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Balanced Anesthesia Using Intravenous Clonidine Injection in Breast Conservation Surgery: A Prospective Randomized Control Trial

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ABSTRACT

Background: *Intra-operative strategies can significantly influence long-term cancer outcomes. Breast cancer surgeries are highly associated with unavoidable pain. Clonidine, an alpha agonist hypotensive agent was highly recommended as an adjuvant with general anesthesia for its analgesic, sedative, anxiolytic, and sympatholytic effects. This study evaluated all its outcomes as an adjuvant in patients undergoing breast conservation surgery.* ***Methods:*** *A prospective, randomized, double blinded interventional trial. Eighty patients of the American Society of Anesthesiologists (ASA) I–III, with ECOG of <0-2 scheduled for breast conservation surgery were randomly divided into Clonidine arm (n=40, clonidine as an adjuvant followed by balanced general anaesthesia) and Placebo arm (n=40, balanced general anaesthesia alone).* ***Results:*** *The HR and MAP of the patients from clonidine arm and placebo arm post-induction was observed to be 83 bpm, 8 1 mmHg and 91 bpm, 90 mmHg, respectively. The sedation score was well maintained in the clonidine arm. Consumption of additional analgesic (fentanyl, n=34) and β-blocker (labetalol, n=35) was evidently high in the placebo arm. Post-operative pain score was well maintained in clonidine arm even after 6 h. The common noticeable side effects in the placebo arm were found to be Post-Operative Nausea and Vomiting (PONV, n=11). Patients from the clonidine arm were found to have better QOR over the placebo arm.* ***Conclusion:*** *Clonidine as an adjuvant provided better intra and postoperative analgesia. It was also found to be effective in achieving controlled hypotension while improving the surgical field in patients undergoing breast cancer surgery without any appreciable side effects.*

Keywords: Balanced anaesthesia, Clonidine, Breast conservation surgery, Prospective study, Randomized control trial

INTRODUCTION

With an estimated 2.3 million new cases and 6,85,000 deaths worldwide, female breast cancer is leading cancer in 2020. It represents approximately one in 4 cancers diagnosed and one in 6 deaths happened [1]. In most of these patients, surgery is an option and it will be either Breast Conserving Surgery (BCS) or mastectomy [2].

Surgery causes physiological stress and blood loss. However, excessive blood loss and bleeding during surgery can obscure the field of operation visibility causing complications to both patients and operating surgeons [3]. In such scenarios, providing the surgeons with a clear field is of prime importance and it can help in minimizing the intra-operative blood loss, risk of injury to vital structures, and surgical time. Hence, balancing anaesthesia can play a vital role. Further, balanced anaesthesia will also help in maintaining other vital parameters such as HR, MAP, and BP within acceptable limits. To achieve such balanced anaesthesia, a non-opioid alpha-2 agonist (clonidine) was used as an adjuvant with general anaesthesia due to its pre-emptive analgesic nature, the anxiolytic effect, and sympatholytic effects.

The primary objective of the present study was to assess the efficacy of clonidine in providing balanced anaesthesia in breast conservative surgeries. The expected outcomes were to achieve minimal blood loss, and to provide a better surgical field by maintaining all the vitals throughout the surgical procedure. The secondary outcomes measured were the requirement of additional analgesia (fentanyl), requirement of beta blocker (labetalol), intraoperative blood loss, surgeon's opinion about surgical field, pain, sedation scores, complications needing medical management, patients 24 h post-surgery well-being status, and Quality of Recovery (QOR).

MATERIALS AND METHODS

This study was a prospective, randomized, double blinded, parallel group, active controlled interventional trial. After approval from the institutional ethics committee, it was registered in the Clinical Trial Registry of India as CTRI/2019/10/021505. Written informed consent forms were obtained from all the patients who participated in the study prior to commencement. The study was conducted in accordance with the ethical guidelines for biomedical research for human population, declaration of Helsinki ethical principles, good clinical practices, and CT rules 2019.

