Research Paper

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Haloperidol Versus Granisetron for Prophylaxis of Post-Operative Nausea and Vomiting. - A Double Blind Prospective Randomised Study

Medical Science

KEYWORDS : Antiemetic Prophylaxis, Haloperidol, Granisetron

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ABSTRACT

Background: Haloperidol a Butyrophenone with a high affinity for Dopamine D2 receptors has a strong antiemetic property.

Materials and methods: 90 ASA I-II patients aged 18-65yrs scheduled for elective laparoscopic surgeries were randomized into three groups. Group H received Haloperidol1mg, Group G received Granisetron 1mg .Group C received no antiemetics. Anaesthesia was standardized. Recovery time, sedation level, pain score, nausea score, episodes of vomiting, rescue antiemetics,ECG and other side effects were evaluated.

Results: There was no significant difference in nausea and vomiting between haloperidol group and granisetron group. Sedation score was significantly more in haloperidol compared to granisetron but recovery was not statically significant. 6 cases (20%) in granisetron group had headache, which is statistically significant. Conclusion: Haloperidol provides antiemetic protection during the peak incidence of post-operative nausea and vomiting (PONV).Antiemetic doses of haloperidol is safe.

1. INTRODUCTION:

Post-operative nausea and vomiting are portrayed as the most common debilitating complication of anaesthesia and surgery[1]. The development of effective antiemetic prophylaxis is one of the most significant steps forward in the area of supportive care. In December 2001, FDA issued a "black box" warning to droperidol because of its adverse cardiovascular event (torsades de pointes)2.Haloperidol is another Butyrophenone with strong antiemetic property.Its method and site of action are similar to Droperidol[3]. Several studies suggested the efficacy of haloperidol for prophylaxis or treatment of PONV [4-8].We hypothesized that Haloperidol can be used as an alternative to Droperidol in preventing PONV and designed a prospective ,randomized, double blind trial to compare the prophylactic antiemetic efficacy of Haloperidol group vs Granisetron group vs control group in patients undergoing laparoscopic surgeries. Our other objective was to determine the safety profile of Haloperidol.

2. MATERIALS AND METHODS:

After ethics committee approval and written informed consent 90 ASA 1-II patients undergoing elective laparoscopic surgeries were enrolled into the study. Patients with Diabetes, Hypertension, cardiovascular, respiratory problems, patients on medications that effect HR or BP, pregnancy, lactating mothers, patients who consumed antiemetics 24 hrs prior to commencing study were excluded. Routine anaesthetic technique was used using propofol, fentanyl, vecuronium, nitrous oxide-oxygen and isoflurane. Standard monitoring with electro cardiography (EKG), pulse oximetry (SpO_2) and non-invasive BP monitoring was done. About 15 minutes before the estimated time of end of surgery, study drug was injected, group H got Haloperidol 1mg,group G got Granisetron 1mg and group C received nothing. Study drug was given 15mins before the end of surgery to achieve peak plasma concentrations[9, 10]. A complete response to the prophylaxis of antiemetic therapy defined as no nausea or emesis and no need for rescue antiemetic during the 24 hrs observation period post-operatively. All patients who had vomiting were given 10mg of Inj. Metoclopramide as rescue antiemetic. Evaluation was done at0-2hrs, 2-24hrs, 0-24hrs. Following observations were made.

2.1. Recovery time ;(in mins)

Time from discontinuation of anaesthesia until opening of eyes.

2.2. Sedation level;

By Modified Observer's Assessment of Alertness/Sedation scale (OAA);

Responsiveness	Score
A. Agitated	6
B. Response readily to name spoken in a normal time	5
C. Lethargic response to name spoken in a normal time	4
D. Response only after name is called loudly and repeatedly	3
E. Response only after mild prodding/ shaking	2
F. Does not respond to mild prodding / shaking	1
G. Does not respond to test stimulus	0

2.3. Pain Score;

By 10 cm Visual Ana log Scale (VAS)
0 cm----- No Pain
10 cm----- Worst Pain

2.4. Nausea Score;

The intensity of each nausea episode was graded as;

Mild---Discomfort noticed but no disruption of anticipated normal activity

Moderate---Discomfort sufficient enough to affect anticipated normal activity.

