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ORIGINAL ARTICLE

Prophylactic Intravenous Glycopyrrolate Bromide and its cardio-protective role in Laparoscopic Cholecystectomy

Shirish Prasad Amatya[1], Anil Shrestha[2], Roshan Piya[3], Manisha Pradhan[4], Niroj Hirachan[5], Jay Prakash Thakur[6]

[1-6]Lecturer, Department of Anaesthesiology, Patan Academy of Health Sciences, Lagankhel, Nepal

ABSTRACT:
Background: Gallstones are the most common & costly digestive disease, it is estimated that more than one million new cases emerge annually worldwide. Since there is little known about the role of Glycopyrrolate in laparoscopic surgeries; this study focuses on prophylactic role of Glycopyrrolate Bromide in prevention of bradycardia during laparoscopic cholecystectomy. **Materials and methods:** Prospective, randomized, double blind comparative study was designed to include 50 patients. Control group (25 patients) was given 1 ml of normal saline and Glycopyrrolate group 1ml = 0.2 mg of Glycopyrrolate during induction of anaesthesia. Data of Heart rate, Systolic and Diastolic Blood Pressure, Mean Arterial Pressure were taken in following manner: baseline (B); 1min after drug / normal Saline (Agent 1); 1 & 5 mins after intubation respectively (I 1 & 5); 1,3,5,15 & 30 mins after Pneumoperitoneum respectively (P ;1,3,5,15 & 30); Before Extubation (E b); After Extubation (E a). **Results:** There was a significant difference in heart rate specially after one, three and five minutes of pneumoperitoneum between group p and g ($p < 0.05$). Diastolic and systolic blood pressure, in both groups also did not changed significantly following administration of agent and event after laryngoscopy and intubation. In both groups heart rate, systolic blood pressure & diastolic blood pressure increased after extubation, but were within acceptable range; comparison between the two groups was not significant. **Conclusion:** Preoperative glycopyrrolate as premedication has a cardioprotective role and should be considered during laparoscopic cholecystectomy to prevent these disastrous consequences which has potential to take life of otherwise healthy individual.
Keywords: Blood pressure, glycopyrrolate, heart rate, laparoscopic Cholecystectomy.

Corresponding author: Dr. Shirish Prasad Amatya, Lecturer, Department of Anaesthesiology, Patan Academy of Health Sciences, Lagankhel, Nepal

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Introduction:
Gallstones are the most common & costly digestive disease, it is estimated that more than one million new cases emerge annually worldwide.[1] Laparoscopic removal of gall bladder, Laparoscopic Cholecystectomy, started in France in 1987 and soon the world embraced it due to its various advantages; such as better cosmetic outcome and early return to normal function as well as reduction of postoperative pain, hospital stay, intraoperative bleed, wound infection, metabolic derangement and total overall cost.[1,2]
Although Laparoscopic surgeries has made advances in the last 40 years; cardiac arrhythmia are common (47%), bradycardia (30%), sever bradycardia and asystole has been reported. There may be various predisposing factors such as carbon dioxide insufflations, reverse Trendelenburg position, gas embolism, traction of the peritoneal structures, patient's preoperative anxiety and anaesthetic drugs.[2-4]
Routine prophylactic use of anticholinergic agents is common in laparoscopic surgeries and has shown beneficial effects to counteract adverse cardiac events such as bradycardia and asystole during and after anaesthesia.[5,6]
There are studies which shows Glycopyrrolate, a newer quaternary ammonium anticholinergic agent, has antimuscarinic properties as effective as those of atropine and superior control of neostigmine induced bradycardia and arrhythmia and better control of oropharyngeal secretions.[7] Mirakhur and Clark[8] has also shown better intraoperative cardiovascular stability in adults with glycopyrrolate premedication than atropine. Since there is little known about the role of Glycopyrrolate in laparoscopic surgeries; this study focuses on prophylactic role of Glycopyrrolate Bromide in prevention of bradycardia during laparoscopic cholecystectomy.

Literature review:
R. Anand in 1993 has shown that laparoscopic cholecystectomy is superior over the conventional open

cholecystectomy for treatment of symptomatic gallstone as there is marked decrease in pain and disability, without apparent increase in mortality or overall morbidity[1].

