

Comparison of Efficacy of Clonidine versus Ondansetron for Prevention of Nausea and Vomiting Post Thyroidectomy: A Double Blind Randomized Controlled Trial

SETTY NAGENDRA GUPTA SHILPA¹, SAMPANGIRAMAIAH SHAILAJA², SELVARAJ SHANTHINI HILDA³

ABSTRACT

Background and Aim: Postoperative nausea vomiting (PONV) is the most common symptom in patients post thyroidectomy. Literature search shows conflicting results regarding use of clonidine in PONV prophylaxis. We undertook this randomized controlled double blind trial to compare the efficacy of clonidine with dexamethasone versus ondansetron with dexamethasone for PONV prophylaxis in these patients.

Materials and Methods: In this prospective study, 60 consecutive patients posted for thyroidectomy from August 2013 to July 2014, were randomly assigned to two groups, ondansetron (N= 30) (Group A) and clonidine (N= 30) (Group B). Patients received either oral ondansetron 8mg or oral clonidine 150µg as premedication. At the end of surgery, both groups received dexamethasone 8mg intravenously. They were monitored for occurrence of PONV and sore throat for next 24 h. Ramsay sedation scores and total time of analgesia was noted. The primary end point was incidence of PONV in post operative for 24 h. Pearson's chi square test and Students

t tests were performed using SPSS for windows version 20 (SPSS Inc., Chicago, IL).

Results: Baseline characteristics of patients were comparable. A higher proportion of patients in clonidine group developed PONV than ondansetron (36.7% vs 30%; p=0.03). Clonidine group patients experienced early nausea and vomiting (1-2hrs of postoperative period), compared to ondansetron group patients (6-12 h). Ramsay sedation scores at arrival were higher in clonidine group compared to ondansetron group (2.1 ± 0.3 versus 2.0; p=0.003). Total time of analgesia was higher with use of clonidine than ondansetron (919.5 ± 622 mins versus 642 ± 631 mins; p=0.09). Moderate sore throat was seen in 2 out of 30 patients in both groups. No major adverse events were observed in either group.

Conclusion: Ondansetron with dexamethasone group was more effective in controlling PONV after thyroidectomy compared to clonidine with dexamethasone group. However, ramsay sedation scores and total time of analgesia were higher with clonidine than ondansetron.

Keywords: Alpha₂ Adrenergic agonist, Postoperative nausea and vomiting, Premedication

INTRODUCTION

Post operative nausea and vomiting (PONV) is one of the most common and distressing symptom after surgery. The estimated incidence of PONV is 40- 60% [1,2]. Thyroidectomy is a high risk surgery with incidence of PONV of 60-84% [3]. The proposed risk factors for PONV in thyroid surgeries are vagal stimulation during surgical manipulation of neck, female gender, prolonged duration of surgery, volatile anaesthetics, nitrous oxide, large dose of neostigmine and opioids [3,4]. PONV following thyroid surgeries can exacerbate bleeding causing neck hematoma and potential airway obstruction and re-exploration of surgical site. Hence, there is need to prevent PONV.

Multimodal therapy is always better than monotherapy as the aetiology of PONV is multifactorial. Multimodal therapy than monotherapy is the recommendation for prevention of PONV in high risk patients. Various drug combinations have been tried and found to be effective [5-7].

Ondansetron a 5HT₃ antagonist, is well established for prophylaxis of PONV as oral and intravenous preparation [1,7-9]. Clonidine an α₂ adrenergic agonist is extensively used as premedication. It is a sedative, suppresses cardiovascular response to laryngoscopy, reduces anaesthetic requirement and used for induced hypotension during anaesthesia, however there are few reports of oral clonidine usage for PONV [10,11]. Dexamethasone has been combined with other drugs when used for prophylaxis of PONV [9].

We hypothesized that use of two drugs having different mechanisms of action would lead to reduction in incidence of PONV. Hence, we performed this randomized double blind controlled study to evaluate the efficacy and safety of combination of oral clonidine with

intravenous dexamethasone versus oral ondansetron with intravenous dexamethasone for prevention of PONV after thyroidectomy.

