Original Article

Role of dexmedetomidine as an anaesthetic adjuvant in breast cancer surgery as a day-care procedure: A randomised controlled study

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ABSTRACT

Background and Aims: Breast cancer surgery can be carried out as day-care procedure to increase patient turnover, decrease disease progression and financial burden. The present study was carried out to assess the role of dexmedetomidine in breast cancer surgery as a day-care procedure. **Methods:** This prospective randomised, double-blind study was carried out on 100 patients screened for day-care breast cancer surgery. They were divided into two groups of 50 each; who received either normal saline (Group NS) or 0.6 μg/kg/h dexmedetomidine (Group D) infusion from 10 min before induction until skin closure. All patients were given general anaesthesia. The incidence of discharge, post-operative pain (POP), average rescue analgesia (fentanyl) required and side effects were noted. Statistical analysis was performed using Student's *t*-test and Chi-square test. **Results:** Incidence of discharge in group NS was 60% compared to 88% in Group D ($P = 0.001$). Average rescue analgesia requirement by group NS was 136.07 ± 43.06 μg, whereas it was 77.5 ± 29.86 μg in Group D ($P = 0.01$). The incidence of POP in 6 h and within 2 h of expected discharge time in Group NS was 56% and 28%, respectively, and in Group D, it was 8% in both the periods ($P < 0.001$ and 0.01). Side effects such as post-operative nausea, vomiting and bleeding were encountered in eight and two patients, respectively, in Group NS and two and one patients, respectively, in Group D**. Conclusion:** Dexmedetomidine as an anaesthetic adjuvant makes breast cancer surgery feasible on day-care basis.

Key words: Breast cancer surgery, daycare, dexmedetomidine, fentanyl

INTRODUCTION

Breast cancer surgeries being widely practised procedures in India puts a huge load on tertiary referral cancer centres. Undertaking these surgeries on day-care basis will hasten patient disposal and by early surgery, it will prevent disease progression, cater to more patients and reduce overall expenditure. This can be achieved by meticulous evaluation of patients suitable for day-care anaesthesia.

Dexmedetomidine is a highly selective α_2–agonist; having sedative, analgesic, sympatholytic, narcotic and volatile agent sparing properties and acceptable side effects. This makes it a potent anaesthetic adjuvant. Although studies have been carried out successfully using dexmedetomidine in the minor day-care procedures under general anaesthesia (GA), availability of literature using dexmedetomidine in major day-care surgery, particularly breast cancer surgery is limited. On the other hand, studies have shown that regional anaesthetic techniques for breast surgery are a feasible option for ambulatory set up,[1,2] with the added advantage of ameliorating persistent post-operative pain (POP).[3,4] Hence, this study was carried out to evaluate the role of dexmedetomidine in facilitating early discharge of patients in breast cancer

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surgery carried out on day care basis under GA. We hypothesised that dexmedetomidine as an adjuvant to GA facilitates early discharge of patients undergoing day-care breast cancer surgery. The primary endpoint of the study was to determine the incidence of discharge in each group six hours after surgery. The secondary endpoint was to determine the average dose of analgesic consumed by each group, the number of patients requiring analgesia postoperatively and within 2 h of the expected time of discharge, side effects, intra-operative haemodynamic stability, post-operative sedation and satisfaction scores.

METHODS

This prospective randomised, double-blind controlled study was conducted at our referral cancer hospital after approval from the Institutional Ethical Committee before pilot study (001-IEC-AHRCC dated 14, July, 2016). All patients planned for breast surgery such as breast conservative surgery or modified radical mastectomy, for carcinoma breast between age group 30–60 years and the American Society of Anaesthesiologists (ASA) physical status I and II were explained and counselled about the day-care procedure. Patients excluded from the study were those of ASA ≥III, obese with body mass index >35 kg/m^2, history of nausea and vomiting, delayed recovery from anaesthesia, those with pregnancy, lactation, pre-existing hypotension, any degree of heart block, cardiac disorder, allergies to dexmedetomidine, receiving β-blockers, benzodiazepines or monoaminooxidase inhibitors. Patients refusing for consent, psychologically unstable, or residing far away from the hospital (travelling time more than 1 h) and not having a competent companion to provide domiciliary care and to bring back to the hospital in case of emergency were also excluded from the study. Patients who gave written informed consent underwent a pre-anaesthetic check-up at least 1 day to 1 week before surgery on an outpatient basis. Routine investigations including chest X-ray and electrocardiograms (ECGs) were also evaluated. Patients were explained about the use of visual analogue scale (VAS) score.

