ANTIEMETIC EFFICACY OF SMALL DOSES OF PROPOFOL FOLLOWING MODIFIED RADICAL MASTECTOMY
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ABSTRACT: BACKGROUND: Breast cancer surgeries under general anesthesia have been associated with relatively high incidence of post-operative nausea and vomiting. Propofol possesses direct antiemetic properties at sub-anaesthetic doses and is devoid of side effects and is cost effective. AIMS AND OBJECTIVES: To study the antiemetic efficacy of propofol when compared to a placebo. To study the minimum effective dose of propofol as an antiemetic among three dosages 0.25mg/kg, 0.5mg/kg & 1mg/kg. MATERIALS AND METHODS: 120 women in the age group of 35-74 years belonging to ASA grade 1 & 2 who were scheduled to undergo modified radical mastectomy under general anesthesia were randomly divided into 4 groups. Group 1-n=30 received placebo (Normal saline) Group 2-n=30 received 0.25mg/kg of propofol Group 3-n=30 received 0.5mg/kg of propofol Group 4-n=30 received 1mg/kg of propofol After skin suture either placebo or propofol in 3 different doses were administered intravenously as bolus doses over 2 minutes randomly to patients according to the group to which they were allocated. Once the patients regained protective airway reflexes they were reversed and extubated. The patients were observed for 24 hrs postoperatively. They were followed up every ½ an hour for first 2 hrs, every 1 hr for the next 4 hrs and thereafter 4th hourly till 24 hrs. Parameters observed were retching and vomiting, and sedation. RESULTS: Study results consisting of data were analysed by Fishers exact probability test and Chi-Square test. A p value less than 0.05 was considered to be statistically significant Samples of 4 groups of age and weight matched with P>0.05. Statistically significant difference in the incidence of vomiting was seen with Group C & Group D at ½ and 1 hour intervals. No statistically significant difference in the incidence of PONV was noted in the four groups at 5 to 24 hours period. Statistically significant difference in sedation was noted with Group C and D at 1 hour and 2 hour interval when compared with placebo. No difference in sedation was noted with any of the four Groups at 5 to 24 intervals. There was a statistically significant decrease in the incidence of nausea and vomiting with doses of 0.5mg/kg and 1mg/kg of propofol at 0-2hrs. We can infer that the therapeautic (Antiemetic) concentrations were achieved and maintained for 2hrs by 0.5 mg/kg and 1 mg/kg of propofol beyond which the dose has decreased to suboptimal levels due to rapid elimination half-life of 1-3 hrs. Dosage of 0.25mg/kg was inadequate to achieve therapeautic plasma concentrations. CONCLUSION: In conclusion this study has shown that propofol decreases the incidence of retching and vomiting with minimal side effects especially in the early postoperative period and 0.5mg/kg is the minimum antiemetic dose to achieve this.

KEYWORDS: PONV, Post-operative nausea and vomiting, sedation, propofol, antiemetic, MRM (Modified radical mastectomy).

INTRODUCTION: Despite significant advances in the delivery of general anesthesia, the incidence of post-operative nausea and vomiting in recent studies has been reported as 20% to 30%. Post-operative nausea and vomiting is a distressing symptom, may lead to significant morbidity from
dehydration, electrolyte imbalance, tension in suture lines, venous hypertension, and increased bleeding under skin flaps and can expose the subject to an increased risk of pulmonary aspiration of vomitus. Breast cancer surgeries under general anesthesia have been associated with relatively high incidence of post-operative nausea and vomiting. Between 60 to 80 percentage of patients who undergo modified radical mastectomy experience post-operative nausea and vomiting. Moreover PONV is a limiting factor in the early discharge of ambulatory surgery patients and is a leading cause of unanticipated hospital readmission. The recent trend of performing more and more surgeries on outpatient basis further emphasizes the need for effective antiemetic therapy.

Propofol possesses direct antiemetic properties at sub-anaesthetic doses and is devoid of side effects and is cost effective. Propofol is also increasingly being used for chemotherapy induced nausea and vomiting and for refractory PONV. Hence propofol is emerging as the promising drug in the treatment of PONV.

AIMS AND OBJECTIVES OF THE STUDY: To study the antiemetic efficacy of propofol when compared to a placebo. To study the minimum effective dose of propofol as an antiemetic among three dosages 0.25mg/kg, 0.5mg/kg & 1mg/kg.

MATERIAL AND METHODS: After approval from institutional ethical committee this prospective randomized study was done.

STUDY: Prospective, randomized, double blind and placebo controlled study. 120 women in the age group of 35-74 years belonging to ASA grade 1 & 2 who were scheduled to undergo modified radical mastectomy under general anesthesia.