MATERIALS AND METHODS

After obtaining clearance from institutional ethical committee the trial was registered with Clinical Trial registry of India no CTRI/2014/01/004345. Written informed consent obtained from 60 patients posted for thyroidectomy between August 2013 to July 2014 of ASA I and ASA II aged between 18-60 y of either sex were included in study. Patients on adrenoreceptor agonists or antagonists, known hypersensitivity to anaesthetics, uncontrolled diabetes mellitus, pregnancy, ASA 3 and above, on perioperative anti emetics, steroids, antihistamine or psychiatric drugs and refusal to participate in the study were excluded.

Based on the previous study the incidence of PONV is 40%, we were interested in decreasing the incidence of PONV, with intervention. Taking power of 80% and significance level of 5%, a sample size of 30 per group was decided. A pre-anaesthetic check was done in all patients with a detailed history and routine lab investigations. The type of surgery planned and thyroid profile were noted. Patients were kept nil per oral overnight. Diazepam 5mg and ranitidine 150mg were given as premedication in the night before surgery to all patients in the protocol. We have followed CONSORT guidelines of RCT. Randomization of the patients were done in the pre-operative period after meeting all the inclusion and exclusion criteria. The block randomization was done with block size of 10. An independent statistician using computer generated random number table did sequence generation. Allocation concealment was done using sequentially numbered opaque sealed envelopes. Consent

obtained by one of the three authors and assigning the patients to either of the treatment groups as per the randomization sequence and administration of the drugs was done by an independent anaesthesiologist not involved in the study. The study investigators and the patients were blinded to the study treatment through identical vials and tablets coded as A & B in the two groups respectively. Patients assigned to Group A (N= 30) were premedicated with Tab ondansetron 8mg orally and those to Group B (N= 30) received tab clonidine 150µg orally one hour before surgery.

Standard anaesthesia technique was followed using thiopentone sodium 5 mg/kg, fentanyl 2µg/kg, and intubated after administration of succinylcholine 1.5mg/kg. They were maintained intraoperatively with isoflurane 0.6-1.5% and 66% nitrous oxide in oxygen. Neuromuscular relaxation was achieved with vecuronium. All patients received Inj dexamethasone 8mg IV before closure of muscle layer and patient reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg. Duration of surgery was noted.

For the study PONV- defined as an episode of nausea, retching (involuntary attempt to vomit without expulsion of stomach contents), and vomiting (actual expulsion of stomach contents) was noted. As clonidine is known for its sedative action and used as premedication in this study, Ramsay sedation score (modified) was noted at arrival and in the postoperative period. Its sedative effect was helpful as premedication in patients with anxiety. Sedation score (modified Ramsay) was noted at on arrival to operation theatre and in the postoperative period [Table/Fig-1].

STATISTICAL ANALYSIS

Descriptive statistics were expressed as Mean±SD or number (%). Numerical variables were compared between groups by students t-test. Categorical variables were compared by Pearson's chi-square test. All statistical tests were performed using SPSS for Windows version 20 (SPSS Inc., Chicago, IL). All analysis was two tailed. A p-value <0.05 implies statistical significance.

RESULTS

After careful assessment, a total of 60 patients fulfilling the inclusion and exclusion criteria were prospectively enrolled from August 2013 to July 2014 and were randomized; 30 patients were assigned to the ondansetron group and 30 patients to clonidine group. The two study groups were well-matched with respect to demographic characteristics, clinical and laboratory data [Table/Fig-2].

In the total of 60 patients, 33.3% (20/60) developed PONV. Out of these, 30% (9/30) were in ondansetron group and 36.7% (11/30) in clonidine group. The need for rescue antiemetic was also statistically significant between the groups (p=0.03). Patients in clonidine group had PONV within one hour after surgery and ondansetron group had PONV in between 6-12 hrs after surgery [Table/Fig-3]. The modified Ramsay sedation scores were significantly higher on arrival in clonidine group as compared to ondansetron group (2.1 ± 0.3 versus 2.0; p=0.003). However, no significant difference was seen in the sedation scores between two groups in post-operative period (2.9 ± 0.3 versus 2.9 ± 0.4; p=0.15) respectively. Moderate sore throat was seen equally in both groups, that is 2 out of 30 patients in each group.

