COMPARATIVE EVALUATION OF QTc INTERVAL CHANGES WITH INTRAVENOUS ONDANSETRON AND PALONOSETRON IN PATIENTS UNDERGOING LAPROSCOPIC CHOLECYSTECTOMY

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ABSTRACT: Post-operative nausea and vomiting (PONV) is a common and distressing symptom after surgery performed under general anesthesia. 5HT₃ antagonists are routinely used for PONV but are dreaded to cause QTc interval prolongation. The aim of our study was to compare the incidence of QTc interval prolongation and quantify the amount of QTc prolongation from the baseline value with IV ondansetron and Palonosetron when given for PONV prevention. 60 patients undergoing elective laproscopic surgery for cholelithiasis were randomly divided into 2 groups of 30 patients each and received 4mg of Ondansetron and 0.075mg of Palonosetron intravenously respectively before induction of anesthesia. Intraoperatively serial ECG was recorded at various intervals 0min, 3min, 15min, 1hr and 2hrs along with other routine monitoring and QTc was calculated in secs by Bazett Formula. **RESULTS:** The QTc interval was prolonged in Ondansetron group at all-time intervals as compared to Palonosetron group where prolongation was observed only at 3 min though this difference was statistically insignificant ($P>0.05$). The difference between Ondansetron and Palonosetron group was comparable.

KEYWORDS: PONV, QTc, Ondansetron, Palonosetron.

INTRODUCTION: Post-operative nausea and vomiting (PONV) is most common and distressing concern after surgery performed under general anaesthesia effecting as many as one third of such patients. It is one of the main complaints after laparoscopy (40-75% of patients)^[1] and the most important factor determining the length of hospital stay after ambulatory anaesthesia thereby increasing hospital cost per patient.^[2]

Overall incidence of PONV has been reported to be between 20% and 30% but can increase upto 80% in patients who are at high risk for PONV.^[3]

PONV is defined as nausea, retching and vomiting occurring during first 24-48hrs after surgery, the three symptoms may occur separately or in combination.^[4]

The causes of PONV are multifactorial and can largely be categorized as patient risk factors, anaesthetic technique, and surgical procedure.

Antiemetics work on several different receptor sites^[5] to prevent or treat PONV. Traditional antiemetics like Anticholinergics (Scopolamine, Atropine) Antihistaminics (Dimenhydranates), Phenothiazines (Promethazine), Butyrophenones (Droperidol, Haloperidol) and Benzamides (Metoclopramide) are used for control of PONV. Some of these are associated with high incidence of adverse effects such as restlessness, dryness of mouth, sedation, hypotension, extrapyramidal symptoms and dystonic effects.

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5HT₃R antagonists, ondansetron and palonosetron, are routinely used for PONV because of their safety and efficacy but these drugs are known to produce multiple effects on ECG particularly on QTc (corrected QT) interval.^[6] Prophylactic palonosetron 0.075mg i/v is considered to be more effective than ondansetron 8mg i/v for prevention of PONV.^[7]

Drug induced prolongation of QTc interval has become the first cause of withdrawal or restricted use of the drug in the past years because of potential risk of life threatening polymorphic ventricular tachycardia and torsades de pointes.^[8]

AIM AND OBJECTIVES: To compare the incidence of QTc prolongation from the baseline and to quantify the amount of QTc prolongation with intravenous Ondansetron and Palonosetron

MATERIAL AND METHODS:

- The study was conducted in Dept. of Anaesthesiology and ICU, GMC Jammu.
- After obtaining approval from institutional ethics committee and informed written consent from the patients, 60 female patients in the age group 25-55 yrs, ASA grade-I or II having average built who were to undergo laproscopic cholecystectomy were enrolled.

Exclusion Criteria: The following criteria were used for excluding patients from the present study;

- Baseline prolonged QTc interval.
- Patients with arrhythmias or conduction defects.
- Patients with electrolyte imbalances.
- Congenital QTc syndrome.

Technique:

- History, examination and relevant investigations were carried out.
- Preanaesthetic preparation was done and patient was kept fasting for 8hrs.
- I/V line with ringer lactate was started in OT and monitors were attached for minimal basic monitoring
- After obtaining baseline ECG, study medication was given 3 min before induction:
 - GROUP O:** Patients received Inj. Ondansetron 4mg I/V and,
 - GROUP P:** Patients received Inj. Palonosetron 0.075mg I/V and simultaneously patients were pre oxygenated.
- Induction with Injection Propofol 2mg/kg i/v, Injection Tramadol 1mg/kg i/v and Injection Atracurium Besylate 0.5mg/kg i/v to facilitate tracheal intubation.
- Maintenance of general anaesthesia was done with O₂+N₂O (40:60) and top-up doses of injection Atracurium Besylate 0.1mg/kg.
- Intraoperative monitoring was done by monitoring HR, SBP, DBP, MAP, ETCO₂ and SPO₂.
- After obtaining baseline ECG, continuous ECG was observed for any changes and recording of lead-II was done with Life-Pak 20- defibrillator monitor at 0min, 3min, 15 min, 1hr and 2hr interval.
- QTc was calculated by using Bazett formula.

