A Randomized Control Study of Hemodynamic Status in Patients Undergoing Modified Radical Mastectomy Receiving Dexmedetomidine Infusion

Pravin Ubale[1], Pallavi Khandare[2]

ABSTRACT

Introduction: Worldwide carcinoma breast is the most common cancer and leading cause of death among females accounting to 23% of cancer cases and 14% cancer deaths. This contributes to more than 30% of all cancers in females. Modified Radical Mastectomy (MRM) is the commonly performed surgery as a standard of care and general anaesthesia is the commonly preferred mode of anaesthesia. Dexmedetomidine is an alpha 2 agonist which has hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without significant respiratory depression. Its sympatholytic effect decreases mean arterial pressure (MAP) and heart rate (HR) by reducing norepinephrine release. Thus it can blunt the hemodynamic response to laryngoscopy, tracheal intubation and extubation. In addition dexmedetomidine has the ability to reduce both anesthetic requirement and opioid analgesic requirements during the peri-operative period. Using dexmedetomidine infusion along with isoflurane reduces the requirement of isoflurane and shortens the recovery time. Hence, we used this combination of dexmedetomidine infusion with isoflurane as an anaesthetic agent in modified radical mastectomy in controlling hemodynamic responses and intraoperative bleeding.

Material and methods: This was prospective randomized double blinded study conducted to study the effect of dexmedetomidine intraoperatively on hemodynamic status of the patients (HR, SBP, DBP) undergoing modified radical mastectomy and assessing the grade of bleeding during the procedure. 60 female patients were divided into two groups.

Group 1: 30 patients received 0.5 mcg/kg dexmedetomidine loading dose over 10 minutes followed by 0.5 mcg/kg/hr. maintenance infusion.

Group 2: 30 patients received an identical amount of saline solution.

Heart rate, Systolic blood pressure and Diastolic blood pressure were recorded intraoperatively along with the grades of bleeding throughout the procedure between the two groups. Additional interventions in the form of fentanyl bolus and nitroglycerine bolus used intra-operatively to maintain the hemodynamics was noted and compared between both the groups

Results: The demographic profiles of the groups were comparable in terms of age, weight, height, BMI, ASA physical status and duration of surgery. Heart rate, Systolic blood pressure and Diastolic blood pressure remain on higher side and surgical bleeding was also more in patient of control group. Requirement of additional intervention was less in patients receiving dexmedetomidine infusion

Conclusion: Dexmedetomidine infusion along with isoflurane provides good hemodynamic response also reduces bleeding at the surgical site during modified radical mastectomy.

Keywords: Dexmedetomidine, Modified Radical Mastectomy, Sedation, α_2 agonist, Hemodynamics.

INTRODUCTION

There is an ever increasing incidence of breast cancer in developing countries. Worldwide carcinoma breast is the most common cancer and leading cause of death among females accounting to 23% of cancer cases and 14% cancer deaths.[1] Breast cancer is the most common malignancy in urban Indian female and 2nd most common cancer in rural women.[2] This contributes to more than 30% of all cancers in females.[3] Modified Radical Mastectomy (MRM) is the commonly performed surgery as a standard of care and general anaesthesia is the commonly preferred mode of anaesthesia. Direct laryngoscopy and endotracheal intubation (ETT) may not lead to serious complications in healthy patients, but the hazards of an increase in the sympathetic activity associated with laryngoscopy & intubation-like hypertension, tachycardia and dysrhythmias, are evident. General anaesthesia (GA) can be safely administered to a vast majority of patients, but certain patients with high risk conditions and declared unfit for general anaesthesia require an alternative mode of anaesthesia to perform the surgery safely as well as avoiding the risks or complications associated with general anaesthesia. Cervical epidural anaesthesia (CEA) for modified radical mastectomy[4] is one of the regional anesthetic techniques that can be done by using a low dose of local anesthetic in combination with epidural adjuvants for better analgesia with minimum weakness of respiratory muscle and sedation. CEA is not used routinely in everyday anesthesia practice, mainly because routine high concentration local anesthetic drugs associated with moderate restrictive pulmonary syndrome with subsequent oxygen desaturation.[5]

