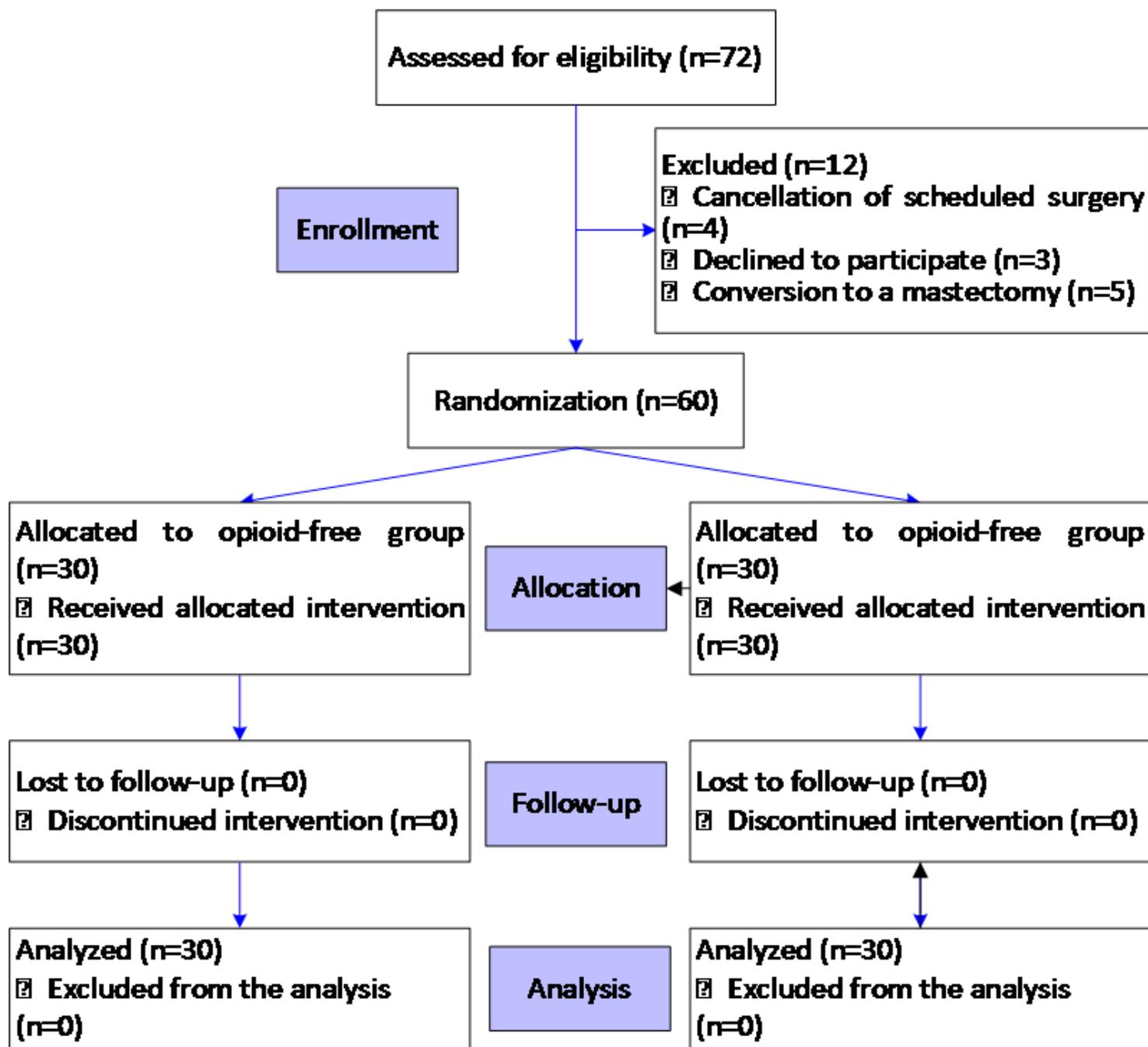


Figure 1

Flowchart of the study

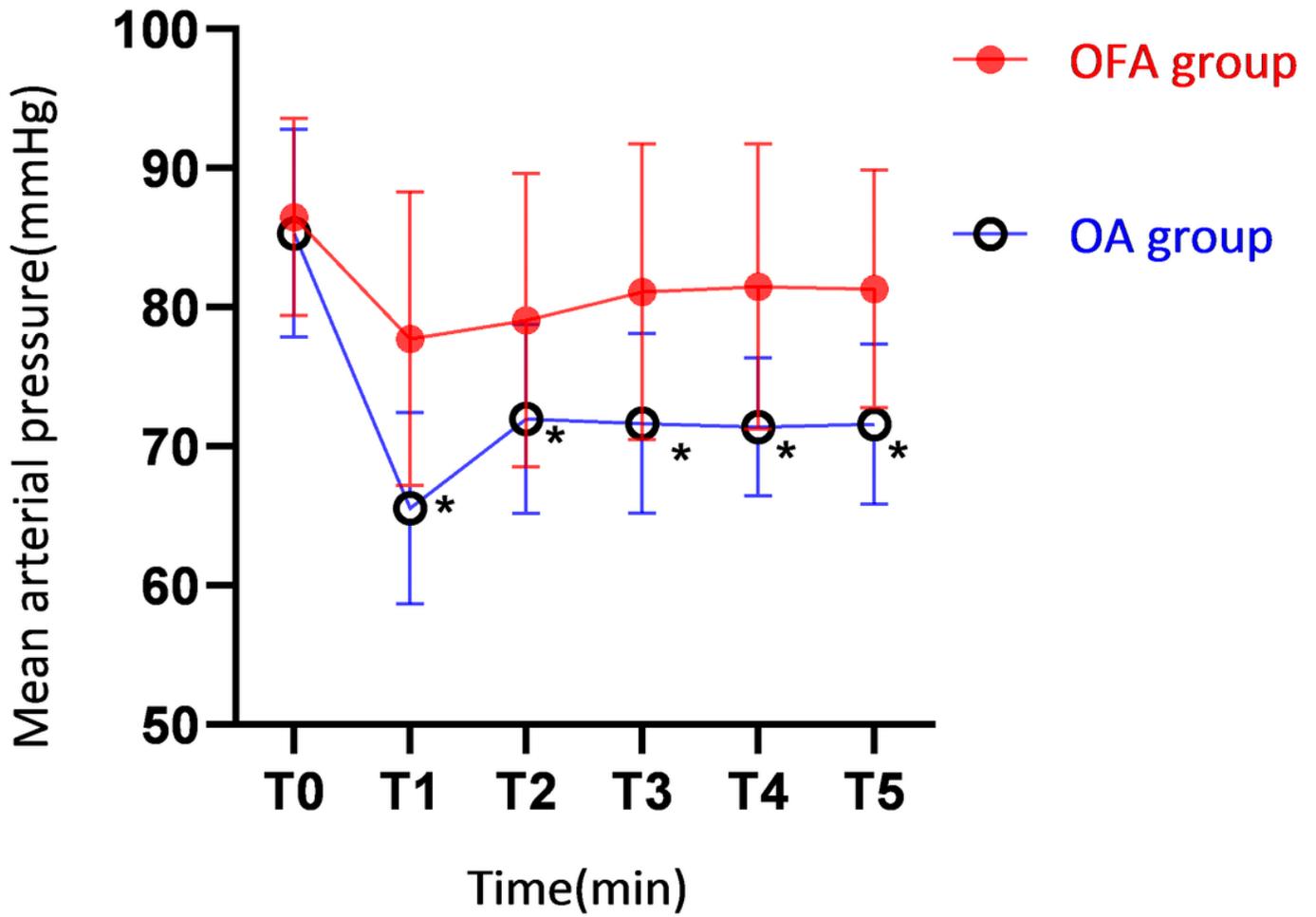


Figure 2

Changes in mean arterial pressure during perioperative period in OFA group or OA group. $P < 0.05$ was considered statistically significant. *Significant to the OFA group.