A study by Paul S at el in 1991 conducted a study on 49 female patients undergoing elective laparoscopy and they concluded that cardiac arrhythmias (47% had arrhythmia, 30% of which are bradyarrhythmias) are common during laparoscopy in which nearly all the episodes occurred during insufflation of carbon dioxide or with traction/ manipulation of pelvic structures[2].

Similarly, an article by Tanvir Samra and Sujata Sharma in 2013 retrospectively studied 63 patients who had undergone laparoscopic Nissen fundoplication for incidence and severity of adverse events and they concluded that bradycardia (22.2%) was second to most common incidence, hypertension (28.5%)[4].

Gautam B, Shrestha BR in 2009 in their case study concluded that cardiac arrest is a feared deadly complication that can occur during Laparoscopic Cholecystectomy and urged to be vigilant and work towards alternative anesthetic regimen[3].

Maharjan SK, Tabdar S[5] in 2013 and Mazin J Al Hawaz et al[6] in 2014 concluded in their double blind, randomized trial where 0.6 mg atropine was compared with control (1 ml Normal Saline) showed that 40% of control group undergoing laparoscopic surgeries developed bradycardia and thus suggested prophylactic use of atropine sulphate, anticholinergic agent, along with carboperitonium during laparoscopic surgeries, in both studies.

A comparison of Atropine and Glycopyrrolate in anaesthesia practice by F Kongsrud and S. Sponheim in 1982 has highlighted the superiority of glycopyrrolate over atropine to prevent cardiac arrhythmia intra and postoperatively. In their study, proportion of bradycardia/arrhythmia was 52% in Atropine group compared to just 15% in Glycopyrrolate group[7].

Methods:

Type: Prospective, Randomized, double blind, comparative study.

Place: Department of Anaesthesiology, Patan Academy of Health Sciences, Lagankhel, Nepal.

Sample Size: Based in the paper "A comparison of Atropine and Glycopyrrolate in Anaesthetic practice."

level of significance = 5%
Power = 80%
Type of test: Two sided
n = Sample Size

Formula,

$$n = 2[(Z\alpha/2 + Z\beta)^2 \times pXq/ d^2$$

p= p1+p2/2 [p1 = Proportion of bradycardia/arrhythmia (52%) in atropine group, p2 = Proportion of bradycardia/arrhythmia in glycopyrrolate group (15%)]

p= 52+15/2=33.5

d = clinically significant difference between the two groups (p1-p2) = 52-15=37

Zα/2 = at 5 % = 1.96

Zβ = 80% power therefore = 0.84

n = 2 X 7.84 X 33.5 X 66.5/37 X 37

= 25 in each group

Total sample = 50

Inclusion Criterion:

ASA PS I
Age: 15 – 50 yrs
Symptomatic Cholecystitis
Elective Cholecystectomy

Exclusion Criterion:

Contraindicated to General Anaesthesia & or Glycopyrrolate, ASA PS II and above, Previous Abdominal Surgeries, Difficult Airway

Premedication: Tab Ranitidine 150 mg HS, Tab Alprazolam 0.25 mg HS

Nil per Oral: NPO from midnight before surgery

Monitor: American Society of Anaesthesiologist (ASA) standard monitors (baseline heart rate, systolic, diastolic and mean arterial pressure)

Standard General Anaesthesia: 20/18 G IV cannula and 1 L Ringer Lactate; Midazolam: 0.03 mg/kg; Fentanyl 2mcg/ kg; Propofol: 2 mg/kg; Vecuronium: 0.1 mg/kg

Airway management: Endotracheal Intubation 3 mins after Vecuronium.

Anaesthesia maintained: 1 – 2 % Isoflurane with 100 % Oxygen.

Control group (25 patients) will be given 1 ml of normal saline and Glycopyrrolate group will be given 1ml = 0.2 mg of Glycopyrrolate during induction of anaesthesia. Test drug will be given by the anaesthetic assistant who will not be involved in data collection and patients will also be aware of the test drug used.