A total of eighty operable carcinoma breast patients undergoing breast conservation surgery in adjuvant and neo-adjuvant setting were enrolled. The inclusion criteria specify all the patients should be adults, aged 18-80 years, American Society of Anesthesiologists (ASA) I–III, ECOG <0–2, with an estimated Life Expectancy>6 months, and without any persistent toxicities from prior medications at screening. The exclusion criteria include patients with prior co-morbidities, patients on β-blockers, hypersensitive to test/comparator drugs, with primary tumors, pregnant or breastfeeding women, and with other serious illness that would prohibit the understanding and giving informed consent. The duration of study for each patient was a maximum of 3 days with total study duration of 6 months.

In this study, patients were blindly randomized into one of the two study groups/arms (each group containing 40 patients with a drop rate of 4 patients in each arm). Based on random allocation, patients will receive either 2 µg/kg clonidine Intravenous (IV) (clonidine arm) or an equal volume of sterile water for injection (placebo arm) 15 min prior to induction of anaesthesia administered over 10 min. Based on previous studies, the effective dose of clonidine to achieve adequate pain management was determined to be 2 µg/kg [4–6].

All the samples were prepared in identical looking syringes by a resident doctor not involved in the study. The anesthesiologist giving the samples was completely unaware of the samples given to the patient. Data collection was also done by two independent resident doctors not involved in the study.

Pre-operative assessment of baseline parameters such as HR, MAP, BP, and oxygen saturation were recorded every 15 min from pre-induction to the recovery period. After inducing with test samples, general anaesthesia (IV propofol 2 mg/kg, xylocard 1 mg/kg ventilation followed by 1.5 mg/kg succinylcholine) was given and intubation was done using appropriate sized Igel.

Anaesthesia was maintained with IV atracurium, oxygen air, and sevoflurane (Drager Fabius plus with advanced gas monitoring) End-tidal CO_2 ($EtCO_2$). ET anaesthetic was concurrently monitored to maintain Minimum Alveolar

Concentration (MAC) of 1.0 sevoflurane (Drager AGM SCIO four-plus). All the patients were given a 15°C head up to improve venous drainage. IV kabilyte solution was given at 1 mg/kg/hr, intraoperatively. If MAP (60-70 mm Hg) and HR were not controlled, further doses of fentanyl (2 µg/kg at 15 min interval) and labetalol (0.5 mg/kg). In patients with MAP <60 mmHg, sevoflurane MAC was reduced to 0.7%. Throughout the surgery, all hypotension related issues were treated with mephentermine (3 mg). In the end, reversal was done with myopyrolate (0.1 ml/kg). All the patients were extubated on gaining consciousness and were transferred to the Post-Anaesthesia Care Unit (PACU) for observation.

