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A Comparative Study of Suppression of Post Operative nausea and vomiting in Elective Cesarean section under Spinal Anaesthesia using Granisetron, Granisetron+Dexamethasone and Granisetron + Dexamethasone+ Glycopyrrolate

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Abstract: *This Study was done to compare efficacy and safety after antiemetic prophylaxis with Granisetron alone (Group I), Granisetron + Dexamethasone (Group II) and Granisetron+ Dexamethasone + Glycopyrrolate (Group III) in suppressing PONV in elective caesarian sections under spinal anaesthesia. The aim was to search for a better drug or combination of drugs for suppression of post operative nausea and vomiting (PONV), to compare haemodynamic* changes*, to observe side effects if any. Patients were allocated randomly into three different groups. Patients belonging to group I received- Inj.Granisetron 3mgIV, Group II received-Inj.Granisetron3mg+Dexamethasone4mgandgroup III received- Inj.Granisetron 3mg+Dexamethasone 4mg +Glycopyrrolate 0.2mg IV. Blood pressure, PR, SPO2 measurements were recorded upto 24 hours. Intra operative and postoperative nausea, retching and emetic episodes were recorded.* A*ddition of Dexamethasone (4 mg) to Granisetron 3mg has shown better response in reducing nausea and vomiting. In Granisetron group significant fall in blood pressure was observed. Fluctuations in pulse rate were persistent for one hour in Granisetron + Dexamethasone + Glycopyrrolate group. Hence, it may be safer to use Granisetron + Dexamethasone combination perioperatively in view of its efficacy, safety, no haemodynamic alterations and no effect on fetal Apgar scores*

Key words: *Dexamethasone, Granisetron, Glycopyrrolate, Nausea, Spinal, Vomiting*

I. Introduction

Despite the rapid progress in the field of modern anaesthesia, the incidence of postoperative nausea and vomiting (PONV) still remains 25-30%[1] and it may be a major factor upsetting postoperative convalescence. . Spinal anaesthesia has been shown to be an easy, rapid and safe technique for Caesarean section. Nevertheless, it has some minor side effects, including nausea and vomiting in more than 60% of the cases.[24] Availability of a large number of agents which prevent emises and continued research for newer drugs to treat emesis indicates the magnitude of the problem and lack of satisfactory results4.This study was done to find an effective regimen to prevent PONV and to compare the antiemetic efficacy and safety after single, double, triple antiemetic prophylaxis with Granisetron alone (Group I), Granisetron + Dexamethasone (Group II) and Granisetron+ Dexamethasone + Glycopyrrolate (Group III) in suppressing PONV in elective caesarian sections under spinal anaesthesia

II. Aims And Objectives

T he aim of present study is to find an effective regimen to prevent PONV.
Objectives

1. To search for better drug or combination of drugs for suppression of post operative nausea and vomiting (PONV)
2. To compare efficacy of various drugs used
3. To compare haemodynamic changes
4. To observe side effects if any.

III. Material & methods

This study has prior approval from institutional Ethical and Review board committee and written informed consent. 90 women of ASA grade I and II aged between 19-35 yrs with body weight ranging from 45-70kgs at term undergoing elective cesarean section were enrolled for the study during the period between December'2012 to September '2013 at Government General Hospital, MCH Block, Siddhartha Medical College, Vijayawada.

Patients were allocated randomly in equal number (n=30 in each group) into three different groups. Patients belonging to group I received Inj.Granisetron 3mgIV, Group II received Inj.Granisetron 3 mg+

Dexamethasone 4mg IV and group III received Inj. Granisetron 3mg+Dexamethasone 4mg +Glycopyrrolate 0.2mg IV. In all the cases the drugs were administered slowly 10 minutes prior to administration of spinal anesthesia.

III.1 Inclusion Criteria:

- ASA Grade I & II
- Patients aged 19-35yrs.

III.2 Exclusion Criteria:

- ASA Grade III & IV
- Previous history of nausea and vomiting
- H/o. antiemetic treatment during previous 24 Hrs.
- H/o. Motion sickness
- H/o. any drug allergy
- Presence of any systemic disease like PIH, Diabetes mellitus, allergies to local anesthetics
- Patients age below 18 yrs.and above 35 years.
- Patients who required prostadin during surgery were also eliminated from the study group.