Severe----Inability to perform normal activity.

2.5. Episodes of vomiting;

A vomiting episode was defined as vomiting events occurring in rapid sequence within a one-minute period. If the interval between two bouts of emesis exceeded one minute, they were considered separate episode.

-- 0

--1 to 2

-- >3

2.6. Rescue Antiemetic—Inj.Metoclopramide 10 mg was given if Patient vomits.

2.7. E C G:

Lead- II for QT INTERVAL will be measured 10 minutes after administration of study drug.

2.8. Side Effects:

Headache

Constipation

Dizziness

Extrapyramidal symptoms.

The parameters were recorded and data was entered into Statistical Package for Social Sciences (SPSS 15.0). Statistical analysis was done using Chi-square tests, ANOVA and post hoc tests.

3. RESULTS:

90 Patients in the three groups were comparable for age, weight, and male: female ratio, ASA physical status, amount of anaesthetic used, duration of surgery, recovery time as shown in Table 1.

Table 1.Patient demographics and clinical data(mean±SD,n)				
	Group H	Group G	Group C	P value
Age(yrs)	40±11.603	41.37 ±12.347	39.60 ±11.661	0.833
Sex(M:F)	11:19	11:19	14:16	0.659
Weight(kgs)	59.67±9.697	60.07 ±8.350	59.57 ±7.691	0.972
Duration of surgery	117.80 ±43.255	138.07 ±62.113	120.40 ±23.745	0.182
Recovery time(mins)	10.77±2.254	10.53 ±3.569	11.63 ±1.771	0.242
P>0.05 not significant-Haloperidol, G –Granisetron, C-Control.				

Between 0-2hrs, the number patients having mild nausea were 4 in haloperidol group, 5 in granisetron group and 6 in control group. The incidence of moderate nausea was, none in haloperidol group, 2 in granisetron group and 5 in control group. This was statistically not significant (P value 0.140).Similarly incidence of nausea was not statistically significant between 2-24hrs and 0-24hrs.

Table 2:Incidence of nausea									
	0-2hrs			2-24hrs			0-24hrs		
	Gp H	Gp G	GpC	Gp H	Gp G	GpC	Gp H	Gp G	Gp C
None	26	23	19	30	28	26	26	23	19
Mild	4	5	6	0	2	4	4	5	6
Moderate	0	2	5	0	0	0	0	2	5
P .140 not significant.									

In haloperidol group 5 subjects, 3 subjects in granisetron group and 13 subjects in control had one episode of vomiting during 0-2hrs.Between 2-24hrs, 1subject each from haloperidol and granisetron group and 3 from control group had one more episode of vomiting. Totally from 0-24hrs, 4subjects in haloperidol group,2 in granisetron, 10 in control group had one episode of vomiting and 1 each from haloperidol and granisetron,3 from control group had further one more episode of vomiting. The incidence of vomiting between 0-2hrs and 0-24 hrs is highly significant in control group. Accordingly rescue antiemetics used in the control group was significant.

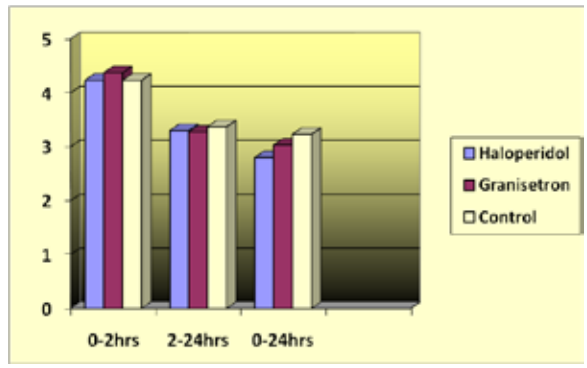
Table 3: Incidence of vomiting.									
	0-2hrs			2-24hrs			0-24hrs		
	Gp H	Gp G	Gp C	Gp H	Gp G	Gp C	Gp H	Gp G	Gp C
None	25	27	17	29	29	27	25	27	17
1st episode	5	3	13	1	1	3	4	2	10
2nd episode	0	0	0	0	0	0	1	1	3
P .005during 0-2hrs and 0.03 during 0-24hrs which are significant.									