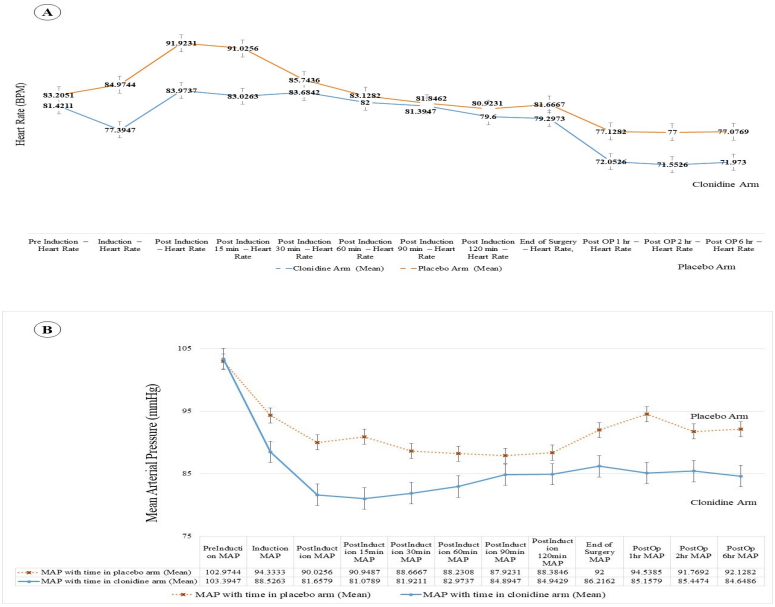
Blood loss was estimated by measuring the number of swabs soaked in blood and volume in the suction bottle used during the procedure [7,8]. The surgical field score was graded by surgeons using the Fromme-Boezaart Scale (Grade 0-5, no bleeding to severe bleeding) [9,10]. Sedation and pain score were determined by using Brussels Sedation Score (level 1-5, over sedation to under sedation) [11] and numeric rating scale (0-10, no pain to worst possible pain) [12], respectively. Quality of Recovery (QOR) was measured after surgery using the QOR15 questionnaire and it is an important measure in representing the postoperative health status of the patients [13,14].

Statistical analysis

Power analysis and sample size calculation was estimated at 5% level of significance ($p \leq 0.05$) [15,16]. Based on the previous literature and to reject the null hypothesis, we needed to study at least 40 patients per group, and this number will be increased to 44 patients per group to eliminate the possibility of dropouts. Results were compiled and statistically analyzed using SPSS 22 (SPSS Inc., Chicago, IL, USA). Analysis of Variance (ANOVA), chi-square test, and paired t-test was applied where deemed appropriate.

RESULTS

In our study, patients were divided into two groups (clonidine arm and placebo arm) and each group consists of 40 patients. The median age of the patients in both the arms was 47 ± 2 years. The pre-induction HR, and MAP of the patients enrolled in both the clonidine arm and placebo arm was observed to be 78 bpm, 105 mmHg and 82 bpm, 103 mmHg, respectively. The HR and MAP of the patients in both the clonidine arm and B was presented in Figure 1A and Figure 1B. Post 15 min of intubation, HR in placebo arm patients were observed to be increased from 83 bpm to 91 bpm. In patients from clonidine arm, HR was observed to be stable at 81 ± 5 bpm till the end of the surgery. With respect to MAP, a significant reduction was observed in both the arms from 103 ± 1 mmHg to 81 mmHg in clonidine arm and 90 mmHg in the placebo arm.



	PreInduction MAP	Induction MAP	PostInduction MAP	PostInduction 15min MAP	PostInduction 30min MAP	PostInduction 60min MAP	PostInduction 90min MAP	PostInduction 120min MAP	End of Surgery MAP	PostOp 1hr MAP	PostOp 2hr MAP	PostOp 6hr MAP
MAP with time in placebo arm (Mean)	102.9744	94.3333	90.0256	90.9487	88.6667	88.2308	87.9231	88.3846	92	94.5385	91.7692	92.1282
MAP with time in clonidine arm (Mean)	103.3947	88.5263	81.6579	81.0789	81.9211	82.9737	84.8947	84.9429	86.2162	85.1579	85.4474	84.6486

Figure 1 A) Comparison of heart rate (bpm) between clonidine arm and placebo arm B) Comparison of mean arterial pressure (mmHg) between clonidine arm and placebo arm