Vital signs like pulse rate, and blood pressure were recorded for every patient. Investigations noted are Urine for albumin, sugar, blood for HB%, urea, sugar, creatinine and blood grouping.

III.3 Procedure: All the patients were under Nil per oral 6 hours prior to surgery; Routine antiemetic prophylaxis with Inj.Rantac and Inj.Perinorm was not given for these patients. A randomization list was generated and identical syringes containing each drug were prepared by personnel blinded to the study according to the list. Patients were randomly allocated to one of the three treatment regimens as mentioned above.

After IV cannulation the study drugs were injected slowly through the intravenous route. Each patient is preloaded with 10ml/kg of lactated ringer solution before administration of spinal anesthesia to prevent hypotension. All patients received oxygen via face mask at flow of 4 lts/minute since the induction of spinal anesthesia.

Women were positioned in left lateral decubitus position and a 25 gauze Quincke spinal needle was introduced through the midline approach at the L3-L4 interspace. Patients were given 1.8ml of 0.5%hyper baric Bupivacaine subarachnoid injection and turned to supine position. Aortocaval compression was avoided by placing a wedge with 15^0 tilt beneath the right buttock for left uterine displacement. The level of analgesia was assessed by pinprick. Blood pressure, PR, SPO2 measurements were recorded before starting spinal anaesthesia and every 5 minutes till the end of surgery and every half an hour up to 24 hours. Readings at 2 hours, 4 hours, 6 hours and 24 hours are taken for comparison. Inj. Oxytocin 10 units were given as IV infusion after the delivery of baby to facilitate uterine retraction.

Hypotension was defined as decrease in systolic blood pressure by 20% from the base line and treated with rapid fluid infusion, administration of Mephenterine was 3mg aliquots if necessary. Duration of operation was noted. Post operative analgesia was achieved by Inj Diclofenac sodium 75mg IM.

Intra operative and postoperative nausea, retching and emetic episodes were recorded. Retching and /or vomiting were taken as positive responses for vomiting. Each patient remained in the recovery room for 2 hours and was observed for the 24 hours in the post operative ward for occurrence of nausea and vomiting.

III.4 Parameters recorded: **Preoperatively** – Pulse rate, SPO2, Blood pressure, previous H/o.PONV, previous H/o. motion sickness, H/o. APD and H/o. Drug Allergy.

Intraoperatively – Pulse rate, blood pressure, SPO2, incidence of nausea, retching and vomiting and APGAR score of the baby.

Postoperatively – Pulse rate, Blood pressure, SPO2,incidence of nausea retching and vomiting.

Presence of headache, drowsiness, flushing, allergic reactions or any other side effects.

The above parameters were assessed by the same observer before and during surgery and up to 24 hours after operation, without the knowledge of which drug the patient has received. Nausea was assessed by asking a patient if they felt nauseated or sick. Both vomiting and retching were considered emetic events. Rescue anti emetics were allowed at the request of patient or after 15 minutes, if nausea is protracted or if there are two emetic episodes.

III.5 interpretation of symptoms (knapp and beecher, 1956)

Nausea: the feeling is best described by the patients as subjectively unpleasant sensation associated with awareness of the urge to vomit, without indulging in expulsive movements.

Retching: defined as labored, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents.
Vomiting: defined as forceful expulsion of gastric contents from the mouth.

III. 6 interpretation of nausea and vomiting score:
A complete response is defined as no emesis and no need for another rescue antiemetic.

Grade 0	-	No nausea
Grade 1	-	nausea
Grade 2	-	nausea + retching
Grade3	-	Single episode of vomiting
Grade 4	-	more than one episode of vomiting

III. Statistical analysis:

Statistical analysis of the data between the treatment groups were performed by using percentages, proportions Chisquare test and Anova test. A 'p' value of <0.05 was considered significant.

All values are expressed as mean ±SD, mean(ranges) or number (%).