TIME OF ANALGESIA

The time for use of rescue analgesic in post operative period was more prolonged in clonidine group as compared to ondansetron group (919.5 ± 622 min versus 642 ± 631 min) but it was not statistically significant (p=0.09). Heart rate and blood pressure increased during laryngoscopy and tracheal intubation in both the groups and the changes were comparable between them. Side effects like bradycardia is seen in clonidine group (2/0) and headache is seen in ondansetron group (2/0) [Table/Fig-2]. Bradycardia responded to injection atropine and patients with headache were treated with injection diclofenac 75mg IM.

Score	Clinical condition
1	Awake and anxious, agitated, or restless
2	Awake, cooperative, accepting ventilation, oriented, tranquil
3	Awake; responds only to commands
4	Asleep; brisk response to light glabellar tap or loud noise
5	Asleep; sluggish response to light glabellar tap or loud noise stimulus but does not respond to painful stimulus
6	Asleep; no response to light glabellar tap or loud noise

[Table/Fig-1]: Ramsay sedation score

Parameter	Group A (n- 30) Mean ± SD Ondansetron	Group B (n- 30) Mean ± SD Clonidine	p-value
Age (in y)	43.5 ± 11.3	39.5 ± 9.9	0.41
Female/male gender	27/3	27 /3	1.0
Weight (in kg)	56.7 ± 8.3	55.8 ± 7.7	0.36
Thyroid function tests			
T ₃ (µg/dl)	1.3 ± 0.3	1.1 ± 0.3	0.2
T ₄ (µg/dl)	7.3 ± 2.4	6.2 ± 2.5	0.9
TSH(µU/ml)	1.4 ± 1.1	1.8 ± 2.2	0.31
Duration of surgery (in min)	151 ± 42.9	143.5 ± 57.5	0.66
Heart rate (beats/minute)	75. 57 ± 11.5	75.3 ± 9.69	0.16
Systolic blood pressure (mm of Hg)	125.8 ± 13.49	129.4 ± 13.85	0.57
Diastolic blood pressure (mm of Hg)	80.5 ± 7.51	83.2 ± 7.42	0.98

[Table/Fig-2]: Demographic data and baseline characteristics in the two groups
Expressed in mean ± SD (Group A- Ondansetron, Group B-Clonidine)

Parameter		Group A (N- 30) Mean±SD Ondansetron	Group B (N- 30) Mean±SD Clonidine	p-value
PONV	Immediate	1.83 ± 0.37	1.8 ± 0.4	0.513
	1 h	1.93 ± 0.25	1.77 ± 0.43	0.0*
	3 h	1.96 ± 0.18	1.93 ± 0.25	0.242
	6 h	1.93 ± 0.25	2.0	0.03**
	12 h	1.96 ± 0.18	2.0	0.043
Modified Ramsay sedation scores	Arrival	2	2.1 ± 0.3	0.003
	Postop	2.9 ± 0.4	2.9 ± 0.3	0.15
Sore throat	Mild	1	1	1
	Moderate	27	27	1
	Severe	2	2	1
Rescue analgesia (in mins)		642 ± 631	919.5 ± 622	0.9
Rescue antiemetic		1.76 ± 0.4	1.63 ± 0.5	0.03
Headache		0	2	0.492***
Bradycardia requiring atropine		2	0	0.492***

[Table/Fig-3]: Clinical observations during study process between two groups
*clonidine group patients had maximum nausea and vomiting in the 1st postoperative hour compared to ondansetron group, statistically significant.
**ondansetron group had PONV more compared to clonidine after 6hrs of surgery, statistically significant.
***Headache was more in ondansetron and Bradycardia was more in clonidine group. Which are statistically significant

DISCUSSION

Postoperative nausea and vomiting is a distressing side effect in thyroidectomy patients. If not effectively prevented, it can lead to higher post operative morbidity and prolonged hospitalization resulting in increased health care cost. PONV is the second cause for readmission after day-care surgery [2].

Multifactorial aetiology of PONV is better addressed by multimodal approach. Enhanced recovery after surgery (ERAS) society and meta-analysis trials recommends ondansetron and dexamethasone combination is ideal for prophylaxis of PONV in moderate to high risk patients [12]. The present study showed that 30% in ondansetron group and 36.7% in clonidine group experienced PONV, which was

comparable to Eun Jim Kim study in which PONV reduced from 80% to 33% [13].

