Original Article

Preemptive Glycopyrrolate and Hemodynamic Consequences in Spinal Anesthesia

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Abstract

Background: Hypotension is most common side effect of spinal anesthesia caused by decrease in systemic vascular resistance or cardiac output.

Materials and Methods: This randomized study was conducted in 104 patients of physical status American Society of Anesthesiologists I and II, who have to undergo total abdominal hysterectomy for various gynecological reasons. Patients were allocated into their respective groups by computer-generated random numbers in blocks of 52 to receive either 2 mL of 0.9% sodium chloride (Group A) or glycopyrrolate 4 mcg/kg made up to 2 mL with 0.9% sodium chloride (Group B). Parameter (heart rate, systolic blood pressure (BP), diastolic BP, mean BP, respiratory rate, and saturation of peripheral oxygen) were recorded at 1 min, 5 min, 10 min, 20 min, 30 min, 45 min, and 60 min after spinal anesthesia. Vasopressor requirement and any side effect were recorded.

Results: It was found that glycopyrrolate group was more hemodynamically stable than control group. There was significant reduction in spinal induce hypotension in Group B (study group) with $P < 0.0001$ after spinal anesthesia. Thus, there was reduced need of vasopressor in the glycopyrrolate group which was statistically significant. Study was also showed that glycopyrrolate prevent spinal induce bradycardia after 10 min of spinal anesthesia. It was also statistically significant with P-value at 10 min = 0.04 and at 20 min = 0.003.

Conclusion: Intravenous glycopyrrolate before spinal anesthesia prevents spinal induce hypotension and bradycardia and also reduces requirement of vasopressor for the treatment of hypotension.

Key words: Bupivacaine, Glycopyrrolate, Hypotension, Normal saline, Spinal anesthesia

INTRODUCTION

Hypotension following spinal anesthesia occurs in up to 83% of cases if no steps are taken to prevent it.[1] Performance of a spinal/epidural block produces vasodilatation within the blocked area and a reflex vasoconstriction in unblocked areas of the body to maintain blood pressure (BP).[2] Imbalance between vasodilatation and vasoconstriction is the most common mechanism underlying hypotension associated with spinal/epidural analgesia and occurs if the block is widespread or in the presence of hypovolemia, even with a limited block.[3] The mechanism for vasodilatation is blockade of the sympathetic nerve fibers at the preganglionic level. It has been generally believed that the sympathetic block extends one to two segments higher than the somatic level.[4] The heart rate (HR) during a high neuraxial block typically decreases as a result of blockade of a cardioaccelerator fibers arising from T1 to T4. The HR may decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins.[5] Despite more than three decades of research, hypotension during spinal anesthesia remains a common clinical problem that is associated with morbidity for the patient. An effective method for preventing hypotension has been referred to as the "Holy Grail" of anesthesia and has yet to be described.[6]

A number of strategies for preventing hypotension have been investigated. These strategies have included the

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use of intravenous fluid preload, gravity (Trendelenburg or leg rising), compression devices on the legs, and prophylactic vasopressor.[7] Ephedrine and phenylephrine are common vasoconstrictor drugs and their effects on hypotension during anesthesia have been compared in many studies. Although no definite difference has been observed between two drugs regarding the prevention of hypotension following spinal anesthesia, some prefer ephedrine and others preferred phenylephrine depending upon the condition of the cardiac status of the patient, that is, whether the patient is able to tolerate tachycardia or not. Each vasopressor, either ephedrine or phenylephrine, has their own pros and cons.[8]

The physiopathological mechanism involved in the occurrence of hypotension is systemic vascular resistance and central venous pressure from sympathetic block with vasodilatation.[9,10] Bradycardia can occur from shift in cardiac autonomic balance toward the parasympathetic system, from activation of the left ventricular mechanoreceptors from a sudden decrease in the left ventricular volume (Bezold-Jarisch reflex).[11] Glycopyrronium bromide is a medication of the muscarinic anticholinergic group. It does not cross the blood–brain barrier and consequently has no to few central effects.[12] Its actions include among others a prolonged inhibition of gastro-intestinal tract motility and secretion. The antisialagogue effect was shown to be about 5 times as potent as that of atropine. Studies in conscious healthy volunteers have consistently shown an absence of significant effects on HR and rhythm following doses of glycopyrrolate which might be used in premedication in anesthetized patients, using larger intravenous doses, glycopyrrolate, and atropine both produced a rise in HR with glycopyrrolate being approximately twice as potent (w/w) as atropine. The effects of the drug on HR in conscious adult patients are not well documented, particularly with reference to dose-response relationships. However, the effects on HR are quite apparent in anesthetised patients.[13] Most recently study has been shown that glycopyrrolate has a significant and prolonged bronchodilating action, leading to an increase in dead space similar to that following the administration of atropine but persisting for a longer period of time.[14,15]

The purpose of this study is to investigate whether the combination of rapid crystalloid cohydration with 0.2 mg of glycopyrrolate would be more effective at preventing hypotension than crystalloid infusion alone and whether this technique would prove to be an effective method for eliminating intraoperative hypotension.