Exclusion Criteria:
- ASA 3, 4, 5.
- Emergency cases.
- Patients with the history of motion sickness, previous post-operative nausea and vomiting, patients with history of head ache and migraine.
- Patient with cerebrovascular, neurological, psychiatric illness.
- Drug allergy to any anaesthetic drug and propofol.

METHOD OF COLLECTION OF DATA: The patients were randomly divided into 4 groups:
- Group 1-n=30 received placebo (Normal saline).
- Group 2-n=30 received 0.25mg/kg of propofol.
- Group 3-n=30 received 0.5mg/kg of propofol.
- Group 4-n=30 received 1mg/kg of propofol.

Preoperative evaluation was done. On the morning of surgery, when patient was brought to operation theatre iv line was secured with 18 gauge cannula and ringer lactate started. Inj. glycopyrrolate 50µg/kg, inj. fentanyl 1.5 µg/kg was given. General anaesthesia was induced with inj. thiopentone 5mg/kg and tracheal intubation facilitated by inj. succinylcholine 1.5mg/kg intravenously. Anaesthesia was maintained using O2 30% - N2O 70% and halothane 1% and inj. vecuronium 0.1mg/kg initially and repeated doses with 0.025mg/kg as and when required. The patient’s vital parameters like pulse, blood pressure, oxygen saturation etc were monitored.
throughout the surgery and in postoperative period. Intraoperative iv fluid 0.9% normal saline and ringer lactate was used. After skin suture either placebo or propofol in 3 different doses were administered intravenously as bolus doses over 2 minutes randomly to patients according to the group to which they were allocated. Once the surgery was completed, nitrous oxide was discontinued. Thorough suctioning of the mouth and throat was done. Neuromuscular blockade was reversed with inj. neostigmine 50 µg/kg and inj. glycopyrrolate 100µg/kg intravenously. Once the patients regained protective airway reflexes they were extubated. Postoperatively iv fluids were administered at maintenance rates. Postoperative pain was treated with inj fentanyl 1mcg/kg. The patients were observed for 24 hrs postoperatively. They were followed up every ½ an hour for first 2 hrs, every 1 hr for the next 4 hrs and thereafter 4th hourly till 24 hrs. Parameters observed were retching and vomiting, and sedation. Scoring systems were used for each parameter as follows.

Vomiting:
- No retching or vomiting.
- Retching.
- Occasional vomiting (1-3 episodes).
- Recurrent vomiting (>3 episodes).

Sedation
- Sleeping not arousable.
- Sleeping but arousable.
- Drowsy.
- Awake.

A rescue antiemetic ondansetron 0.15mg/kg was administered intravenously when the patient experienced two episodes of retching and or vomiting.

RESULTS:
Statistical Analysis: Study results consisting of data were analysed by Fishers exact probability test and Chi-Square test. A p value less than 0.05 was considered to be statistically significant.

| Age in years | Group I |      | Group II |      | Group III |      | Group IV |      |
|--------------|---------|------|----------|------|-----------|------|----------|------|
|              | No      | %    | No       | %    | No        | %    | No       | %    |
| 35-40        | 5       | 16.7 | 6        | 20.0 | 4         | 13.3 | 5        | 16.7 |
| 41-50        | 8       | 26.7 | 8        | 26.7 | 10        | 33.3 | 6        | 20.0 |
| 51-60        | 11      | 36.7 | 7        | 23.3 | 8         | 26.7 | 13       | 43.3 |
| 61-70        | 4       | 13.3 | 7        | 23.3 | 7         | 23.3 | 4        | 13.3 |
| >70          | 2       | 6.7  | 2        | 6.7  | 1         | 3.3  | 2        | 6.7  |
| Total        | 30      | 100.0| 30       | 100.0| 30        | 100.0| 30       | 100.0|

