Research Paper

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Central Venous Catheter-Related Infections. A Prospective and Non Randomised Study.

Medical Science

KEYWORDS : Central Venous Catheters, Infections, Intensive Care Unit.

Dr. Suhas Ramaswamy	Assistant Professor, Department of Anaesthesia,Kasturba Medical College, Mangalore.
Dr. Reshmy Padmanabhan	Resident, Department of Anaesthesia,Kasturba Medical College, Mangalore.
Dr. Madhusudan Upadya	Professor, Department of Anaesthesia,Kasturba Medical College, Mangalore.

ABSTRACT

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

Materials and methods: Ninty 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 at 3post operative time periods.

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.No patient in any group had QTc prolongation or extra pyramidal side effects.

Conclusion: Haloperidol provides antiemetic protection during the peak incidence of 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 1970 FDA approved Droperidol for use as an antiemetic. However 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 Droperidol3.In doses 1-4mg haloperidol prevented or treated nausea and vomiting due to chemotherapy,irradiation and gastrointestinal disorders [4,5].The antiemetic effect of haloperidol was the topic of a metanalysis.Several studies suggested the efficacy of haloperidol for prophylaxis or treatment of PONV 6-11. 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 objectives was to determine the safety profile of Haloperidol in terms of adverse cardiovascular events and to look for any side-effects caused by either haloperidol or granisetron.

2.MATERIALS AND METHODS:

After ethics committee approval and written informed consent 90 ASA 1-II patients undergoing elective lapascopic 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 commemcing study were excluded. Routine anesthetic technique was used using propofol, fentanyl, vecuronium, nitrous oxide-oxygen and isoflurane. Standard monitoring with electrokardiography (EKG), pulse oximetry (SpO 2) and noninvasive BP monitoring was done. About 15 minutes before the estimated time of end of surgery, study drug was injected, group H got haloperiodol 1mg,group G got granisetron 1mg and group C received nothing. Study drug was given15mins before the end of surgery to achieve peak plasma concentrations[12,13]. 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. Metochloperamide as rescue antiemetic.Evaluaton 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 Analog 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.Metochloperamide 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. P value <0.05 was considered as statistically significant.

3.RESULTS:
90 Patients in the three groups were comparable for age, weight, 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,H-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 were,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.

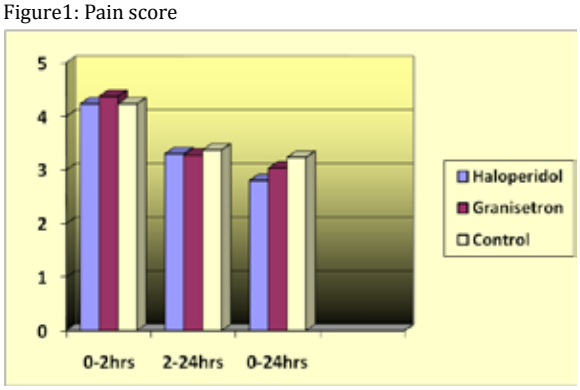
Table 3:Incidence of vomiting.									
	0-2hrs			2-24hrs			0-24hrs		
	Gp H	Gp G	Gp C	Gp H	Gp G	Gp C	Gp H	Gp G	Gp C
None	25	27	17	29	29	27	25	27	17
1st episode	5	3	13	1	1	3	4	2	10
2nd episode	0	0	0	0	0	0	1	1	3
P .005during 0-2hrs and 0.03 during 0-24hrs which are significant.									

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:
PONV is one of the main complaints in patients undergoing laparoscopic surgeries under General Anaesthesia. It is one of the most important factors that determine the length of the hospital stay after ambulatory anaesthesia14. Infact its contribution to patient dissatisfaction is such that over 70% of patients considered avoidance of PONV to be very important15. Numerous factors can affect PONV, such as age, gender, obesity, motion sickness, h/o PONV, duration of surgery, anaesthetic technique, use of opioids and pain16.

BUTYROPHENONES are powerful antiemetics. Haloperidol, a butyrophenone with a high affinity for dopamineD_2 receptors, has been available since 1958 and received US FDA approval as an antipsychotic drug in 1967. It has been used not only in psychiatry but also in medical and surgical patients for the control of severe agitation. Haloperidol has been widely used as an antiemetic for more than 40 ysr10.

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. The available evidence from published and unpublished randomized trials suggests that it may not even be worthwhile to increase the dose above 1 or 2 mg to prevent PONV15.Most PONV antiemetic dose range from 0.5mg -2.0mg [17,18]. 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[19,20]. With such low doses extrapyramidal symptoms are rare, there is no marked sedation, and cardiac arrhythmias have not been reported, QT prolongation is dose dependent[21]. When given immediately before emergence from anaesthesia Haloperidol provides antiemetic protection during the peak incidence

of PONV. Haloperidol is an inexpensive drug compared with the new 5-hydroxy tryptamine3 antagonists.

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 doesnot have dopaminergic or muscarinic effects.Headache,dizziness and constipation are the most commonly reported side effects[22].

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 be shifted to post-operative unit.

A concern regarding haloperidol is its potential to cause sedation, extrapyramidal symptoms,hypotension and serious electrocardiographic changes.Hypotesion is less likely with haloperidol as it has a decreased alpha blocking action[10]. Sedation is a rare adverse event and many clinicians consider the drug to be non-sedating[23]. In our study, sedation was significantly more (P = 0.033) when compared to granisetron.But none of the patients required any interventions as the sedation score was above 4. QTc prolongation and Torsades de pointes mostly occurs in psychiatric patients receiving >35mg in 24hr period [24,25]. Antiemetic doses of haloperidol are much smaller 0.5-2mg [17,18]. In our study, none of the patients had QT interval prolongation. However we recommend to avoid Haloperidol in patients with electrolyte disturbance(hypokalemia,hypomagnesemia),cong estive cardiac failure,dysrhythmias,acute coronary syndromes and patients taking monoamine oxidase inhibitors or tricyclicantidepressants.

Considering side effect profiles of granisetron and haloperidol we mainly noted headache about 6 cases(20%) in granisetron group , which is statistically significant[22]. Incidence of dizziness was not significantly different among the 3 groups. None of the patients had constipation or extrapyramidal side effects.

Carl E. Rosow demonstrated no statistical difference between haloperidol and granisetron in complete response, nausea, emesis, retching or sedation score[26]. In another study by Aouad et al also proves haloperidol as an effective antiemetic in the early post-operative period without significant side effects[11]. Our study reflects these results.

5.CONLUSION:

Haloperidol and Granisetron have similar safety and efficacy for PONV prophylaxis in patients undergoing laparoscopic surgeries.Butyrophenones have proved to be very effective antiemitics. 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. Common formulation of haloperidol is 5mg/cc which is inconvenient hence repackaging may be required[26].

6.LIMITATIONS:

1. Patients with h/o motion sickness are known to have a higher incidence of PONV. This study does not evaluate such patients and their response to being treated with haloperidol or granisetron.
2. Patients with previous h/o PONV were also not evaluated separately.
3 This study has not assessed cost-effectiveness of PONV prophylaxis.
4 Does not validate in children.

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