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$$QT_{cB} = \frac{QT}{\sqrt{RR}}$$

- QTc is said to be prolonged when value exceeds 470 ms in female but we measured prolongation from the baseline (0 min).
- Residual effect of muscle relaxant was reversed with Injection Glycopyrrolate 10mcg/kg and Injection Neostigmine 50mcg/kg.

STATISTICAL ANALYSIS: Statistical analysis of the data was done using student t-test and P-value using SPSS-16 software. A p value <0.05 was taken to be significant.

OBSERVATIONS:

Group (n-30)	Age in Years Mean $\pm$ S.D.	Weight Mean $\pm$ S.D.	Duration of Surgery Mean $\pm$ S.D.
Group O	36 $\pm$ 10.77 (25-55 Years)	57 $\pm$ 4.6 (49 - 67 Kg)	67 $\pm$ 13 (40 - 90 Min)
Group P	38 $\pm$ 10 (23-55 Years)	56 $\pm$ 5.6 (39 - 65 Kg)	68 $\pm$ 15 (45 - 90 Min)
P-Value	0.704 NOTHING SIGNIFICANT	0.470 NOTHING SIGNIFICANT	0.743 NOTHING SIGNIFICANT

Table 1: Showing the Mean Age in years, Weight in kg and Duration of surgery

Graphical representation of mean Age in years

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Graphical representation of mean Weight in kgs

Graphical representation of mean Duration of surgery

Time Interval	% of QTc interval (No. of patients)				P value
	Group O		Group P		
	No	Yes	No	Yes	
0 min	96	4	100	0	0.082 NS
3 mins	92	8	96	4	0.060 NS
15 mins	90	10	100	0	0.126 NS
1 hr	94	6	100	0	0.168 NS
2 hr	96	4	100	0	0.599 NS

Table 2: Showing Incidence of QTc prolongation

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TIME	GROUP O Mean±SD(sec)	GROUP P Mean±SD(sec)	P-VALUE
0 Min	0.403 ± 0.041	0.401 ± 0.036	.901 NS
3Min	0.406 ± 0.044	0.404 ± 0.027	.607 NS
15 Min	0.406 ± 0.044	0.399± 0.032	.08 NS
1Hour	0.401± 0.036	0.400 ± 0.032	.129 NS
2 Hour	0.402 ±0.066	0.400 ± 0.032	.600 NS

Table 3: Showing the Mean QTc interval changes at 0min, 3min, 15 min, 1hr and 2hr.

Graphical representation of QTc interval changes

DISCUSSION: The present study was conducted on 60 patients divided into 2 groups of 30 patients each, Group O (ondansetron group) and Group P (palonosetron group).

Results show that no statistically significant difference was observed between two groups with respect to age, weight and duration of surgery.

We observed a prolongation of QTc interval from the baseline more so in Group O patients where the incidence varied from 4% to 10% with the maximum incidence seen at 15mins (10%). On the contrary in Group P the incidence of patients showing prolongation from baseline was 0% at all-time intervals except at 3 mins where 4% showed a prolongation from baseline, but this difference was statistically insignificant ($p > 0.05$).

In our study we found that QTc interval was prolonged at all-time intervals in ondansetron group. A prolongation of QTc in patients receiving Inj Ondansetron was also observed by Charbit et al^[9] in their comparative study between Inj. Droperidol and Inj Ondansetron. Gupta S D et al^[10] observed that 1 mg i/v ondansetron effectively prevented PONV without causing prolongation of QTc interval whereas significant QTc prolongation was noted with 4mg and 8mg ondansetron given in

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healthy adult participants. Hafermann M J et al^[11] concluded that i/v ondansetron in doses approved by FDA can significantly prolong QTc interval leading to torsades de pointes in high risk cardiac patients. Lee et al^[12] in 2014 reported that prolongation of QTc interval with Inj. Palonosetron might occur. We also observed the prolongation with palonosetron at 3 min interval though could not prove it statistically. The reason for this could be that they included patients who were concomitantly taking other drugs too, which we did not include in our study (as is cited in their article). Kim HJ et al^[13] showed that preanaesthetic administration of palonosetron (0.075mg) did not affect the QTc interval during intraoperative period.

In our study we found that QTc interval prolongation from the baseline levels were comparable in both groups and at all intervals and in no patient QTc interval was more than 470 ms. Navari R M et al^[14] in their study reported that ECG interval changes are a class effect of 5-hydroxytryptamine 3 receptor antagonists. Theoretical concern regarding cardiovascular adverse events with these agents is not supported by clinical experience. The significant benefits of these agents outweigh the theoretical small risk of meaningful cardiovascular event.

CONCLUSION: We concluded that both i.v Ondansetron and Palonosetron might induce the prolongation of corrected QT interval but the incidence was found to be more in patients who received Ondansetron. As in no patient QTc prolongation was found to be more than 470ms with these agents, the minimal risk of ECG interval changes can be ignored over the significant benefits of these in preventing PONV.

In high risk patients with cardiac disease, Palonosetron might be a safer agent. Further research work needs to be done in evaluating the efficacy in patients with already prolonged QTc interval and to consider all of the factors related to QTc prolongation, albeit caution has to be taken while using this drug in patients at high cardiac risk group and in all those medical situations which predispose to arrhythmias.

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