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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.*

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.

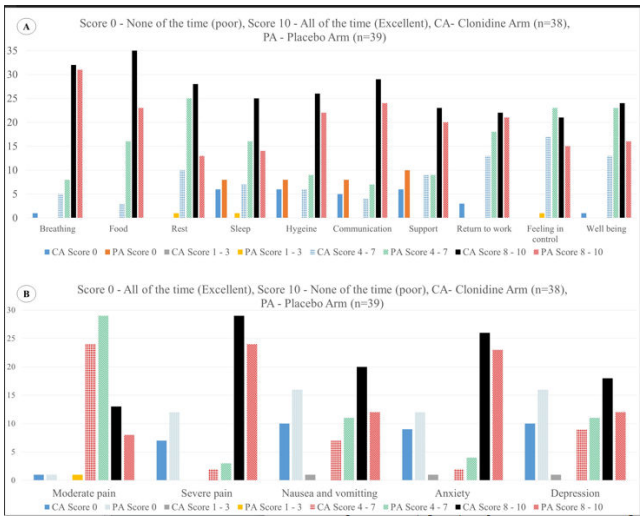

Figure 5: Quality of Recovery (QOR) in patients from clonidine arm and placebo arm.

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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