One hundred eligible patients were allocated into two groups of 50 each as per computer generated randomisation and were denoted as either Group NS or Group D. Group NS patients were administered GA as per the hospital protocol, whereas Group D received dexmedetomidine followed by GA. All patients reported between 7 and 8 am on the day of surgery after overnight fasting for 6 h. The entire procedure was performed under GA by a team of surgeons according to standardised hospital protocol. The injectable solution of the study drug dexmedetomidine and normal saline (ns) was prepared by a staff unaware of the study, and the principal investigator was also unaware of the contents of the solutions administered during the study. The injectable solution of dexmedetomidine was prepared by dissolving 1 ml (100 μg) of the drug in ns to make final volume up to 50 ml to make a concentration of dexmedetomidine 2 μg/ml and used in Group D patients. For Group NS patients 50 ml of ns was taken in a syringe. Intravenous (IV) access was established with a 20G cannula, and ringer lactate was infused at 10–12 ml/kg/h. All patients received ceftriaxone 1 g, ondansetron 4 mg, and pantoprazole 40 mg IV 30 min before surgery. Their baseline blood pressure (BP), heart rate (HR) and oxygen saturation (SpO_2) were recorded. Ten minutes before induction of GA, glycopyrrolate 0.004 mg/kg IV was administered following which the infusion of ns or dexmedetomidine by a syringe infusion pump (Top Medical System, Model–Top-5300, Tokyo, Japan) was started in respective groups at a rate of 0.3 ml/kg/h (0.6 μg/kg/h for dexmedetomidine) via a separate infusion line, piggyback into the main line and continued until skin closure. Following pre-oxygenation with 100% oxygen, and administration of analgesia with IV fentanyl 2 μg/kg in both groups, anaesthesia was induced with IV propofol until there was loss of response to verbal commands. Vecuronium 0.08 mg/kg were administered, and the lungs were ventilated for 3 min after which a supraglottic airway device (i-gel®) was inserted. Maintenance of anaesthesia was done with isoflurane minimum alveolar concentration 0.5–1 to maintain the bispectral index (BIS) between 40 and 60 and vecuronium 0.02 mg/kg was used as a maintenance muscle relaxant. Ventilation was carried out with oxygen and nitrous oxide (33:67) using the tidal volume of 6–8 ml/kg, and the respiration rate was adjusted to maintain an end-tidal carbon dioxide ($ETCO_2$) of about 35–40 mmHg. Fentanyl 1 μg/kg was planned to be administered if intra-operative mean arterial pressure (MAP) was >20% of baseline. Hypotension below 20% of baseline MAP was managed with 250 ml IV boluses of fluid and ephedrine 6 mg. Bradycardia <50 bpm was treated with atropine 0.6 mg IV. Intra-operative recording of BP, HR, SpO_2, ECG, $ETCO_2$, BIS were noted at various time intervals, i.e., 10 min after drug infusion, after induction, after i-gel® insertion, at 20 min intervals thereafter until completion of

the procedure. Ten minutes before completion of the procedure, infusion diclofenac sodium was given at 1.5 mg/kg until the end of the procedure, and the inhalational agent was discontinued. Neuromuscular reversal was done with IV neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. When patients showed adequate tidal ventilation with pressure support, i-gel® was removed; oxygen was given through face mask and they were transferred to post-anaesthetic care unit (PACU).