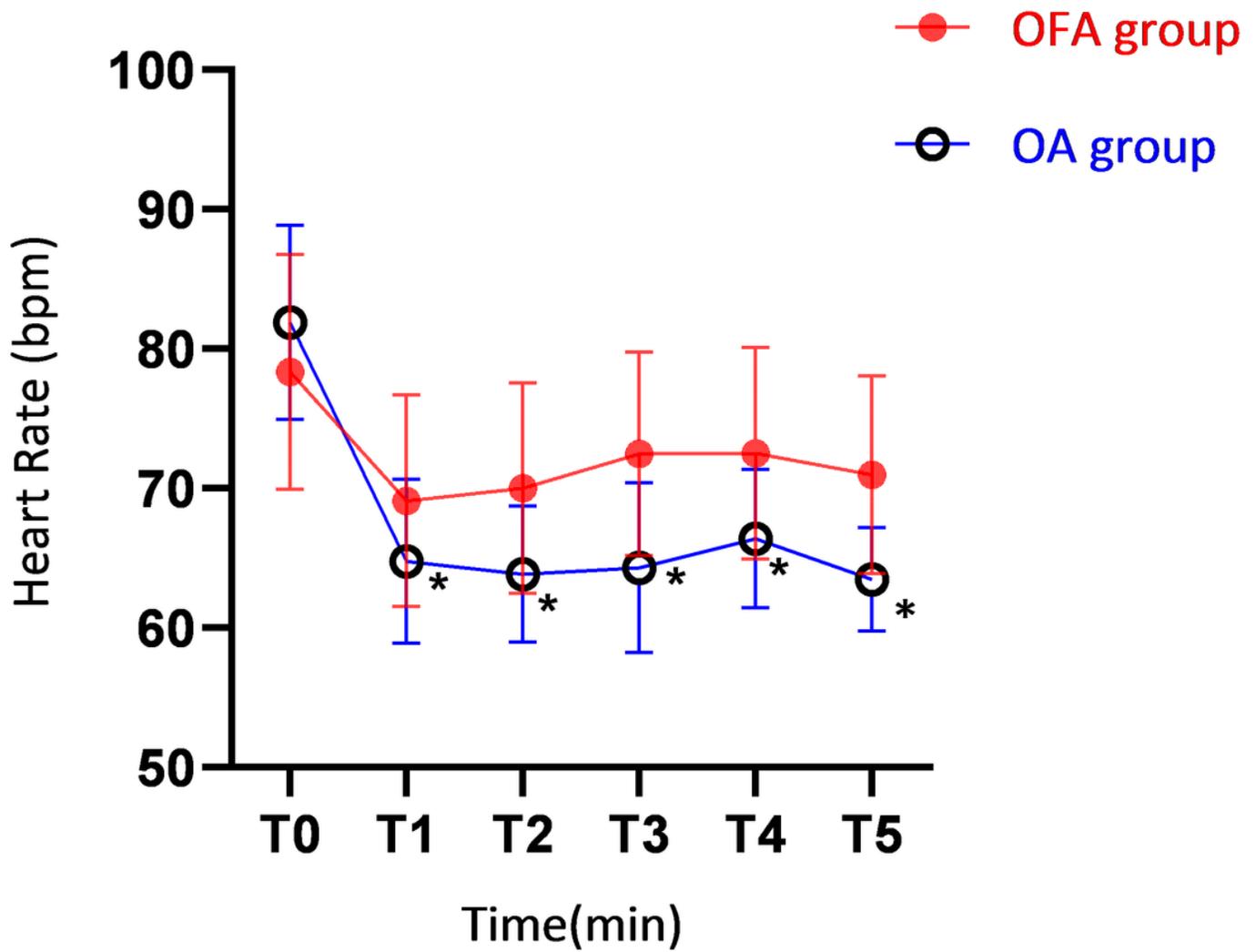


Figure 3

Changes in heart rate s during perioperative period in OFA group or OA group. P <0.05 was considered statistically significant. *Significant to the OFA group.