IV. Observations & results

There were no significant differences between the three groups regarding patient characteristics (Age, Body Weight, Height and Previous H/o. of Motion sickness and PONV) type of surgery, type of anaesthesia, and duration of pre operative starvation, duration of surgery and administration of post operative analgesics. Patient data were analyzed by Chi-Square test, Anova test and standard error or difference between proportions. P value of 0.05 or less was considered significant.

Table I: duration of surgery

Duration of Surgery (Minutes)	Group I		Group II		Group III		Total	
	No.	%	No.	%	No.	%	No.	%
40-59	16	53.33%	15	50.00%	14	46.67%	45	50.00%
60-79	14	46.67%	15	50.00%	14	46.67%	43	47.78%
80-99	0	0.00%	0	0.00%	2	6.67%	2	2.22%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Mean +/- SD	**55 +/- 6.16**		**55.33 +/- 7.18**		**57.33 +/- 10.96**			
ANOVA F-Statastic	**0.683**							
P Value	**0.507**							
Inference	**Not Significant**							

Inference: Duration of anaesthesia and surgery in the three groups were compared there is no significant statistical difference.

Table 2: incidence of nausea

Nausea	Group I		Group II		Group III		Total	
	No.	%	No.	%	No.	%	No.	%
Intra Operative								
Absent	22	73.33%	27	90.00%	27	90.00%	76	84.44%
Present	8	26.67%	3	10.00%	3	10.00%	14	15.56%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Chi-Squre Value = 2.72 at 'df' = 2 and P-value >0.05 Not Significant								
Post Operative (0-2hrs)								
Absent	29	96.67%	30	100.00%	30	100.00%	89	98.89%
Present	1	3.37%	0	0.00%	0	0.00%	1	1.11%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Post Operative (2-24hrs)								
Absent	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Present	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%

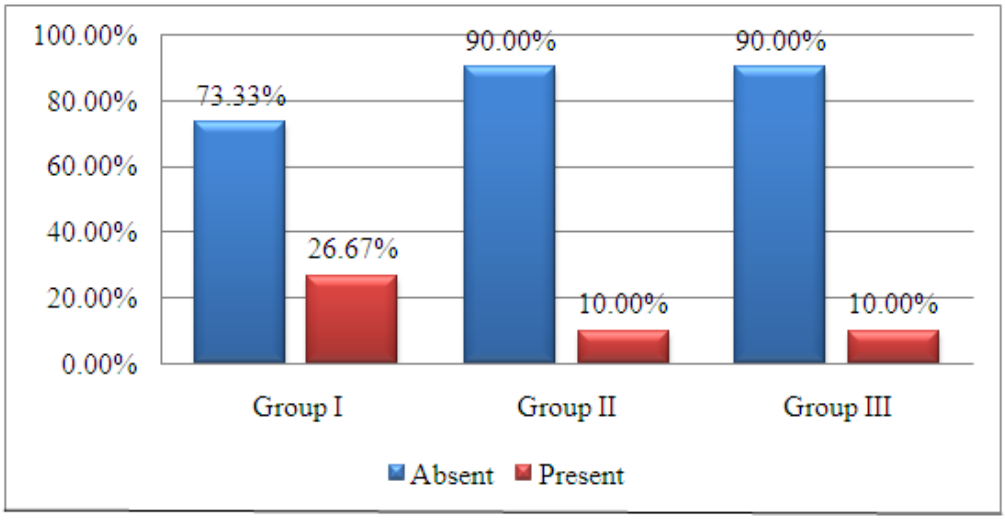

Fig I: Incidence of nausea

Inference: Intra opertively incidence of nausea is lower in Group II & Group III when compared Group I. Post operatively 0-2 hours very minimal nausea was seen(3.3%) in Group I.Post operative 2-24 hours no incidence of nausea in all three groups. The differences are not statistically significant.