Dexmedetomidine is an alpha 2 agonist which has hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without significant respiratory depression. Its sympatholytic effect decreases mean arterial pressure (MAP) and heart rate (HR) by reducing norepinephrine release. Thus it can

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How to cite this article: Ubale P, Khandare P. A Randomized control study of hemodynamic status in patients undergoing modified radical mastectomy receiving dexmedetomidine infusion. International Journal of Contemporary Medical Research 2021;8(11):K24-K29.

blunt the hemodynamic response to laryngoscopy, tracheal intubation and extubation. In addition dexmedetomidine has the ability to reduce both anesthetic requirement and opioid analgesic requirements during the peri-operative period. Isoflurane, sevoflurane and desflurane are the inhalational agents that are used to maintain anaesthesia during various surgeries. For increasing the depth of anaesthesia there may be an increase in the requirement of anaesthetic maintenance agent which would lead to its more consumption. Therefore it would be prudent to use adjuvants which would control the hemodynamic changes and also reduce the requirement of anaesthetic agents. Several adjuvants have been used to decrease the dose of inhalational agents and to provide better sedation, hypnosis and analgesia. Dexmedetomidine has the ability to reduce minimum alveolar concentration (MAC) of volatile anaesthetic significantly up to 90% and hence decreases the anaesthetic agent requirement.[6] Using dexmedetomidine infusion along with isoflurane reduces the requirement of isoflurane and shortens the recovery time. Hence, we used this combination of dexmedetomidine infusion with isoflurane as an anaesthetic agent in modified radical mastectomy in controlling hemodynamic responses and intraoperative bleeding. [7]

MATERIAL AND METHODS

This was prospective randomized double blind controlled study conducted in tertiary care teaching public hospital after obtaining ethical permission and well-informed written consent from the patients. The study was conducted over a period of one year from November 2018 to November 2019

Inclusion Criteria

- Females aging between 30-65years
- ASA1 & ASA2
- Patients scheduled for elective modified radical mastectomy surgery under general anaesthesia lasting for less than two & half hours

Exclusion Criteria

- ASA 3 & ASA 4
- Patient with uncontrolled hypertension
- Severe cardiac or respiratory disease
- Hepatic Or renal dysfunction
- Body Mass Index (BMI)>30kg/M2
- Bleeding or coagulation disorders
- Patients refusal to participate in the study
- Allergic to drugs
- Pregnant females
- Currently breast feeding females

Patients were randomized according to computer generation method into two groups in a double-blinded manner. A total of 60 female patients were included in the study. The identity and consent of the patient was confirmed prior to induction of anaesthesia. Standard ASA monitors like pulse oximetry, non-invasive blood pressure (NIBP), electrocardiography, capnometer were attached and baseline readings were noted. The patients in Group1 received a loading dose of intravenous dexmedetomidine 0.5µg/kg over 10 min, followed by a maintenance infusion of 0.5µg/kg/hr. Patients in Group2 (Control group) were given an identical amount of saline solution. In both groups, infusion was continued until 15 min prior to the end of surgery. All solutions were prepared by an anesthesiologist not participating in the study. The anaesthetic technique was standardized and modified radical mastectomy was performed by the same surgical team to ensure consistency in the estimation of the surgical field and bleeding. All patients were premedicated with intravenous ondensetron (0.08mg/kg), ranitidine (1mg/kg) followed by fentanyl (2 µg/kg) before induction of anaesthesia. After preoxygenation for 3 min, anaesthesia was induced with propofol 2 mg/kg along with 50% oxygen, nitrous oxide and isoflurane in all of the patients. All of the patients were maintained on mechanical ventilation after vecuronium bromide 0.08 mg/kg. The patients were initially ventilated at 14 breaths/min, with a tidal volume of 6 ml/kg and later adjusted to keep the end-tidal carbon dioxide (ETCO2) level between 35 and 45 mmHg (normocapnia). Intraoperatively, the HR, NIBP, ECG, ETCO2 and SpO2 were monitored and recorded at 5 minutes interval until the end of surgery. During the surgery, systolic blood pressure were maintained between 100 and 120 mmHg and diastolic blood pressure between 60 and 90 mmHg by adjusting the dial concentration of isoflurane (0.6–1%). The isoflurane concentration was recorded as a percentage every 15 min until the end of surgery in all of the patients. The patients were observed for bradycardia (HR < 60 beats/min), tachycardia (HR > 100 beats/min), and arrhythmias. All unexpected intraoperative events requiring intervention were recorded and treated according to standard clinical protocols. During the surgery, bleeding was assessed by the surgeon using the following scoring system:

0 = no bleeding, excellent surgical conditions;
1 = minimum bleeding, sporadic suction;
2 = diffuse bleeding, repeated suction;
3 = considerable and troublesome bleeding, continuous suction.

The ideal value for the surgical conditions was predetermined to be 1. All drug infusions were discontinued 15 minutes prior to the end of surgery. Once the surgery was complete, all of the anaesthetic agents were withdrawn. When spontaneous breathing movements began, the residual neuromuscular blockade was reversed with neostigmine (2.5 mg) and glycopyrrolate (0.4 mg). The recovery time, defined as the interval between the discontinuation of anaesthetic and eye opening to verbal commands, was recorded. Analgesics administered post operatively was iv paracetamol 15mg/kg. Post operatively patients were shifted to the post anaesthesia care unit, received oxygen and iv fluids. HR, SBP, DBP, SpO2 were recorded every 15 min thereafter for 2 hours.

STATISTICAL ANALYSIS

The sample size was calculated from previous study data taking into consideration of Heart rate and SBP at 10 mins and 20 mins respectively by comparison of mean method at 95% confidence interval, 80% power of study and 5%

alpha error, minimum sample size is found to be 24 and 36 for Heart rate and SBP respectively. Thus, 60 patients were enrolled to account for a dropout rate of 5% with each group containing 30 patients using the formula

$$N=\frac{2\times K\times 2\ \mu 1 - \mu 2\ 30}{\sigma}$$

Where

N - Sample size

K - Constant

σ - Standard Error

μ - Mean of group

All recorded data was tabulated and the results were expressed as means ± SD, which would be considered the best predictor for the statistical analysis. After data collection, data entry was done in excel and data analysis was done in application software. The demographic data for the categorical variables was compared using the chi-square test. Statistical significance in terms of the mean difference between groups, were assessed using Student's t-test and repeated measured analysis of variance. A P value less than 0.05 were deemed to indicate statistical significance.

Assessment Parameters

- Patients age, weight, height, BMI, ASA physical status and duration of surgery, grade of bleeding
- Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) were recorded at baseline, after drug administration, after induction, after intubation, and 10 min , 30 min, 45min, 60 min, 90min, 120min and postoperatively in both the groups.
- Patients receiving more Fentanyl and NTG boluses were recorded

RESULT

The demographic profiles of the groups were comparable in terms of age, weight, height, BMI, ASA physical status and duration of surgery. (Table1)

10 patients out of 30 patients receiving dexmedetomidine have grade1 surgical field at 30 minutes after start of surgery whereas none of the patients had grade 1 surgical field from group2. (Table 2A)

19 patients out of 30 patients had grade1 surgical field at 45 minutes after start of surgery as compared to group2 in which only 3 patients had grade1 of surgical field among the 30 patients in the control group. Majority of the patients in group 2 had grade 2 or grade 3 surgical field. (Table 2B)

21 patients of group1 had grade 1 of surgical field at 60minutes as compared to 3 patients in group 2 of control group. (Table 2C)

In majority of the cases surgery was finished before 90 minutes. 22 patients out of 30 patients in group1 and 15 patients out of 30 patients in group2 had finished their surgery before 90 minutes. Only 8 patients out of 30 patients had their surgery duration more than 90 minutes as compared to 15 patients out of 30 patients of control group who had duration of surgery more than 90 minutes. (Table2D)

The baseline value for mean HR was comparable between the two groups. Intraoperatively, the mean HR values were also comparable between the groups, and the patients receiving dexmedetomidine had significantly lower heart rate as compared to the patients in the control group ($p< 0.05$). Mean heart rate was found to be higher in the patients of group 2 intra operatively as well as post operatively**.** (Table 3)