Data of Heart rate, Systolic and Diastolic Blood Pressure, Mean Arterial Pressure will be taken in following manner: baseline (**B**); 1min after drug / normal Saline **(Agent 1);** 1 & 5 mins after intubation respectively (**I 1 & 5**); 1,3,5,15 & 30 mins after Pneumoperitoneum respectively (P ;**1,3,5,15 & 30**); Before Extubation (**E b**); After Extubation **(E a)**

Complication if any will also be recorded: Arrhythmia

For the purpose of this study:

Bradycardia: heart rate < 60 beats/ minute
Tachycardia: heart rate > 160 beats/minute
Hypotension: > 30 % reduction from baseline systolic blood pressure
Arrhythmia: disorder of rate or rhythm observed.

Data analysis was done in SPSS 24; comparison of means was done using Independent Samples t test. Here, p value less than 0.05 in Levene's Test for equality of variances was taken as statistically significant.

Results:

This study included 50 patients. As shown in Table 1, we have 25 participants in group p (control group), the mean age is 37.72 with SD of 9.55, mean weight is 61.80 with SD of 10.20 and for sex, there are 18 females and 7 males. Same number of patients were in group g (Glycopyrrolate group) where the mean age is 36.16 with SD of 9.67, mean weight of this group is 63.60 and SD is 8.83 and for sex, we have 22 females and 3 males.

Table 1: Demographic variables

		Group	
		Control group (group p)	**Glycopyrrolate group (group g)**
Age in years (mean ± SD)		37.72 ± 9.55	36.16 ± 9.67
Weight in kg (mean ± SD)		61.80 ± 10.20	63.60 ± 8.83
Sex	Male	7	3
	Female	18	22

As shown in Table 2 a & b and 3 a & b, the difference between the variables are not significant, It means that our sample among the groups p and g are similar.

Table 2a: Group Statistics of age, weight, baseline Heart Rate, Basleline Blood pressure

	Group_number	N	Mean	Std. Deviation	Std. Error Mean
Age	g	25	36.16	9.672	1.934
	p	25	37.72	9.559	1.912
weight	g	25	63.60	8.836	1.767
	p	25	61.80	10.206	2.041
HRb	g	25	79.56	13.727	2.745
	p	25	80.84	13.698	2.740
SBPb	g	25	128.28	13.536	2.707
	p	25	131.56	15.259	3.052
DBPb	g	25	76.84	8.980	1.796
	p	25	79.76	11.889	2.378

Table 2 b: Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	.163	.689	-.574	48	.569	-1.560	2.720	-7.029	3.909
	Equal variances not assumed			-.574	47.993	.569	-1.560	2.720	-7.029	3.909
weight	Equal variances assumed	.533	.469	.667	48	.508	1.800	2.700	-3.629	7.229
	Equal variances not assumed			.667	47.037	.508	1.800	2.700	-3.632	7.232
HRb	Equal variances assumed	.026	.872	-.330	48	.743	-1.280	3.878	-9.078	6.518
	Equal variances not assumed			-.330	48.000	.743	-1.280	3.878	-9.078	6.518
SBPb	Equal variances assumed	.104	.748	-.804	48	.425	-3.280	4.079	-11.482	4.922
	Equal variances not assumed			-.804	47.327	.425	-3.280	4.079	-11.485	4.925
DBPb	Equal variances assumed	1.409	.241	-.980	48	.332	-2.920	2.980	-8.912	3.072
	Equal variances not assumed			-.980	44.659	.332	-2.920	2.980	-8.923	3.083

Table 3a: Sex Cross tabulation

		Group_number		Total
		G	P	
Sex	**f**	22	18	40
	m	3	7	10
Total		25	25	50

Table 3b: Chi-Square Tests for Sex

	Value	df	Asymptomatic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.000[a]	1	.157		
Continuity Correction[b]	1.125	1	.289		
Likelihood Ratio	2.046	1	.153		
Fisher's Exact Test				.289	.145
N of Valid Cases	50				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.00.					
b. Computed only for a 2x2 table					