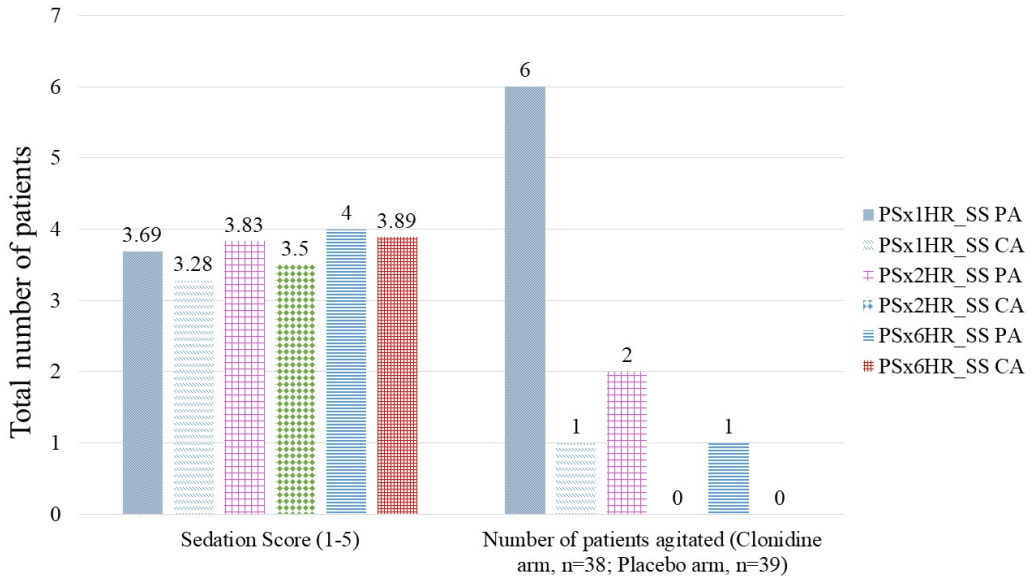


Figure 2 Sedation score and agitation in clonidine arm and placebo arm patients

Post-surgical sedation scores at 1 h, 2 h, and 6 h were presented in Figure 2. It was noticed that a total of 7 patients were seen to be agitated. In which, 1 patient was of clonidine arm and 6 patients were from placebo arm. Requirement of additional analgesic (fentanyl) intraoperatively was needed in 2 patients of clonidine arm and 34 patients of placebo arm with a significance of P<0.001 (Figure 3A). Whereas, the requirement of an additional β-blocker (labetalol) was also required in 3 patients of clonidine arm and 35 patients of placebo arm (P<0.001, Figure 3B)