Table 3: incidence of vomiting

Vomiting	Group I		Group II		Group III		Total	
	No.	%	No.	%	No.	%	No.	%
Intra Operative								
Absent	29	96.67%	30	100.00%	28	93.33%	87	96.67%
Present	1	3.33%	0	0.00%	2	6.67%	3	3.33%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Post Operative (0-2hrs)								
Absent	30	100.00%	30	100.00%	29	96.67%	89	98.89%
Present	0	0.00%	0	0.00%	1	3.33%	1	1.11%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Post Operative (2-24hrs)								
Absent	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Present	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Total	1	100.00%	0	0.00%	2	100.00%	3	100.00%

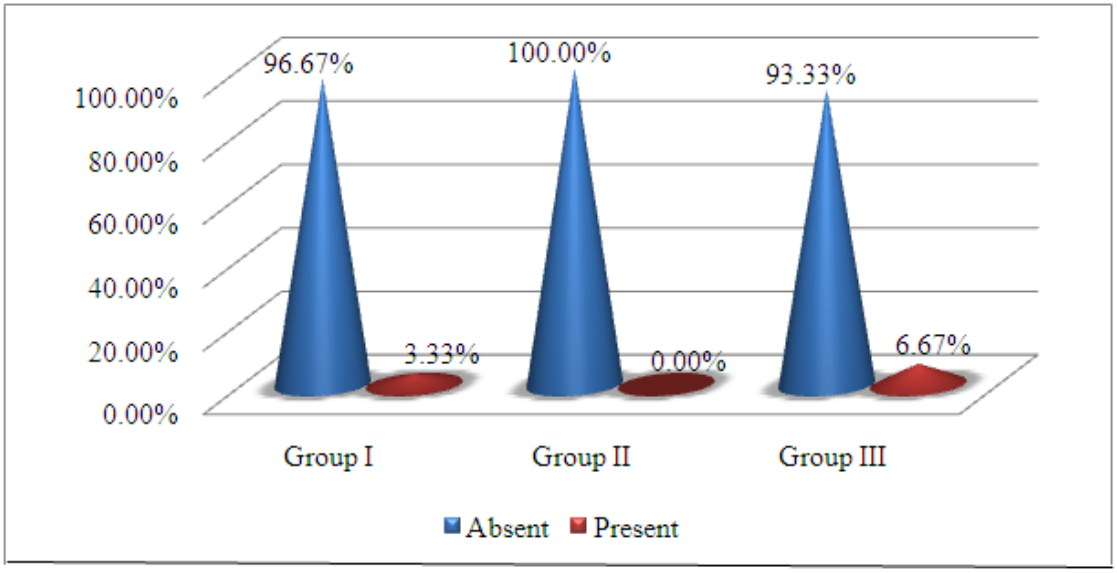

Fig 2: Incidence of vomiting

Inference: Intraoperatively incidence of vomiting is 0.0% in Group II compared to 3.3% in Group I, and 6.67% in Group III. Post operatively 0-2 hours incidence of vomiting is slightly more 3.3% in Group III compared to 0.0% in Group I & II.Post op. 2-24 hours no incidence of vomiting in all the three groups. The differences are not statistically significant.

Table 4: apgar score

APGAR Score	Group I Granisetron	Group II Grani + Dexa	Group III Grani+Dexa+Glyco	't' value	'p'value
At 1 Min	7.88±1.03	7.76±0.88	7.48±0.86	0.1222	P>0.005
At 5 Min	9.76±0.64	9.84±0.46	9.79±0.58	0.1392	p>0.05

Inference: Apgar scores are more or less similar in all the three groups.

Table -5: adverse effects

Rescue	Group I	Group II	Group III	Total
Antiemetic given	0	0	0	0
Adverse Effects				
Head Ache	1	2	1	4
Drowsiness	0	2	2	4
Allergic Reaction	0	0	0	0
Others if any	0	0	0	0