Table 1: Age distribution of patients
| Study Period | Vomiting         | Group A | Group B | Group A-B | Group C | Group A-C | Group D | Group A-D |
|--------------|------------------|---------|---------|-----------|---------|-----------|---------|-----------|
| ½ hr         | No vomiting      | 25      | 83      | 24        | 80      | 30        | 100     | 30        |
|              |                  | 4       | 13      | 6         | 20      | 0         | 0       | 0         |
|              | Occ vomiting     | 1       | 3.3     | 0         | 0       | 0         | 0       | 0         |
|              | Rec vomiting     | 0       | 0       | 0         | 0       | 0.731     | 0       | 0         |
|              |                  |         |         |           |         | 0.052+    |         | 0.052+    |
| 1 hr         | No vomiting      | 24      | 80      | 21        | 70      | 30        | 100     | 30        |
|              |                  | 2       | 6.7     | 6         | 20      | 0         | 0       | 0         |
|              | Occ vomiting     | 4       | 13      | 3         | 10      | 0         | 0       | 0         |
|              | Rec vomiting     | 0       | 0       | 0         | 0       | 0.329     | 0       | 0.023*    |
|              |                  |         |         |           |         | 0         |         | 0.023*    |
| 1 ½ hr       | No vomiting      | 26      | 87      | 25        | 83      | 28        | 93      | 30        |
|              |                  | 4       | 13      | 1         | 3.3     | 2         | 6.7     | 0         |
|              | Occ vomiting     | 0       | 0       | 4         | 13      | 0         | 0       | 0         |
|              | Rec vomiting     | 0       | 0       | 0         | 0       | 0.086+    | 0       | 0.671     |
|              |                  |         |         |           |         | 0         |         | 0.671     |
| 2 hr         | No vomiting      | 25      | 83      | 26        | 87      | 27        | 90      | 29        |
|              |                  | 0       | 0       | 2         | 6.7     | 1         | 3.3     | 0         |
|              | Occ vomiting     | 4       | 13      | 2         | 6.7     | 2         | 6.7     | 1         |
|              | Rec vomiting     | 1       | 3.3     | 0         | 0       | 0.428     | 0       | 0.549     |
|              |                  |         |         |           |         | 0         |         | 0.195     |
| 3 hr         | No vomiting      | 28      | 93      | 29        | 97      | 30        | 100     | 30        |
|              |                  | 1       | 3.3     | 1         | 3.3     | 0         | 0       | 0         |
|              | Occ vomiting     | 1       | 3.3     | 0         | 0       | 0         | 0       | 0         |
|              | Rec vomiting     | 0       | 0       | 0         | 0       | 1         | 0       | 0.491     |
|              |                  |         |         |           |         | 0         |         | 0.491     |
| 4 hr         | No vomiting      | 29      | 97      | 26        | 87      | 27        | 90      | 28        |
|              |                  | 0       | 0       | 0         | 0       | 1         | 3.3     | 1         |
|              | Occ vomiting     | 0       | 0       | 4         | 13      | 2         | 6.7     | 1         |
|              | Rec vomiting     | 1       | 3.3     | 0         | 0       | 0.112     | 0       | 0.023*    |
|              |                  |         |         |           |         | 0         |         | 0.619     |

Statistically significant difference in the incidence of vomiting was seen with Group C & Group D at ½ and 1 hour intervals & also Group C at 4th hour.
Fig. 1: Vomiting Group A & B 1-4 hrs
Fig. 2: Vomiting Group C & D 1-4 hr
Study Period | Vomiting | Group A | Group B | Group A-B | Group C | Group A-C | Group D | Group A-D | P Value |
|-------------|---------|---------|---------|----------|---------|----------|---------|----------|---------|
| 5 hr | No vomiting | 27 | 90 | 26 | 87 | 29 | 97 | 29 | 97 | 5.961 |
| 5 hr | Retching | 2 | 6.7 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0.003 |
| 5 hr | Occ vomiting | 1 | 3.3 | 3 | 10 | 1 | 3.3 | 1 | 3.3 | 0.003 |
| 5 hr | Rec vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.704 |
| 6 hr | No vomiting | 27 | 90 | 28 | 93 | 28 | 93 | 28 | 93 | 1.331 |
| 6 hr | Retching | 1 | 3.3 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0.003 |
| 6 hr | Occ vomiting | 2 | 6.7 | 1 | 3.3 | 2 | 6.7 | 1 | 3.3 | 0.003 |
| 6 hr | Rec vomiting | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.741 |
| 10 hr | No vomiting | 30 | 100 | 29 | 97 | 28 | 93 | 28 | 93 | 1.331 |
| 10 hr | Retching | 0 | 0 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0.003 |
| 10 hr | Occ vomiting | 0 | 0 | 0 | 0 | 2 | 6.7 | 2 | 6.7 | 0.003 |
| 10 hr | Rec vomiting | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.245 |
| 14 hr | No vomiting | 30 | 100 | 30 | 100 | 30 | 100 | 29 | 97 | 1.331 |
| 14 hr | Retching | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 |
| 14 hr | Occ vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.333 |
| 14 hr | Rec vomiting | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.119 |
| 18 hr | No vomiting | 30 | 100 | 30 | 100 | 30 | 100 | 30 | 100 | 1.331 |
| 18 hr | Retching | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 |
| 18 hr | Occ vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 |
| 18 hr | Rec vomiting | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.119 |
| 24 hr | No vomiting | 30 | 100 | 30 | 100 | 30 | 100 | 30 | 100 | 1.331 |
| 24 hr | Retching | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 |
| 24 hr | Occ vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 |
| 24 hr | Rec vomiting | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.119 |

Table 4: Evaluation based on Vomiting contd..