The baseline mean systolic blood pressure was comparable between the two groups but with comparatively lower systolic blood pressure during surgery in patients of group1, with statistically significant difference. Patients receiving dexmedetomidine maintained their systolic blood pressure between 100 to 120 mm hg whereas the patients not receiving dexmedetomidine had their systolic blood pressure beyond 120 mm hg. After administration of the drug infusion, at the end of surgery mean systolic blood pressure is lower in group1 ($p<0.05$). (Table 4)

The baseline mean diastolic blood pressure was comparable in between the groups. Diastolic blood pressure in group

Parameters	Group 1(n=30)	Group 2(n=30)
Age(yr)	50.65±9.301	50.63±9.725
Weight(kg)	57.4±7.276	58.4±6.526
Height(cm)	156.23±4.289	156.83±5.477
BMI(kg/m2)	24.09±3.297	23.67±2.67
ASA(I/II)	15/15	6/24
Surgery Duration	82.7±21.085	96.83±19.64

Table-1: Demographic data of the patients:

(A) Quality of Field 30 Minutes after the Start of Surgery			
Grade of surgical field	**Group 1 (n=30)**	**Group 2 (n=30)**	**p-value**
0	0	0	
1	10	0	0.000532
2	13	15	0.6048
3	7	15	0.0321
(B) Quality of Surgical Field 45 Minutes after the Start of Surgery			
Grade of surgical field	**Group 1 (n=30)**	**Group 2 (n=30)**	**p-value**
0	0	0	
1	19	3	0.00001816
2	11	15	0.299
3	0	12	0.004231
(C) Quality of Field 60 Minutes after the Start of Surgery			
Grade of surgical field	**Group 1 (n=30)**	**Group 2 (n=30)**	**p-value**
0			
1	21	3	0.000002101
2	9	25	0.00003067
3	0	2	0.1504
(D) Quality of Field 90 Minutes after the Start of Surgery			
Grade of surgical field	**Group 1 (n=30)**	**Group 2 (n=30)**	**p-value**
0	0	0	
1	6	3	0.2793
2	2	12	0.002271
3	0	0	

Table-2: Assessment of Intraoperative Bleeding

	Group 1	Group 2	p-value
Baseline	86.63±10.46	85.6±6.81	0.12
After study drug administration	77.33±8.18	80.5±7.445	0.122
1 min after induction	74.2±11.792	85.7±5.5	0.001
1 min after intubation	80.37±10.14	90.37±8.636	0.001
10 min	73.47±9.544	87.6±8.573	0.001
30 min	72.17±10.21	84.2±7.107	0.001
45 min	71.67±12.85	83.67±6.46	0.001
60 min	71.6±8.699	82.6±6.463	0.001
90 min	69.29±6.604	82.18±8.269	0.001
120 min	82.5±17.59	80.92±6.934	0.787
Post-operative	78.2±7.107	84.3±5.338	0.001

Table-3: Comparison of changes in Heart Rate among the study groups

	Group 1	Group 2	p-value
Baseline	126.73±10.66	127.9±7.072	0.031
After study drug administration	116.43±12.331	130.87±8.157	0.001
1min after induction	113.93±11.96	124.93±8.959	0.001
1min after intubation	117.83±13.91	139.1±9.866	0.001
10min	110.67±12.85	134.5±14.35	0.001
30min	109.73±12.188	132.57±16.608	0.001
45min	110.3±12.868	123.03±15.384	0.001
60min	109.4±12.29	117.57±11.98	0.011
90min	107.52±10.55	117.11±9.832	0.002
120min	107.75±11.266	116.77±8.877	0.114
Post-operative	119.1±8.187	126.97±8.311	0.001