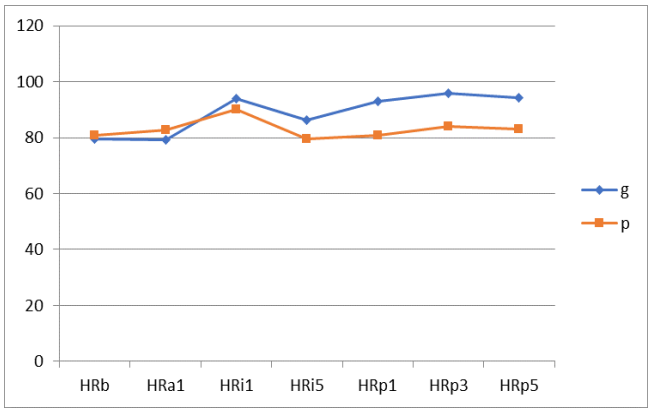
When heart rate was compared with baseline, after giving the agent, intubation and pneumoperitoneum; group p showed slight increase in heart rate 1 mins after the administration of the agent whereas there was no significant rise of heart rate in group g. In both groups heart rate, slightly increased {group p: 90.20 (14.074), group g:93.92 (14.248)} following laryngoscopy and intubation. Heart rate in both groups slowly decreased; in group p, heart rate was near baseline before pneumoperitoneum but after pneumoperitoneum in 24% bradycardia was seen (6 patient had bradycardia out of which 5 required treatment with injection Atropine 0.3mg intravenous). In contrast to this, heart rate in group g patient was slightly greater than baseline even after pneumoperitoneum {92.96 (22.235) after1min, 95.80 (20.496) after 3 min, &94.24 (18.260) after 5min} with no incidence of bradycardia. Thus, there was a significant difference in heart rate specially after one, three and five minutes of pneumoperitoneum between group p and g ($p < 0.05$), table 4 & graph 1.

Table 4: shows the HR and BP 1 min after administration of the agent,1 & 5 mins after intubation, and 1, 3 &5 min after pneumoperitoneum

	g (SD)	p (SD)	P value (Sig. (2-tailed))
HRa1	79.28 (12.736)	82.68 (16.800)	.424
HRi1	93.92 (14.248)	90.20 (14.074)	.358
HRi5	86.12 (16.344)	79.48 (12.420)	.112
HRp1	92.96 (22.235)	80.68 (15.708)	.029
HRp3	95.80 (20.496)	83.92 (18.216)	.035
HRp5	94.24 (18.260)	83.16 (19.401)	.043
SBPa1	127.96 (14.695)	129.32 (15.329)	.750
SBPi1	122.20 (17.758)	124.32 (16.648)	-2.120
SBPi5	109.32 (17.855)	106.32 (19.196)	3.000
SBPp1	130.88 (24.439)	119.92 (20.222)	10.960
SBPp3	135.76 (20.189)	122.48 (21.635)	13.280
SBPp5	139.32 (26.012)	125.68 (18.479)	13.640
DBPa1	76.36 (10.563)	76.80 (12.379)	.893
DBPi1	77.60 (12.155)	78.16 (14.516)	883
DBPi5	65.08 (12.945)	65.64 (12.233)	-.560
DBPp1	85.88 (19.251)	81.72 (13.350)	4.160
DBPp3	91.20 (15.322)	82.20 (14.201)	9.000
DBPp5	91.64 (15.187)	82.08 (13.964)	9.560

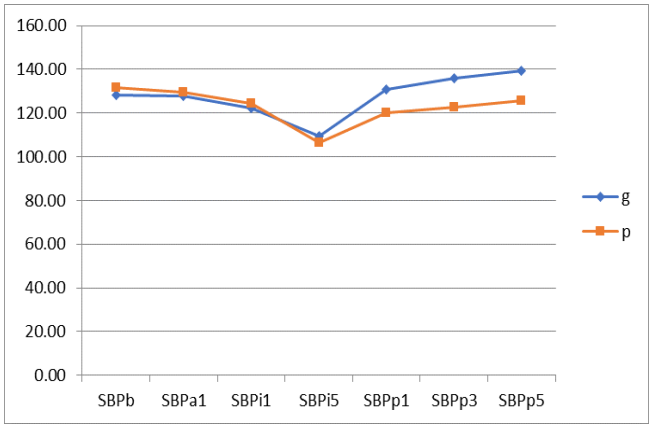
Systolic blood pressure, in both groups did not changed significantly following administration of agent and event after laryngoscopy and intubation. After 5 mins of laryngoscopy, both group showed decrease in {group p: 106.32 (19.196), group g: 109.32 (17.855)} which gradually increased following pneumoperitoneum. Systolic blood pressure was slightly higher in group g throughout pneumoperitoneum {group p: 125.68 (18.479), group g: 139.32 (26.012)}, graph 2.