After recovery, all patients were administered acetaminophen 1000 mg IV. Fentanyl 1 μg/kg IV bolus was given as rescue analgesia to those who further complained of pain of VAS ≥4 in first 6 h post-operative period. Immediately following neuromuscular reversal, post-operative sedation score was recorded using observer's assessment of alertness/sedation (OAAS) score and was reassessed 1 h after and at discharge.[5] Patients were kept under observation for 6 h in PACU and monitored for the need of rescue analgesia and other post-operative complications such as nausea, vomiting, and bleeding. At the end of 6 h, patient satisfaction was assessed using satisfaction score (1-poor, 2-fair, 3-good, and 4-excellent). Patients who met the discharge criteria (modified Aldrete score ≥9) and did not complain of pain within 2 h of expected discharge time and other side effects were allowed to go home with proper post-operative advice.

Sample size calculation was based on an initial pilot study involving thirty patients in each group. The incidence of discharge in NS group was 53% while in D group was 86%. So taking α error as 0.05, the power of study (1-β) at 95% sample size was calculated approximately 48 in each group. We have included fifty patients in each group for possible dropouts. All patients' data and characteristics were categorised and analysed appropriately using Student's paired and unpaired *t*-test for comparing variables with normal distribution and Chi-square test to analyse categorical data. $P < 0.05$ was considered as statistically significant. Analysis of result was performed using MS office excel 2010 software, SPSS for windows version 24 (IBM®SPSS® Statistics 24. USA).

RESULTS

Figure 1 shows the consort diagram for the flow of participants through each stage of the study. Both the groups were comparable in terms of age and weight and duration of surgeries [Table 1].

In our study, total number of admissions due to post-operative complications was higher in Group NS. Patients who required rescue analgesia within 2 h of expected discharge time failed to meet the discharge criteria and most of them belonged to Group NS. Of the 8 patients in Group NS who had to be admitted due to post-operative nausea and vomiting (PONV) 4 had concomitant pain. Bleeding was another complication we encountered in one patient from each group and had to admit them both [Table 2]. None of our patients who were discharged required readmission within 72 h.

Immediate post-operative median OAAS score was found to be higher in NS group though it was not significant statistically. Six hours post-operatively the

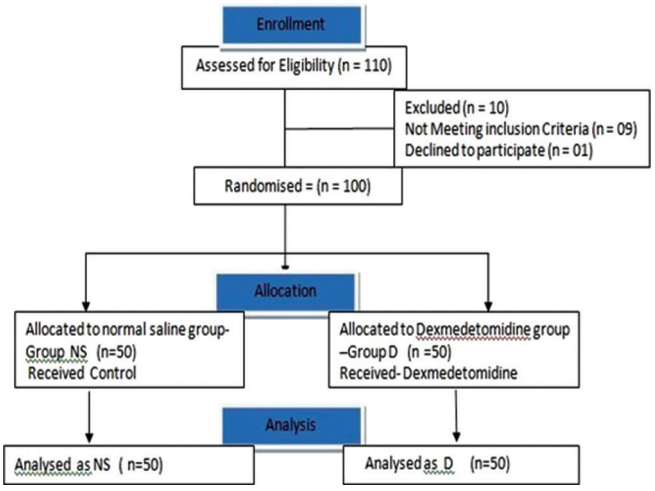

Figure 1: Consort diagram

Table 1: Patients demography

Parameters	Group NS (*n*=50)	Group D (*n*=50)	*P*
Age (years)	47.92±8.08	50.74±9.05	0.103
Weight (kg)	60.12±7.53	59.43±8.4	0.667
Duration of surgery (min)	100.32±10.62	101.68±11.31	0.537

Values expressed as mean±SD. *n* – Number of patients; SD – Standard Deviation; NS – Normal saline; D – Dexmedetomidine

Table 2: Incidence of discharge (number and percentage) and admission due to different causes

Incidence	Group NS (*n*=50)	Group D (*n*=50)	*P*
Discharge (%)	30 (60)	44 (88)	0.001
Admission (%)	20 (40)	6 (12)	
Only POP	10	3	
Only PONV	4	1	
POP and PONV	4	1	
Bleeding	2	1	
Sedation	14	4	

Values expressed as number and percentage. *n* – Number of patients; POP – Post-operative pain; PONV – Post-operative nausea vomiting; NS – Normal saline; D – Dexmedetomidine