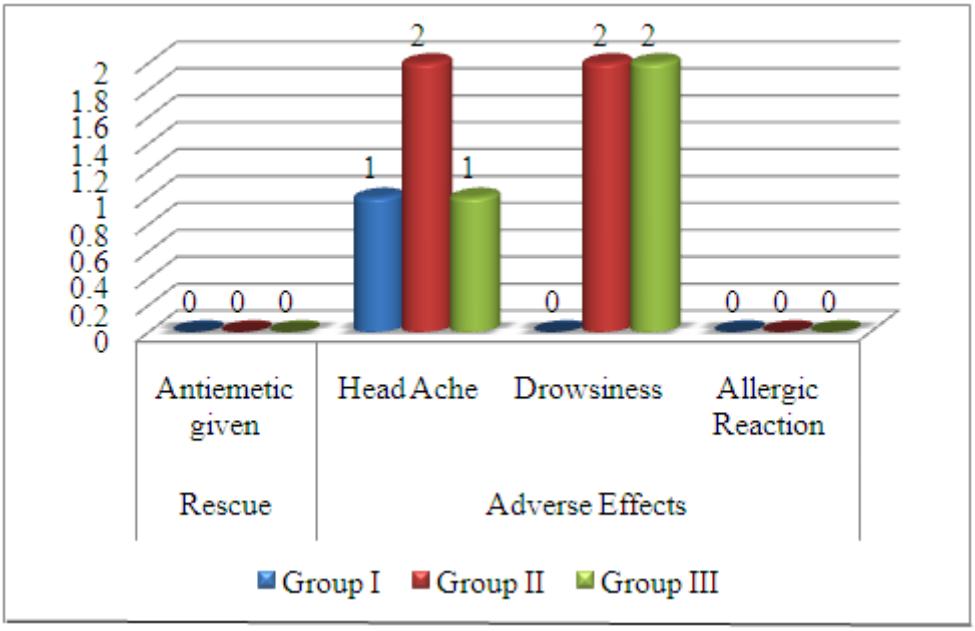

Fig 3 Adverse effects

Inference: No rescue antiemetic medications is required to any patient either intra op. or up to 24 hours post op. statistically no significant difference in incidence of adverse effects.

Haemodynamic observations

Table -6: mean arterial pressure

Mean Arterial Pressure	Group I		Group II		Group III		ANOVA F-Statistic	P-Value	Inference
	Mean	SD	Mean	SD	Mean	SD			
BEF	86.30	11.47	84.80	12.42	86.43	8.28	0.21	0.81	NS
IMM. AFT	80.60	16.40	87.50	15.89	84.13	11.58	1.63	0.20	NS
5 Mts	74.20	14.11	75.47	13.97	83.50	11.07	4.43	0.01	S
10 Mts	77.53	11.29	79.07	14.49	78.53	14.13	0.10	0.90	NS
15 Mts	78.50	11.17	81.93	10.37	84.17	13.44	1.78	0.18	NS
30 Mts	76.93	11.18	78.37	10.36	81.77	12.61	1.42	0.25	NS
45 Mts	80.40	9.68	80.03	11.14	81.67	11.14	0.19	0.82	NS
60 Mts	81.40	8.60	82.60	9.40	83.40	10.22	0.34	0.71	NS
1-2hrs	80.37	8.58	82.30	10.09	85.17	9.75	1.94	0.15	NS
4hrs	79.87	9.68	80.70	8.74	84.57	8.94	2.26	0.11	NS
6hrs	79.73	9.38	80.60	7.39	83.97	9.97	1.86	0.16	NS
24hrs	79.50	9.14	80.57	7.41	82.93	9.75	1.19	0.31	NS