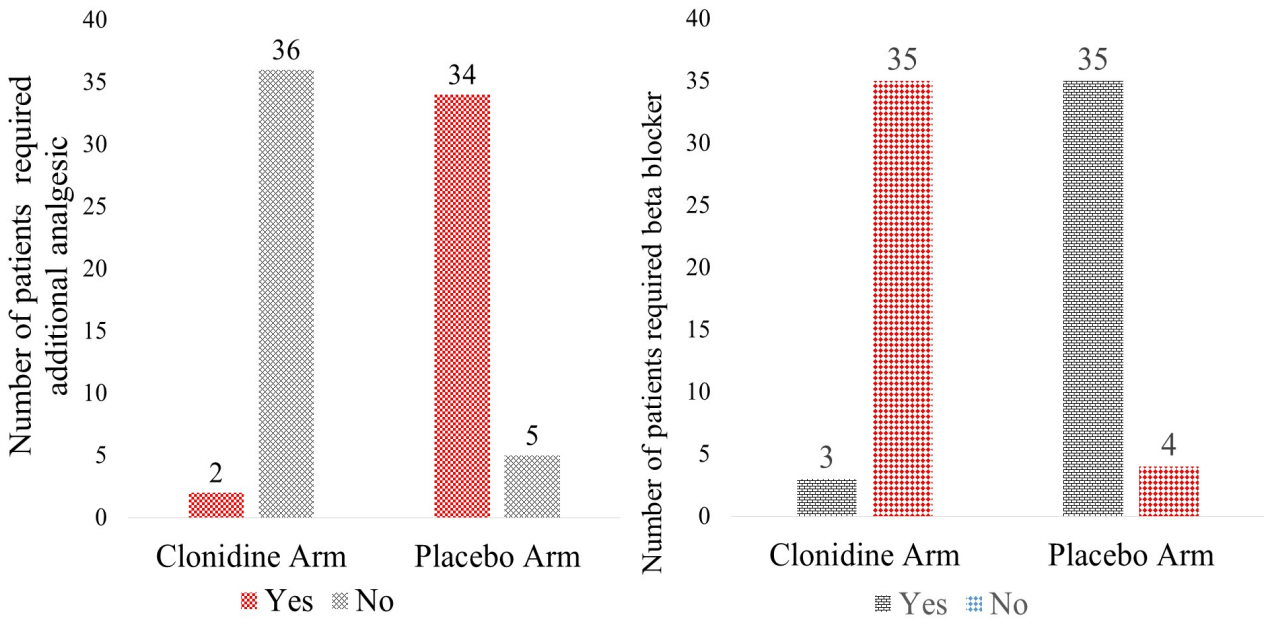


Figure 3 Intraoperative requirement of rescue analgesic (A) and β-blocker (B)

Post-op pain score in patients at 1 h, 2 h, and 6 h were recorded and presented in Figure 4A. According to Fromme-Boezart surgical field grading, the surgical field score was found to be excellent in 32 patients of clonidine arm and 10 patients of placebo arm (Figure 4B).

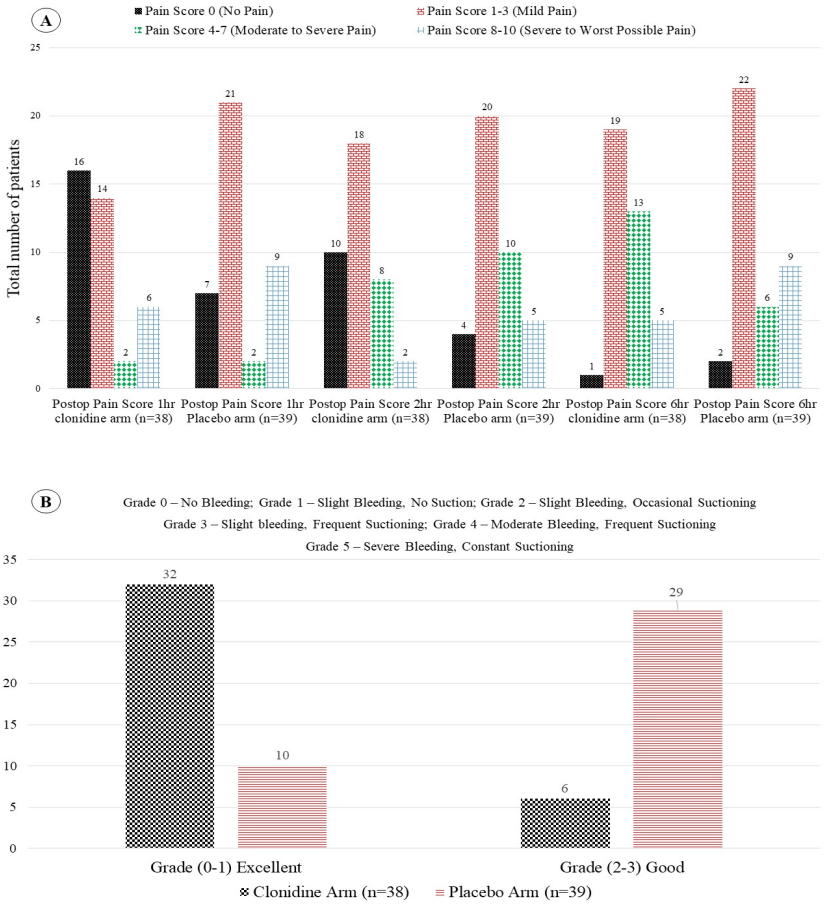


Figure 4 A) Post-operative pain score (Visual Analog Scale) among clonidine arm and placebo arm B) Comparison of surgical field score between clonidine arm and placebo arm

The incidence of side effects was presented in Table 1, where the meantime for rescue analgesic in the placebo arm was found to be 1.5 h with a total analgesic consumption of 2.6 times. The other common side effects observed to be Postoperative Nausea and Vomiting (PONV, clonidine arm, n=1; placebo arm, n=11), bradycardia (<60 bpm, clonidine arm, n=2), and hypotension (80/60 mmHg, clonidine arm, n=1) (Table 1).