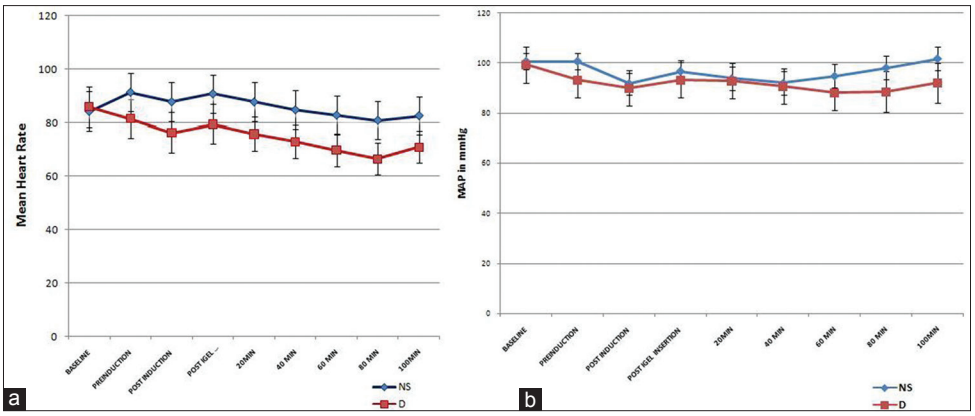

Figure 2: Comparison of HR (a) and MAP (b) in Group D and group NS. HR = Heart rate. MAP = Mean arterial pressure

median OAAS score of Group NS was equal to Group D with a higher interquartile range ($P = 0.03$) [Table 3] and more patients in Group NS were found to be sedated and unfit for discharge.

Intra-operative top up fentanyl was not required by any patients of either group. Number of patients requiring fentanyl as rescue analgesia and the average dose of the drug required per person postoperatively in NS group was higher than Group D [Table 4]. Average time to the first dose of rescue analgesia was 139.82 ± 97.14 min in Group NS as compared to 290.25 ± 62.76 min in Group D. Of the 28 patients requiring rescue analgesia in group NS, it was observed that 15 patients required three doses, 9 required two doses and 4 required single dose whereas in group D, 4 patients only required rescue analgesia; from these 3 patients required single dose and 1 required double dose. In Group D, the fall in the mean HR at different point of time was significantly low compared to the baseline value, but in Group NS, at post-infusion, post-induction, post i-gel insertion and 20 min after HR values were significantly higher than the baseline value, but after 40 min it decreased significantly. Two patients from Group D had an HR <50 bpm, one at 80 min and the other at 60 min that required atropine [Figure 2a].

Group NS showed a decline in MAP following induction which was followed by a transient rise post i-gel® insertion. The MAP showed an initial decline thereafter, but 40 min onward there was a increase in the same. Except at pre-induction and at 100 min the difference was significant as compared to the baseline value. Group D experienced a lower MAP compared to the baseline which was significant at all point of time. Intergroup MAP was found to be significantly lower in Group D at post-drug infusion, pre-induction, and at 60, 80 and 100 min [Figure 2b], but no patient required ephedrine.

Table 3: Sedation scores in two groups

OAAS scores	Group NS	Group D	*P*
Immediate post-reversal	5 (5-5)	5 (4-5)	0.09
1 h post-reversal	5 (5-5)	5 (5-5)	-
At discharge	5 (3.25-5)	5 (5-5)	0.04

Figures are expressed as median (interquartile range). OAAS – Observer's assessment of alertness/sedation; NS – Normal saline; D – Dexmedetomidine

Overall patient satisfaction was better in Group D as compared to Group NS ($P = 0.0001$).

DISCUSSION

In this randomised, controlled trial, we found that significantly more patients receiving dexmedetomidine (88%) could be discharged on the same day after surgery compared to patients who did not receive dexmedetomidine (88% vs. 60%). This was most likely due to the higher numbers of patients in the NS group who required rescue analgesia within 2 h of expected discharge and who experienced PONV.