Dexamethasone is a glucocorticoid known for its antiemetic activity in chemotherapy patients. It is both centrally and peripherally acting. In central nervous system, it regulates neurotransmitter levels, receptor densities and neurone configuration in nuclei which are known to have significant effect on nausea and vomiting [14,15]. In thyroid patients, oedema and inflammation around the neck tissues may sustain evoked parasympathetic impulses through vagus, recurrent laryngeal and glossopharyngeal nerve to the vomiting centre. Dexamethasone reduce tissue inflammation and reduce the ascending parasympathetic impulses to the vomiting centre [16]. Wide range of single dose is used (8-32mg), most commonly 8mg, but optimal dose is yet to be defined. Jaleel F, Basanth Bhattarai and Ming Shan Chen in their studies have shown that dexamethasone have shown good prophylactic effect for PONV when given one hour prior to surgery or beginning of surgery [17-19]. Three randomized controlled studies on timing of dexamethasone have demonstrated that no significant statistical difference between timing of giving in beginning or end of surgery [16,17,20]. Hence, we administered dexamethasone at the end of surgery.

Ondansetron is a 5HT₃ antagonist. According to the Society for Ambulatory Anaesthesia [12], 16mg ondansetron is suggested one hour before the surgery as a prophylaxis for PONV and it also suggests that repeat dose is essential after 6 h after the first dose. The results in our study support this evidence, as majority of patients in ondansetron group had PONV 6-12 h after the surgery.

Clonidine is an alpha 2 agonist known for its utility in induced hypotensive anaesthesia. In some studies it has shown antiemetic effect when used as premedication [10,11,21]. Clonidine is known for other beneficial effects in anaesthesia with low cost of drug which has onset of action 0.5-1 h and longer duration of action of upto 12h [22]. Moreover, it has been reported to reduce shivering and PONV when administered systemically and epidurally [23]. Oddby-Muhrbeck et al., [21] showed that clonidine reduced PONV from 73.33% in placebo group to 40%, which is comparable to our study. Tehari A [10], in his study, on patients posted for ear surgery found that clonidine reduced PONV from 66.6% to 33% which is also comparable to our study. Important side effects of clonidine are bradycardia and hypotension. In our study, only 2 out of 30 patients needed atropine for bradycardia.

LIMITATIONS

The possible limitations in the study were, it was a single centre study including a small group of patients and monitored only for 24h. The outcome of the study was quite gratifying as the results strongly indicate that probably this protocol based treatment can modulate the post operative course in a proportion of patients post thyroidectomy. This is probably the first randomized controlled double blind trial which compared oral clonidine with dexamethasone versus oral ondansetron with dexamethasone. We did not include a placebo group due to ethical reasons.

CONCLUSION

Oral clonidine with intravenous dexamethasone was less effective than oral ondansetron with intravenous dexamethasone in counteracting PONV following thyroidectomy surgery. Clonidine group experienced early PONV while ondansetron group had late onset of PONV. However, combination of oral ondansetron with dexamethasone or oral clonidine with dexamethasone reduced the overall incidence of PONV in thyroidectomy patients. Ramsay sedation scores were high in clonidine group on arrival to operation theatre however no difference in scores between two groups in postoperative period. Time of first analgesic in clonidine group is more compared to ondansetron group. None of the patients in either group experienced sorethroat while some patients in ondansetron had headache and in clonidine group 2 patients needed atropine for bradycardia.