Table 1 Incidence of side-effects

	Placebo arm	**Clonidine arm**
Mean time for rescue analgesic	1.5 h	>6 h
Total consumption of analgesic in 6 h (frequency)	2.6 times	0.2 times

Nausea and vomiting (scale 0-10)		
1-3 (minimum)	4	1
4-7 (moderate)	7	0
8-10 (maximum)	0	0
Bradycardia (<60 bpm)	0	2
Hypotension (80/60 mmHg)	0	1

In Figure 5, QOR of patients in both the arms was represented, where the clonidine arm patients were found to have better QOR compared to patients from the placebo arm.

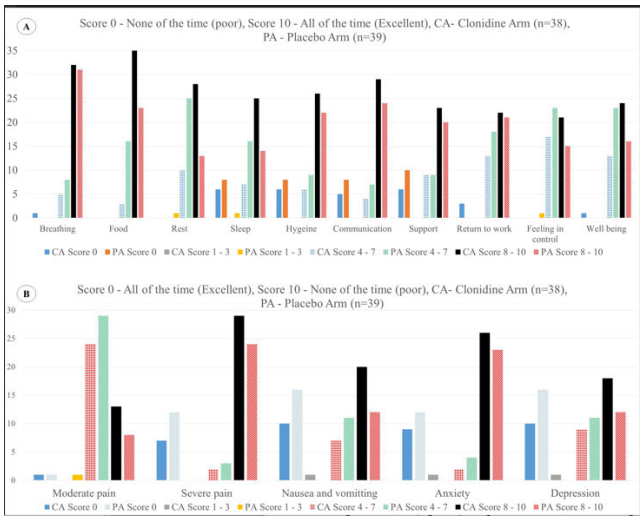


Figure 5: Quality of Recovery (QOR) in patients from clonidine arm and placebo arm.

DISCUSSION

Chronic pain [17] following breast cancer surgery was seen in most of the patients leading to decreased Quality of Life (QOL), [18] and post-traumatic stress disorder, respectively [18,19]. Inadequate pain management during surgery can also cause both short and long-term complications in patients such as pulmonary embolism, deep vein thrombosis, pneumonia, basal atelectasis, promotion of neoplastic propagation, metastasis, etc. [20-22]. By developing excellent pain management protocols, a sharp decrease in anxiety, morbidity, length of hospitalization, and its related expenses can be expected [23,24].

In all the breast cancer patients, controlling hemodynamic responses and pain management plays a crucial role in delivering desired outputs. Usage of adjuvants such as clonidine before induction of general anaesthesia can help in delivering such desired outputs by maintaining hemodynamic stability, lowering pain scores, decreasing usage of fentanyl and β-blocker consumption, and controlling the occurrence of PONV and other side effects in the post-operative period [25–27]. Possible mechanisms and success of clonidine in controlling all those variables together due to its pre-emptive analgesic nature, the anxiolytic effect, analgesic-sparing effect, and residual additive effect. Findings from our study were also in agreement with the results from the previous studies. where an induction of pre-operative clonidine prior to anesthesia induction in the patients cohort has shown a significant prolongation of postoperative analgesia duration with improved pain relief, and a decrease in intraoperative anaesthetic requirement.

A significant reduction in HR and MAP was observed in clonidine arm patients after induction is due to the decrease in sympathetic nervous system outflow from the central nervous system to peripheral tissues causing peripheral vasodilation leading to a decrease in HR and MAP, respectively [6,28].