Dexmedetomidine a known analgesic and anaesthetic sparing agent is used perioperatively for postoperative pain.[6] It has been successfully employed as a total anaesthetic agent in minor surgical procedures and in day-care minimally invasive procedures and other minor procedures facilitating early discharge.[7-9] It has been seen to improve post-operative analgesia following radical mastectomy, but there is a paucity of literature regarding its influence on early discharge of patients undergoing breast cancer surgery.[10] Lower POP, decrease rate of nausea and vomiting and early mobilization are factors that foster such surgeries on daycare basis.[11,12] We carried out our study to assess if addition of dexmedetomidine to GA facilitated early discharge of such patients and observed a higher incidence of discharge in our study group.

Table 4: Post-operative analgesia requirements

Parameters	Group NS (*n*=50)	Group D (*n*=50)	*P*
Average intraoperative fentanyl required per person (μg)	119.4±15.04	117.8±16.45	0.61
Average post-operative fentanyl required per person (μg)	136.07±43.06	77.5±29.86	0.01
Number (%) of persons requiring analgesia 6 h post-operatively	28 (56)	4 (8)	<0.001
Number (%) of persons requiring analgesia within 2 h of expected discharge time	14 (28)	4 (8)	0.01

Dose of fentanyl expressed as mean±SD. SD – Standard deviation; NS – Normal saline; D – Dexmedetomidine

Wei Fan demonstrated that intra-operative use of dexmedetomidine reduced the post-operative consumption of patient-controlled analgesia with morphine in breast cancer surgery patients.[10] Manne *et al*. in their study observed that a significant number of patients did not require rescue analgesia with dexmedetomidine at a dose of 0.4 μg/kg/h.[13] In our study, only four patients of Group D required rescue analgesia. Thus, a satisfactory and prolonged post-operative analgesia can be achieved with intra-operative use of dexmedetomidine.

PONV in breast surgery is as high as 56% and 41%, respectively, as reported by Jaffe *et al*. in their study on 101 women.[14] IV pre-treatment with a single dose of ondansetron also does not substantially prevent this.[15] Bakri *et al*. reported that reduction in the incidence and severity of PONV due to use of dexmedetomidine was almost similar to dexamethasone with analgesic superiority.[16] In our study, post-operative incidence of nausea and vomiting was significantly less in Group D in comparison to NS group.

The study showed that patients in Group D had a lower sedation score than patients in group NS immediately after i-gel® removal but had a better sedation score at discharge. Turan also observed no delay in the recovery profile if the infusion of dexmedetomidine was <2 h.[17]

Sudheesh *et al*. has pointed out that dexmedetomidine has a varying effect on BP and HR depending on the dose and manner of administration.[18] A fall in the PR requiring intervention has been observed when a loading dose followed by a maintenance dose of dexmedetomidine is used.[19,20] In our study, mean fall of HR was 13.58%, which was significantly lower in Group D due to intra-operative infusion without a loading dose. HR <50 bpm was observed in only two patients which was similar to the study by Manne *et al*.[13]

Intra-operative dexmedetomidine maintained BP when used at a rate of 0.4 μg/kg/h infusion in a study by Tanskanen *et al*.[21] Manne *et al*. in his study encountered hypertension in two patients and hypotension in one patient in group dex 0.2 and more so in group dex 0.4.[13] Our fall of the MAP in the study group at post i-gel® insertion and later part of the surgery was significantly more than the control group, but none of our patients required ephedrine.

This is also comparable to the result of Patel *et al*. who observed an average of 8% fall in systolic BP and diastolic BP as compared to 3.6% rise in the control group intraoperatively.[22]

Satisfaction scores were better among patients of Group D due to less side effects and early ambulation.

The limitation of this study was that we could not cater to a larger population and the bias due to the subjective nature of pain assessment by VAS. We tried to overcome the latter by explaining patients in detail about it during pre-operative counselling. We could have given paracetamol in a dose of 2 g postoperatively whereby the number of patients meeting the discharge criteria in either group could have increased. We have not segregated nausea and vomiting contributing to post-operative admissions.

Future research will be to follow-up the patients for chronic pain.

CONCLUSION

Intra-operative dexmedetomidine infusion combined with GA minimises usage of narcotics, produces good post-operative analgesia and less complications leading to early post-operative discharge; thus making breast cancer surgery feasible as a day-care procedure.

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Conflicts of interest
There are no conflicts of interest.

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