Table-4: Comparison of changes in Mean Systolic Blood pressure among the groups

	Group 1	Group 2	p-value
Baseline	81.047±6.23	83.4±5.799	0.222
After study drug administration	74.7±6.098	82.3±6.38	0.001
1min after induction	72.7±6.182	79.3±6.879	0.001
1min after intubation	74.87±7.427	87.931±6.716	0.001
10min	70.57±5.184	85.03±8.075	0.001
30min	69.3±5.44	83.17±8.694	0.001
45min	68.9±5.44	79.17±8.558	0.001
60min	69.23±6.5	75.50±6.113	0.001
90min	69.19±6.09	75.96±6.447	0.001
120min	71±8.869	74.92±5.693	0.305
Post-operative	74.57±5.412	79.17±4.921	0.001

Table-5: Comparison of Mean Diastolic Blood Pressure between the Study Groups

Intervention	Group 1	Group 2	P value
Fentanyl			
Yes	5 (16.66%)	30(100)	0.001
No	25 (83.34%)	0 (0)	
Total	30 (100)	30(100)	
NTG			
Yes	0 (0)	30(100)	0.001
No	30(100)	0(0)	
Total	30(100)	30(100)	

Table-6: Comparison of additional interventions used to maintain hemodynamics among study groups

1 was comparatively lower as compared to group 2, with statistically significant difference. After discontinuation of the drug infusion, at the end of surgery mean diastolic blood pressure is significantly lower in group1 ($p<0.05$). (Table 5) The table shows that 16.66% (5 out of 30) patients required additional fentanyl to maintain hemodynamics in Group 1 as compared to Group 2 where all the 30 patients required additional fentanyl in the intra-operative period to maintain the hemodynamics. This difference was found to be statistically significant ($p< 0.05$). A statistically significant reduction was also observed in the percentage of isoflurane required (0.82 ± 0.80%) to maintain the systolic blood pressure between 100 and 110 mmHg in patients receiving dexmedetomidine infusion compared with the Group II (1.50 ± 0.90%). The mean intraoperative fentanyl consumption in patients in the Group I was also significantly lower compared with that of the Group II (38.43 ± 5.40 µg vs. 75.12 ± 4.60 µg). The mean recovery time from anesthesia did not show

any clinically significant difference between the groups. (Table 6)