No statistically significant difference in the incidence of PONV was noted in the four groups at 5 to 24 hours period.
Fig. 3: Vomiting Group A & B 5-24 hrs
Fig. 4: Vomiting Group C & D 5-24 hrs
### Table 5: Evaluation based on sedation

| Study Period | Sedation   | Group A | Group B | Group A-B P value | Group C | Group A-C P Value | Group D | Group A-D P Value |
|--------------|------------|--------|--------|------------------|--------|------------------|--------|------------------|
| ½ hr         | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 11 37 | 15 50 |                  | 15 50  | 15 50            |        |                  |
|              | Drowsy      | 19 63 | 15 50 |                  | 15 50  | 15 50            |        |                  |
|              | Awake       | 0 0   | 0 0   | 0.438            | 0 0    | 0.438           | 0 0    | 0.438            |
| 1 hr         | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 5 17  | 2 6.7 |                  | 0 0    | 0 0              |        |                  |
|              | Drowsy      | 19 63 | 23 77 |                  | 25 83  | 21 70            |        |                  |
|              | Awake       | 6 20  | 5 17  | 0.404            | 5 17   | 0.053+          | 9 30   | 0.059            |
| 1 ½ hr       | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 1 3.3 | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Drowsy      | 11 37 | 15 50 |                  | 11 37  | 10 33            |        |                  |
|              | Awake       | 18 60 | 15 50 | 0.435            | 19 63  | 0.814           | 20 67  | 0.689            |
| 2 hr         | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 1 3.3 | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Drowsy      | 11 37 | 3 10  |                  | 1 3.3  | 0 0              |        |                  |
|              | Awake       | 18 60 | 27 90 | 0.011*           | 29 97  | 0.001*          | 30 100 | 0.001            |
| 3 hr         | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Drowsy      | 3 10  | 1 3.3 |                  | 0 0    | 0 0              |        |                  |
|              | Awake       | 27 90 | 29 97 | 0.611            | 30 100 | 0.237           | 30 100 | 0.237            |
| 4 hr         | Not arousable | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Arousable   | 0 0   | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Drowsy      | 2 6.7 | 0 0   |                  | 0 0    | 0 0              |        |                  |
|              | Awake       | 28 93 | 30 100| 0.491           | 30 100 | 0.491           | 30 100 | 0.431            |

Statistically significant difference in sedation was noted with Group C and D at 1 hour and Group C at 2 hour interval when compared with placebo.
Table 6: Evaluation based on sedation

No difference in sedation was noted with any of the four Groups at 5 to 24 intervals.
### Table 7: Overall Incidence of Vomiting

| Vomiting | Group I       | Group II       | Group III      | Group IV       | P value |
|----------|---------------|---------------|---------------|---------------|---------|
| Absent   | 20 (66.7%)    | 21 (70.0%)    | 24 (80.0%)    | 26 (86.7%)    | 0.265   |
| Present  | 10 (33.3%)    | 9 (30.0%)     | 6 (16.6%)     | 4 (13.3%)     |         |
| Total    | 30            | 30            | 30            | 30            |         |
DISCUSSION: PONV is a distressing symptom, may lead to significant morbidity from dehydration, electrolyte imbalance, tension in suture lines, venous hypertension and a risk of pulmonary aspiration of vomitus. The surgeries associated with greatest incidence of PONV are breast surgery, strabismus surgery, adenotonsillectomy, orchidopexy, herniotomy and laparoscopic surgery. Breast cancer surgery under general anaesthesia has been associated with relatively high incidence of PONV. Between 60-80% of patients who undergo MRM complain of PONV. This high incidence is due to high dose of intraoperative opioids and inhalational agents to gain a deeper plane of anaesthesia during surgery. Etiology of PONV is multifactorial, management ranges from antiemetics to acupuncture and hypnosis.