Graph 1: shows heart rate baseline, 1 min after administration of the agent,1 & 5 mins after intubation, and 1, 3 &5 min after pneumoperitoneum.



Similarly, diastolic blood pressure, in both groups also did not changed significantly following administration of agent and event after laryngoscopy and intubation. After 5 mins of laryngoscopy, both group showed decrease {group p: 65.64 (12.233), group g: 65.08 (12.945)} which gradually increased following pneumoperitoneum. Diastolic blood pressure was slightly higher in group g throughout pneumoperitoneum {group p: 82.20 (14.201), group g: 91.64 (15.187)}, graph 3.

Graph 2: Systolic Blood Pressure



In both groups heart rate, systolic blood pressure & diastolic blood pressure increased after extubation, but were within acceptable range; comparison between the two groups was not significant, table 5.

Graph 3: Diastolic Blood Pressure

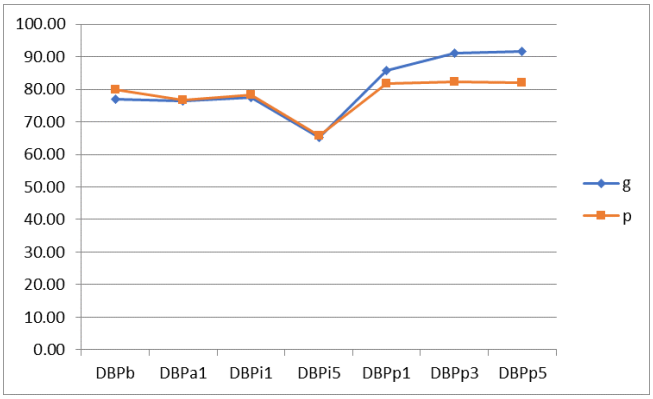


Table 5: Heart rate, systolic blood pressure & diastolic blood pressure before and after extubation

	Group g (SD)	Grouo p (SD)	P value (Sig. (2-tailed))
HRbE	92.92 (21.134)	89.12 (16.937)	.486
HRaE	107.72 (22.082)	100.16 (17.238)	.184
SBPbE	127.00 (20.508)	122.76 (15.514)	.414
SBPaE	140.92 (15.623)	137.36 (15.116)	.417
DBPbE	79.08 (13.083)	74.96 (11.092)	.236
DBPaE	85.84 (11.313)	85.48 (14.483)	.922

Discussion:

Laparoscopic Cholecystectomy is prone to vagally mediated bradycardia and sometimes even cardiac arrest. In these circumstances, anticholinergic agents, such as Glycopyrrolate blocks muscarinic receptors of parasympathetic autonomic nervous system preventing bradycardia. In this study, 24% of patient had bradycardia requiring some kind of intervention. Glycopyrrolate given preoperatively before induction of anaesthesia has shown to prevent bradycardia even cardiac arrest and has cardioprotective role in Laparoscopic cholecystectomy following carbon dioxide insufflation and traction of gallbladder. Paul S. Myles concluded that incidence of bradycardia in laparoscopic surgery is about 30% some requiring intravenous treatment with atropine to prevent progression to cardiac arrest.[2] This was similar to our study where 24% had episodes of bradycardia majority requiring intravenous atropine. Gautam B and BR Shrestha also encountered cardiac arrest during laparoscopic cholecystectomy, although it has multifactorial origin all cases occurred following pneumoperitoneum increasing mortality and morbidity.[3] Maharjan SK & Tabdar S in 2013 suggested prophylactic use of atropine during laparoscopic surgery to prevent bradycardia and subsequent cardiac arrest.[5] But F. Kongsrud and S. Sponheim had already proved glycopyrrolate, superior newer quaternary anticholinergic agent for premedication, is as effective as atropine with lesser adverse effect[7]. Onset of action following injection glycopyrrolate begins at 2 minutes and peaks in 3 to 7 minutes and vagal blocking effect persist for 2 to 3 hours.

Conclusion:

Bradycardia and cardiac arrest is a frequently encountered during laparoscopic cholecystectomy performed under general anaesthesia and the cause may be multifactorial. Thus, preoperative glycopyrrolate as premedication has a cardioprotective role and should be considered during laparoscopic cholecystectomy to prevent these disastrous consequences which has potential to take life of otherwise healthy individual.

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