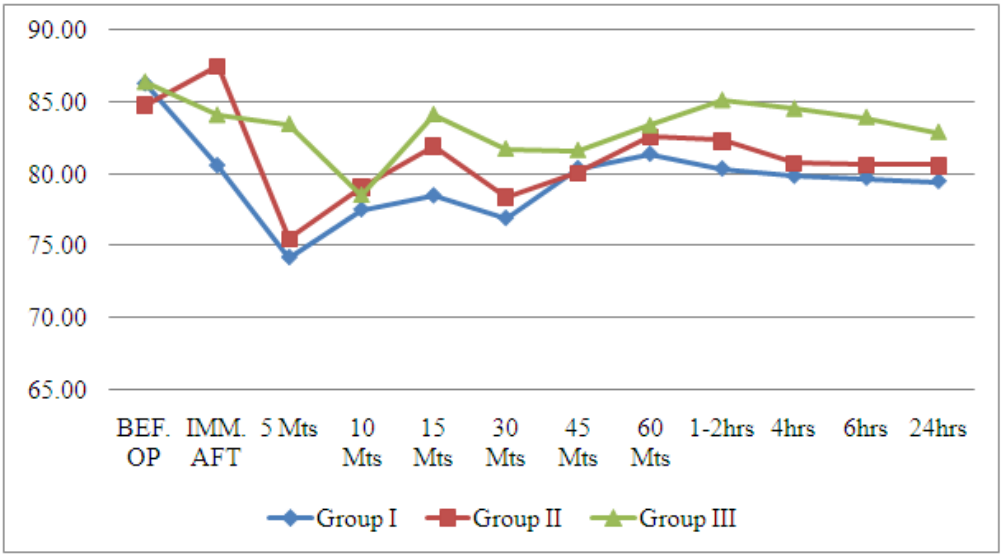

Fig 4.Mean arterial pressure at different times

Inference: the mean arterial pressure in perio op.period was calculated in each group at specified intervals of time and compared. Statistically significant fall was found in MAP of group I and Group II compared to Group III in early 5 minutes, however with 3mg Mephenterine IV Group II patients recovered quickly compared to Group I.

Table -7: pulse rate

Pulse Rate	Group I		Group Ii		Group Iii		Anova F-Statistic	P-Value	Inference
	Mean	Sd	Mean	Sd	Mean	Sd			
BEF	96.03	12.31	96.07	18.27	100.17	28.92	0.385	0.682	NS
IMM. AFT	95.17	17.54	97.57	22.09	111.30	18.90	5.916	0.004	S
5 MTS	93.90	15.51	97.03	24.57	105.37	24.02	2.224	0.114	NS
10 MTS	94.33	15.42	97.67	21.73	99.90	30.83	0.425	0.655	NS
15 MTS	93.93	21.76	99.67	19.47	105.03	23.00	2.007	0.141	NS
30 MTS	97.93	16.73	97.63	13.61	107.37	15.80	3.857	0.025	S
45 MTS	94.17	14.75	97.23	12.32	103.37	19.80	2.594	0.081	NS
60 MTS	92.33	12.30	94.00	12.21	100.70	17.87	2.849	0.063	NS
1-2HRS	90.00	7.61	90.80	8.80	97.13	16.96	3.251	0.043	S
4HRS	90.00	7.04	89.37	7.69	91.13	25.83	0.093	0.911	NS
6HRS	87.33	7.90	85.37	6.30	92.73	14.94	4.026	0.021	S
24HRS	84.37	5.42	83.83	5.79	87.97	13.16	1.928	0.152	NS

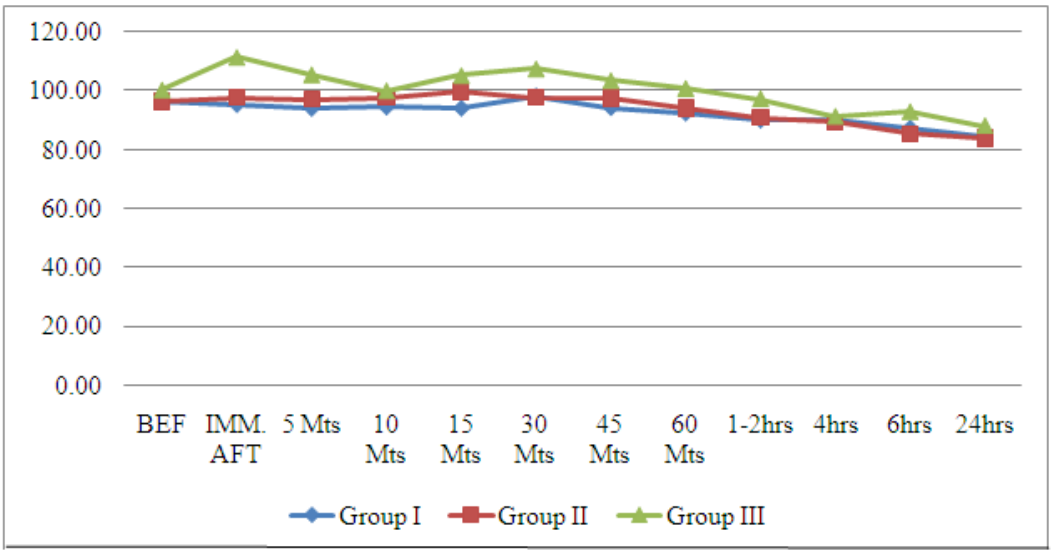

Fig 5: Mean pulse rate

Inference: the mean pulse rate in peri op.period was calculated in each group at specified intervals of time and compared .statistically significant and sustained increase pulse rate seen in Group III may be due to increase in HR effect of Glycopyrrolate.