REFERENCES

- [1] Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. *Anesthesiology*. 1997;87(6):1277-89.
- [2] Watcha MF, White PF. Postoperative nausea and vomiting. Its aetiology, treatment, and prevention. *Anesthesiology*. 1992;77(1):162-84.
- [3] James M. Sonner, MD, James M. Hynson, MD, Katz JA. Nausea and vomiting following thyroid and parathyroid surgery. *Journal of Clinical Anesthesia*. 1997;9(5):398-402.
- [4] Gan Tong J. Risk Factors For Postoperative nausea and vomiting. *Anaesthesia and Analgesia*. 2006;102(6):1884-98.
- [5] Scuderi PE, James RL, Harris L, Mims GR III. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. *Anesth Analg*. 2000;91(6):1408-14.
- [6] Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med*. 1995;332:1-5.
- [7] Lopez-Olaondo LL, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of post-operative nausea and vomiting. *Br J Anaesth*. 1996;76(6):835.
- [8] Scuderi P, Wetchler B, Sung YF, Mingus M, DuPen S, Claybon L, et al. Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT₃ antagonist ondansetron. *Anesthesiology*. 1993;78(1):15-20.
- [9] Lesser J, Lip H. Prevention of nausea and vomiting using ondansetron, a new, selective, 5HT₃ receptor antagonist. *Anesth Analg*. 1997;72(6):751-55.
- [10] Taheri A, Javadimanesh MA, Ashraf H. The effect of oral clonidine premedication on nausea and vomiting after ear surgery. *MEJ Anesth*. 2010;20(5):691-94.
- [11] Gulhas N, Turkoz A, Durmus M, Tugal T, Gedik E, Ersoy Mo. Oral clonidine premedication does not reduce postoperative vomiting in children undergoing strabismus surgery. *Acta Anaesthesiol Scand*. 2003;47(1):90-93.
- [12] Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, et al. Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting. *International Anesthesia Research Society*. 2007;105(6):1615-28.
- [13] Kim EJ, Ko JS, Choi DH. Combinations of Antiemetics for the Prevention of PONV in high risk patients. *J Korean Med Sci*. 2007;22(5):878-82.
- [14] Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neurosci Res*. 1996; 26(3): 235-69.
- [15] Funder JW. Mineral corticoid receptors and glucocorticoid receptors. *Clin Endocrinol*. 1996;45(6):651-56.
- [16] Feo CV, Sortini D, Ragazzi R, Pe Perma M, Liboni A. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg*. 2006;93(3):295-99.
- [17] Farhat J, Riflat J, Mohammad IA. Efficacy and timing of single dose Dexamethasone as prophylactic Antiemetic in major surgeries. *Journal of Surgery Pakistan*. 2009;14(2):48-52.
- [18] Battarai B, Shrestha S, Singh J. Comparison of ondansetron and combination of ondansetron and dexamethasone as a prophylaxis for postoperative nausea and vomiting in adults undergoing elective laparoscopic surgery. *J Emerg Trauma Shock*. 2011;4(2):168-72.
- [19] Chen M, Hong C, Chung H, Peter PC Tan, Tsai C, Han-Hsiang Su, et al. Dexamethasone Effectively Reduces Postoperative Nausea and Vomiting in A General Surgical Adult Patient Population. *Chang Gung Med J*. 2006;29(2):175-80.
- [20] Ho ST, Wang JJ, Tzeng JI, Leu HS, Ger LP. Dexamethasone prophylaxis of nausea and vomiting associated with epidural morphine: A dose regimen Study. *Anesth Analg*. 1999;89(1):117-20.
- [21] Oddby-Muhrbeck E, Eksborg S, Bergendahl HT, Muhrbeck O, Lonngvist PA. Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. *Anesthesiol*. 2002;96(5):1109-14.
- [22] Mikawa K, Nishina K, Maekawa N, Obara H. Oral Clonidine Premedication Reduces Postoperative Pain in Children. *Anesth Analg*. 1996;82(2):225-30.
- [23] Johr M. Clonidine in Pediatric anaesthesia. *Eur J Anaesthesiology*. 2011;28(5): 325-26.

PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Resident, Department of Anaesthesiology, Father Muller Medical College, Mangalore, India.
2. Assistant Professor, Department of Anaesthesiology, Father Muller Medical College, Mangalore, India.
3. Senior Resident, Department of Anaesthesiology, Father Muller Medical College, Mangalore, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Shailaja S,
Assistant Professor, Department of Anaesthesiology, Father Muller Medical College, Mangalore-575002, India.
E-mail: drshaila@rediffmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: Jan 05, 2015
Date of Peer Review: Feb 17, 2015
Date of Acceptance: Mar 19, 2015
Date of Publishing: May 01, 2015