The sedation data showed that sedation score was significantly more in haloperidol group compared to granisetron (P 0.033).

Table 4:Sedation score		
	Number	Mean±SD
Haloperidol	30	4.70±.466
Granisetron	30	4.93±.254
Control	30	4.90±.305
P .033 significant in haloperidol compared to granisetron		

When pain score analysed using post hoc tests, we found higher pain scores in the control group when compared to haloperidol and granisetron with P value of 0.007.

Figure1: Pain score



Most adverse events noted was headache.6 subjects in granisetron and 1 subject in control group complained of headache. This 20% incidence of headache in granisetron was statistically significant compared to haloperidol. (P 0.008).

Table 5:Incidence of Headache			
Headache	Haloperidol	Granisetron	Control
Yes	0	6	1
No	30	24	29
P .008 significant in granisetron compared to haloperidol			

4. DISCUSSION:

HALOPERIDOL causes blockade of dopaminergic D_2 receptors of chemoreceptor trigger zone in the area postrema of brain. Haloperidol is antiemetic at doses that are considerably lower than those used for the treatment of psychosis or the control of agitation. Most PONV antiemetic dose range from 0.5mg -2.0mg[10]. With these very low doses, the degree of antiemetic efficacy of haloperidol is markedly strong and comparable with many other antiemetic interventions that are used for the prevention and treatment of PONV[11]. With such low doses extrapyramidal symptoms are rare, there is no marked sedation, and cardiac arrhythmias have not been reported.

GRANISETRON is a $5HT_3$ receptor antagonist used as an antiemetic to treat PONV.Its main effect is to reduce the activity of vagus nerve on medulla oblongata. It does not have dopaminergic or muscarinic effects. Headache, dizziness and constipation are the most commonly reported side effects[12].

In our study, factors like age, gender, weight, duration of procedure, anaesthetic technique, and medications were not significantly different among the three study groups. During the study period 0-24hrs there was no statistically significant difference in the incidence of nausea between the groups. During 0-2hrs of study significant subjects in control group had vomiting, according rescue medicines were used. Whereas later on that is 2-24hrs there was no significance in the incidence of vomiting. This indicates that haloperidol and granisetron provides protection during the peak incidence of vomiting. When we analysed the pain score using Post Hoc Tests, it showed statistically significant pain scores in the control group P 0.007 than in the haloperidol or granisetron group.The higher pain scores in the control group may explain the increase incidence of vomiting in this group.The sedation data showed that sedation was significantly more in haloperidol group than in the granisetron. Mean score in haloperidol group was 4.7 which was between response readily to name spoken in a normal time and lethargic response to name spoken in a normal time. It did not alter the recovery time from anaesthesia and the patients were safer to

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be shifted to post-operative unit.

QTc prolongation and Torsades de pointes mostly occurs in psychiatric patients receiving >35mg in 24hr period13. In our study, none of the patients had QT interval prolongation. However we recommend avoiding Haloperidol in patients with electrolyte disturbance (hypokalemia, hypomagnesemia), congestive cardiac failure, dysrhythmias, acute coronary syndromes and patients taking monoamine oxidase inhibitors or tricyclic antidepressants.

Considering side effect profiles of granisetron and haloperidol we mainly noted headache about 6 cases (20%) in granisetron group , which is statistically significant14. Incidence of dizziness was not significantly different among the 3 groups. None of the patients had constipation or extrapyramidal side effects.

5.CONLUSION:

Haloperidol and Granisetron have similar safety and efficacy for PONV prophylaxis in patients undergoing laparoscopic surgeries. Haloperidol when given immediately before emergence from anaesthesia provides antiemetic protection during the peak incidence of PONV with minimal toxicity. Halopeidol which is an old and inexpensive drug may prove to be an interesting and cost effective antiemetics especially in healthcare systems with scarce resouces.

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