V. Discussion

The incidence of emetic symptoms is high during pregnancy because of increased levels of progesterone. Progesterone decreases gastrointestinal motility and reduces lower oesophageal pressure. These physiological changes along with anatomical changes may predispose the pregnant women to develop emetic tendency.

The etiology of PONV is multifactorial and includes factors both related to anaesthesia and unrelated to anaesthesia. The later include age, gender, weight. Operative factors include type and duration of surgery, surgical skill, peritoneal retraction, fundal pressure during difficult delivery which along with anaesthetic management further contributes to increased incidence of PONV in women undergoing caesarean delivery under spinal anesthesia.

The incidence of post operative emetic symptoms after caesarean delivery is more under spinal anaesthesia that is about 60% when no antiemetic prophylaxis is provided. (**Chest nut DH 1987**)[1], (**Lussos-SA, Bader AM et al 1992**)[9]

A variety of pharmacological approaches including Butyrophenones eg. Droperidol, Dopamine receptor antagonists eg., Metoclopromide have been reported to be effective in preventing these emetic symptoms. **(Santos A, Datta S 1984)[4] (Lussos- SA, Bader AM et al 1992)[72]** However these drugs may produce undesirable adverse effects such as drowsiness, restlessness, distonic reactions and extrapyramidal signs. **(Watcha MF, White PF1992)[2]**.Recent awareness in patient care has led to continuous search for an effective and safe antiemetic drug The role of new selective 5HT3 antagonists Ondensetron and Granisetron have been proved to be effective when used prophylactically to reduce the incidence of intra and post operative nausea and vomiting. **(Pan P Moore CH1996)[10]**. Granisetron is more potent and longer lasting than Ondensetron. **(Andrews PLR, Bhandari P, et al 1992)[11]** and its efficacy is superior to other commonly used and well established antiemetics like Droperidol, Metoclopramide for preventing post operative nausea and vomiting in patients undergoing caesarian section. **(Fuzi Y , Tanaka H et al 1998)[5]**. However Granisetron alone cannot entirely control emetic symptoms in this population.

Dexamethasone, a glucocorticoid decreases chemotherapy induced emesis when added to antiemetic regimen. **(Smith DB, Newlands ES et al 1991[12], Lancet et al 1991[13])** It also acts as a potentially useful agent in prophylaxis of postoperative nausea and vomiting especially when combined with 5 HT3 antagonists like Granisetron. **(Kocamanoglu IS, Baris S, Karakaya et al 2005)[15], (Habib E et al 2004.[7] (Fujii Y, Saitoh Y et al 1999)[6] (Eberhart LH J and Morin et al2000).[16]** Glycopyrrolate, an anticholinergic drug has also been reported to successfully minimize the incidence of nausea and vomiting in combination with other antiemetic drugs like metoclopromide during spinal anaesthesia for caesearian section without affecting neonatal outcome**. (Ali Melkikilia T , Kaila T et al 1990)[3]. (Dinesh Thakur, Mihir Goswami and Himanshu Shah et al 2011)[8]**. Mechanism of action of Glycopyrrolate may be due to heart rate mediated increase in cardiac output and subsequent reduction in hypotension episodes. **(Ure D James KS, Mc Neil M, Booth JV et al 1999).** As per consensus guidelines for managing PONV study **Tong S and Gan MD et al 2003** use of monotherapy is for patient at moderate risk for PONV. Double and triple antiemetic combinations are recommended for patients at higher risk for PONV. Updated Guidelines for managing PONV were announced at 2006 Annual meeting of American Society of Anaesthesiologist. Evaluating Medical Literature they recommended use of antiemetics with emphasis on 5HT3 receptor antagonists and potential benefit of combination prophylaxis. They recommended "Prophylactic Therapy with combination of three or more interventions for patients at high risk for PONV".