DISCUSSION

Dexmedetomidine is an alpha 2 agonist which has hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without significant respiratory depression. Its sympatholytic effect decreases mean arterial pressure (MAP) and heart rate (HR) by reducing norepinephrine release. Thus it can blunt the hemodynamic response to laryngoscopy, tracheal intubation and extubation. In addition Dexmedetomidine has the ability to reduce both anesthetic requirement and opioid analgesic requirements during the peri-operative period. Isoflurane, sevoflurane and desflurane are the inhalational agents that are used to maintain anaesthesia during various surgeries. For increasing the depth of anaesthesia there may be an increase i n the requirement of anaesthetic maintenance agent which would lead to its more consumption. Therefore it would be prudent to use adjuvants which would control the hemodynamic changes and also reduce the requirement of anaesthetic agents. Several adjuvants have been used to decrease the dose of inhalational agents and to provide better sedation, hypnosis and analgesia. Dexmedetomidine has the ability to reduce minimum alveolar concentration (MAC) of volatile anaesthetics significantly up to 90% and hence decreases the anaesthetic agent requirement. Modified radical mastectomy has been used as the surgical modality for carcinoma breast. Appropriate surgical field visibilities with steady intraoperative hemodynamics are of utmost important during the intraoperative period. The present study aimed at minimizing the bleeding at the surgical site by using dexmedetomidine infusion during modified radical mastectomy. Our study was conducted to study the effect of dexmedetomidine intraoperatively on hemodynamic status of the patients (HR, SBP, DBP) undergoing modified radical mastectomy and assessing the grade of bleeding during the procedure. 60 female patients were enrolled for the study undergoing modified radical mastectomy over a period of one year. These patients were divided into two groups randomly by computer generation method as the study being double blinded. The groups were: Group 1: 30 patients received 0.5 mcg/kg dexmedetomidine loading dose over 10 minutes followed by 0.5 mcg/kg/hr maintenance infusion. Group 2: 30 patients received 0.9% Normal saline in place of dexmedetomidine. Heart rate, Systolic blood pressure and Diastolic blood pressure were recorded intraoperatively along with the grades of bleeding throughout the procedure between the two groups. Additional interventions in the form of fentanyl bolus and nitroglycerine bolus used intra-operatively to maintain the hemodynamics was noted and compared between both groups. Gupta K[8] et al conducted a randomized control study on dexmedetomidine infusion as an anaesthetic adjuvant to general anesthesia for appropriate surgical field visibility during modified radical mastectomy using i-gel. In their study 60 female patients belonging to ASA 1 and 2 of age group of 40 to 65 years, were blindly randomly divided into 30 patients in each group. Group I received i.v dexmedetomidine at a loading dose of 1 µg/kg over 10 min, followed by maintenance infusion of 0.4 to 0.7 µg/kg/h, while Group II received an identical amount of saline infusion until 15 min prior to the end of surgery. Parameters noted were bleeding at the surgical field and hemodynamic changes; isoflurane requirement, intraoperative fentanyl requirement and recovery. It was observed that the patients receiving dexmedetomidine infusion showed significantly less bleeding at the surgical field ($P < 0.05$). Percentage of isoflurane required ($0.82 \pm 0.80\%$) to maintain the systolic blood pressure between 100 and 110 mmHg in patients receiving dexmedetomidine infusion shows significant reduction as compared with the Group II ($1.50 \pm 0.90\%$) which was statistically significant. Fentanyl requirement in patients in the Group I was also significantly lower compared with that of the Group II (38.43 ± 5.40 µg vs. 75.12 ± 4.60 µg). There is no significant difference in the mean recovery time from anesthesia between the groups. From this it was concluded that dexmedetomidine infusion can be used safely to decrease the bleeding at the surgical field with smooth recovery from anesthesia. In our study similar results were obtained: The mean systolic blood pressure was comparatively lower during surgery in patients of group1 who received dexmedetomidine infusion as compared to patients in group 2 who received normal saline, with statistically significant difference. Patients receiving dexmedetomidine maintained their systolic blood pressure between 100 to 120 mm hg whereas the patients not receiving dexmedetomidine had their systolic blood pressure beyond 120 mmHg. Diastolic blood pressure in group 1 was comparatively lower as compared to group 2, with statistically significant difference. It was also observed that the patients receiving dexmedetomidine had significantly lower heart rate as compared to those the control group. Thus proving that dexmedetomidine had a beneficial effect on intraoperative hemodynamics of the patient.

Khan[9] et al. also conducted a study on effects of dexmedetomidine on isoflurane requirements in healthy volunteer and concluded that dexmedetomidine infusion reduces the requirement of an inhalational anesthetic agent and concluded that concentration of the isoflurane required in patients receiving dexmedetomidine is comparatively less. Similar results were obtained in our study indicating that the use of dexmedetomidine infusion reduces the isoflurane concentration to maintain the systolic blood pressure and diastolic blood pressure at a lower level during the intraoperative period

Ulger[10] et al. compared dexmedetomidine with nitroglycerine to achieve controlled hypotension in patients in middle ear surgeries. Mean arterial pressure was between 65 and 75 mmHg and accordingly the infusion rate was titrated. Thus, it was concluded that dexmedetomidine was better for maintaining appropriate surgical field along with hemodynamic stability and there was no reflex tachycardia and rebound hypertension. Similar results have been observed in our study that patients receiving dexmedetomidine infusion showed lower systolic and diastolic blood pressure

as compared to the patients not receiving dexmedetomidine.

Limitations of the Study

- Patients with age group below 18 yrs. and above 65 years were not included in the study
- ASA 3 and ASA 4 patients were excluded
- Patients with baseline heart rate less than 55 beats per minute and patients with heart blocks were not a part of the study
- Patients with BMI more than 30 were not a part of the study
- Lack of BIS for monitoring the depth of anaesthesia. Hence confirmation about intra-operative awareness could not be entirely ruled out.

CONCLUSION

Dexmedetomidine infusion as an anaesthetic adjuvant reduces the requirement of inhalational agent, provides good hemodynamic stability, also reduces bleeding at the surgical site and provides appropriate surgical field visibility during modified radical mastectomy.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 05-10-2021; **Accepted:** 29-10-2021; **Published:** 30-11-2021