In both arms, patient's sedation levels were assessed using Brussels sedation score. Where, patients in the clonidine arm were found to be more sedated over the placebo arm at each time point recorded. A high number of agitated patients were observed in placebo arm over clonidine arm and such agitation in placebo arm patients might be due to the early anaesthetic dose wear off. Whereas with Visual Analog Scale (VAS) score, patients in clonidine arm were observed to have better VAS score and anxiety score. With respect to the consumption of additional analgesic and β-blocker, a higher level of consumption was observed in patients from the placebo arm ($P<0.001$) and the same was supported by multiple previous studies [24,25,29,30]. However, contrary results were found from the study reported by Turan, et al. where clonidine does not reduce the pain scores or opioid consumption in patients recovering from noncardiac surgery [31].

In the present study, excellent surgical field scores were obtained in clonidine arm patients over the placebo arm. A possible reason for such an excellent surgical field in clonidine arm patients might be due to the controlled effect of clonidine in achieving hypotension, which ultimately leading to significantly less blood loss compared to patients from the placebo group ($P<0.001$). Jiwanmall et al. have also observed similar results, where 30 of 60 patients from clonidine arm have shown significant intraoperative blood loss with excellent surgical field score [30]. The most common side effects throughout the study include PONV, bradycardia, and hypotension. Bradycardia and hypotension were observed in the clonidine arm but not very prominent. Our results are contrary to multiple previous studies, where bradycardia and hypotension were observed to be common in the placebo arm [24,25,27,30,32]. In a study conducted by Mukherjee et al. bradycardia was found to be more in the dexmedetomidine group compared to the clonidine group [27].

In another study reported by Kumar et al., more patients with bradycardia were present from the clonidine group over the placebo group similar to our study patients [33]. However, in a meta-analysis conducted by Munoz et al., the safety of clonidine in terms of its concerns over bradycardia (14 of 15 trials were not statistically significant) and hypotension (13 of 15 trials were not statistically significant) were clearly analyzed and confirmed to be safe to use [32].

Other major risk includes PONV suffering and it was realized to be high in placebo arm patients compared to clonidine arm patients. A possible reason for such a low incidence of PONV in the clonidine arm might be due to clonidine's ability to reduce emetic sequelae by decreasing the need for analgesic immediately after surgery. In a prospective, randomized study conducted by EVA et al. same was confirmed, where co-induction of general anaesthesia with clonidine significantly reduced the incidence of PONV in patients undergoing breast cancer surgery [34]. Data from a meta-analysis reported from 6 clinical trials including 412 patients have also confirmed our observation, where the risk of suffering from PONV was found to be very low in patients induced with clonidine with general anaesthesia over general anaesthesia alone [32].

In the present study, postoperatively, patients from the clonidine arm have demonstrated better QOR without any serious symptoms and side-effects over the placebo arm, explaining the overall well-being, positive improvement and outcomes in clonidine arm patients. A review by Amaya et al. also confirmed the same, where patients in clonidine arm have shown a better QOR after the surgery over placebo arm patients [23]. The major limitation of the present study is its pre-operative single-dose administration of clonidine as an adjuvant without the knowledge of the appropriate dose regimen. Restrictive data collection of only early post-operative period. Intra-operative strategies and their influence on long-term cancer outcomes are not reported.

CONCLUSION

Preoperative clonidine administration as an adjuvant has shown better results in effectively prolonging the duration of anaesthesia without major hemodynamic alteration and side effects. Clonidine has also minimized the blood loss, HR and BP changes providing an excellent surgical field to the surgeons. Intra and post-operative requirement of analgesic and β-blocker was reduced. Post-surgical patient centered outcomes such as QOR and patient's satisfaction were reported positive. Overall, the use of clonidine is recommended as an adjuvant and it was proven to be safe, and cost-effective in patients undergoing breast conservation surgery.

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Conflicts of interest/Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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