Also as per Guidelines for management of PONV by Society for Ambulatory Anaesthesia (SAMBA) 2007,adults at moderate risk of PONV should receive combination therapy with one or more prophylactic drugs from different classes. Combination therapy has superior efficacy compared with monotherapy for PONV prophylaxis. The purpose of the present study is to compare the combined effect of antiemetic drugs Granisetron + Dexamethasone + Glycopyrrolate with single antiemetic (Granisetron) and combination of two antiemetic drugs (Granisetron + Dexomethasone) for prevention of nausea and vomiting in women undergoing caesarian section.

In our study incidence of nausea was found more in Granisetron alone group, 8 of 30 patients (26.67%) compared to 3 of 30 (10%) in Granisetron+ Dexamethasone group and 3 of 30(10%) in Granisetron + Dexamethasone +Glycopyrrolate. The incidence of vomiting was also more in Granisetron alone (GroupI) 1 of 30 (3.33%) compared to 0.00% in Granisetron + Dexamethsaone (GroupII). Complete response (defined as no emetic symptoms and no need for another rescue antiemetic medication) in intraoperative and post delivery period was 73% in Granisetron group (Group I) compared to 90% in Granisetron + Dexamethasone(Group II)

and Granisetron+ Dexamethasone + Glycopyrrolate(Group III). Corresponding values during first 24 hours after surgery was 96.6% in Granisetron group compared to 100% in Granisetron + Dexamethasone and Granisetron + Dexamethasone + Glycopyrrolate. The difference is clinically significant though not statistically. **Yoshitaka Fuji, Yuhji Saitoh et al 1999[17] , Fujii Y, Tanakha H, Toyooka H et al[19] (1998)** studied the effects of Granisetron alone and Granisetron + Dexamethasone combination on post operative nausea and vomiting in women undergoing caesarean section under spinal anaesthesia. In the intraoperative period a complete response was seen in 83% in Granisetrron group and 98% in those of Granisetron + Dexamethasone group. The corresponding rates during the first 24 hours after surgery were 85% and 98%. Thus, they found that Granisetron + Dexamethasone combination was superior to Granisetron alone. Our findings are clinically similar to their studies.

Even though Glycopyrrolate group patients (Group III) maintained better mean arterial pressure and raised pulse rate than the other two groups the incidence of vomiting is slightly high 2 of 30(6.67%) in this group compared to 0.00% in Granisetron + Dexamethasone group. A complete response was attained in 96.6% in Granisetron group compared to 100% in Granisetron + Dexamethasone group and 93.3% in Granisetron + Dexamethasone + Glycopyrrolate group

APGAR scores were more or less similar in all three groups in our study as shown in Table -7. These findings are similar to those of **B.N.Biswas, SK Das et al 2003[64] and Ure D, James KS , Mc Neik M , Booth JV[14](1999).**

In our study adverse effects were noted and compared. We have found that incidence of mild headache is noted in Granisetron + Dexamethasonegroup i.e., 2 of 30 compared to 1 of 30 in Granisetron+ Dexamethasone+ Glycopyrrolate group and Granisetron alone group. Drowsiness is noted in both Granisetron + Dexamethasone and Granisetron+ Dexamethasone + Glycopyrrolate group. This is not statistically significant

There was no need for rescue antiemetic in all three groups, as there was no repeated incidence of vomiting or persistent nausea (more than 15 minutes) in any of the patients in all the three groups.

VI. Conclusion & summary

In our study addition of Dexamethasone (4 mg) to Granisetron 3mg has shown better response in reducing nausea and vomiting.

In Granisetron group significant fall in blood pressure was observed which reverted to normal with treatment. Fluctuations in pulse rate were persistent for one hour in Granisetron + Dexamethasone + Glycopyrrolate group.

Hence, it may be safer to use Granisetron + Dexamethasone combination perioperatively in view of its efficacy, safety, no haemodynamic alterations and no effect on fetal Apgar scores.

Addition of Glycopyrrolate to Granisetron + Dexamethasone is not found to be advantageous in our study but further studies with larger sample size may be more conclusive.

No significant difference in adverse events is observed.

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