Even though a battery of powerful antiemetics are available, the use of propofol, an IV anaesthetic agent, for preventing nausea and vomiting is a newer concept evolving since 2 decades. Propofol is considered cost–effective than 5HT3 antagonists. The mechanism of propofol induced antiemesis is quite unclear. The antiemetic properties have been explained by its possible action on the vomiting centre and the CTZ. Propofol has a profile of CNS depression that differs from other anesthetic drugs. In contrast to thiopental, propofol uniformly depresses the CNS including the subcortical centres where most of the antiemetics act. Hence modulation of the subcortical structures could be the possible mechanism of propofol antiemesis. Other postulated mechanisms are antidopaminergic activity, decreased release of glutamate and aspartate from olfactory cortex and reduction of serotonin concentrations in area postrema.

The median plasma concentration of propofol associated with an antiemetic property was found to be 343 ng/ml which can be achieved by propofol infusion of 10-20 microgram/kg/min. Propofol given at the end of surgery as a bolus has been shown to decrease the PONV incidence. Propofol has also been effective for chemotherapy induced nausea and vomiting and for nausea and vomiting refractive to conventional antiemetics.
Various studies have shown that therapeutic plasma which concentrations needed for prevention of PONV is in the range of 197-592\text{ng/ml}\textsuperscript{13} is several times less than the concentration required to achieve anesthesia (2.5-6\text{µg/ml}) and sedation (0.5-1.5\text{µg/ml}).\textsuperscript{14}

In our study we randomly administered intravenously normal saline (Placebo), propofol (0.25mg/kg), propofol (0.5mg/kg), propofol (1mg/kg) to groups of 30 patients in age groups of 35-74 yrs undergoing MRM under general anaesthesia. We found that the incidence of retching and vomiting was 33.33\% in normal saline group as against 30\% of propofol 0.25mg/kg, 16.66\% of propofol 0.5mg/kg and 13.33\% of propofol 1mg/kg. There was a statistically significant decrease in the incidence of nausea and vomiting with doses of 0.5mg/kg and 1mg/kg of propofol at 0-2hrs. We can infer that the therapeutic (Antiemetic) concentrations were achieved and maintained for 2hrs by 0.5 mg/kg and 1 mg/kg of propofol beyond which the dose has decreased to suboptimal levels due to rapid elimination half-life of 1-3 hrs. Dosage of 0.25mg/kg was inadequate to achieve therapeutic plasma concentrations.

A study done by Mitsuko Numazaki and Yoshitaka Fujii have reported the incidence of PONV to be 60\% with Normal Saline,55\% with propofol (0.25mg/kg), 15\% with propofol 0.5mg/kg and 15\% with propofol 0.75 mg/kg in patients undergoing thyroidectomy.\textsuperscript{15} This study is however comparable with our study. The incidence of vomiting in this study is comparable with our study.

Gan Tong J et al in their study have administered propofol (20mg), propofol (40mg) or intralipid (placebo) on demand to adult patients undergoing ambulatory surgeries who received a standardized general anesthetic They found that he incidence of vomiting was 56\% with placebo as against 12\% with propofol 20mg and 23\% with propofol 40mg. This study also is consistent with our study with respect to decrease in the incidence of vomiting following administration of propofol as against placebo. However they have not standardized the weights of patients included in the study and doses are not mg/kg basis.\textsuperscript{16}

Ramanathan et al have administered normal saline or propofol 20mg iv at the end of surgery to women undergoing hysterectomies under subarachnoid block with 4 ml of 0.5\% bupivacaine. They reported a decrease in the incidence of nausea and vomiting with propofol 20mg (25\%) as against normal saline (60\%). Women who were included in this study weighed between 40-50kgs which means the dosage of propofol administered is in the range of 0.4mg/kg to 0.5mg/kg.\textsuperscript{17} This is comparable with our study where the incidence of vomiting with 0.5mg/kg of propofol is 17\%.

Increased sedation was noted only at 1/2 and 1 hour period at a dose of 1mg/kg of propofol which was comparable with Gan Tong J et al’s study who reported 2 incidences of over sedation at a dose of 40mg of propofol. No other side effects were noted in our study or in the above studies mentioned. Hence we can infer that propofol 0.5mg/kg is the effective dose from this study.

**CONCLUSION:** The statistical analysis revealed significant difference in vomiting only during first 2hrs with propofol at doses of 0.5mg/kg and 1mg/kg. The incidence of vomiting was not found to be decreased with 0.25mg/kg of propofol as against placebo. For sedation score statistical significance is found with propofol 0.5mg/kg and 1mg/kg during ½ an hour and 1hour following surgery while in 1-24 hrs there is no significant difference in sedation score. In conclusion this study has shown that propofol decreases the incidence of retching and vomiting with minimal side effects especially in the early postoperative period and 0.5mg/kg is the minimum antiemetic dose to achieve this.
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