MATERIALS AND METHODS

A total of 104 patients were enrolled for the study of age group 18–65 years of physical status American Society of Anesthesiologists I and II, after the approval from Institutional Ethics Committee. The design of the study was prospective randomized, comparative study. Patients who have undergone total abdominal hysterectomy for various gynecological reasons and fulfilling the criteria for regional anesthesia were taken for study after written informed consent. A detailed history, thorough physical examination, routine investigation such as complete blood count, blood sugar, renal profile, serum electrolytes, and any special investigation if required was done for the study. Patients who had coagulopathy, sepsis at the site of intrathecal injection, major organ pathology such as heart disorder, hepatic, and renal disorder were excluded from the study. After all standard preparations, routine monitoring devices such as electrocardiogram leads, noninvasive BP cuff, and pulse oximetry probe, were attached to patient. An intravenous access with 18 gauge intravenous cannula was secured. Patients were allocated into their respective groups by computer-generated random numbers in blocks of 52 to receive either 2 mL of 0.9% sodium chloride (Group A) or glycopyrrolate 4 mcg/kg made up to 2 mL with 0.9% sodium chloride (Group B), prepared with the identical syringe, contents of which were unknown to the anesthetists involved in the case. Preload of 15 mL/kg Ringer's lactate solution was given over 10 min. The study drug or placebo was then given over 2 min. The subarachnoid space was then located using a 26-guage Quincke needle and 0.5% hyperbaric bupivacaine 3.0 mL injected intrathecally. Parameter (HR, systolic BP [SBP], diastolic BP [DBP], mean BP [MBP], respiratory rate [RR], and saturation of peripheral oxygen [SPO$_2$]) was recorded at 1 min, 5 min, 10 min, 20 min, 30 min, 45 min, and 60 min after spinal anesthesia. Atropine atropine was given if HR is <60, and mephentermine was given if BP falls below 30% from baseline values. Vasopressor requirement was reported if needed during procedure. Any side effect also to be recorded if occurs such as nausea, vomiting, and dryness of mouth. Sample size was estimated using formula for simple random sampling as given below-

$$n = \frac{Z^2 p(1-p)}{l^2}$$

where *n* = required sample size, z = 1.96 at 95% confidence intervals (CIs) and 80% power, 5% alpha (type I error), p is the probability of difference in HR changes between glycopyrrolate and saline groups which was considered 23% based on pertaining literature as reported by Yentis[1] 2000. l = precision (marginal error) which was considered as 11.5% (a 50% relative precision to given p) this accumulation 51.44, thus we planned to enroll 52 samples in each group for the proposed study.

RESULTS

Table 1 shows the demographic parameters of age in both the groups [Graph 1].

Table 2 depicts the comparison of preoperative vital parameters among both the groups [Graph 2].

Table 3 depicts the comparison of vasopressor requirement [Graph 3]. In Group A, 44 required vasopressor and in Group B, only eight patient required vasopressor. $P < 0.05$ which was statistically significant.

Table 4 shows the comparison of frequency of vasopressor requirement in both the groups [Graph 4]. All the patients in Group A and only eight patients in the Group B required vasopressor. Only once in glycopyrrolate group whereas 14 patients in NS group required once, 15 patients required twice, 14 patients required thrice, and one patient required the vasopressor for the 4th time. $P < 0.05$ was

statistically significant. Thus, there was higher frequency of vasopressor requirement in Group A in comparison to glycopyrrolate group.

Table 5 depicts the comparison of HR. Trend of HR showed that the groups differ significantly at 10, 20, and at 30th min with a $P = 0.04$, 0.003, and 0.028, respectively [Graph 5].

Table 6 shows the comparison of SBP where *P*-value of SBP at 5 min, 10 min, 20 min, and 30 min among the groups was <0.0001 which was statistically significant [Graph 6].

Table 7 shows the comparison of DBP where *P*-value of DBP at 1 min, 5 min, 10 min, 20 min, and 30 min among the groups was <0.0001 which was statistically significant [Graph 7].

Table 1: Demographic data: Age (years)

Age group	Treatment group (%)		Total (%)
	NS	Glycopyrrolate	
28–30 years	2 (3.8)	2 (3.8)	4 (3.8)
31–40 years	13 (25)	18 (34.6)	31 (29.8)
41–50 years	13 (25)	13 (25)	26 (25)
51–60 years	19 (36.5)	13 (25)	32 (30.8)
61–70 years	5 (9.6)	6 (11.5)	11 (10.6)
Total	52 (100)	52 (100)	104 (100)

Chi-square=2.02; *P*=0.73

Table 2: Comparison of pre-operative vital parameters

Variables	Group				*t*-test	*P*-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
Age	48.33	10.504	46.94	10.513	0.672	0.503
Preop Pulse	77.79	7.212	77.31	8.886	0.303	0.763
Preop Sys	110.56	8.123	111.52	9.076	0.569	0.57
PreopDia	74.04	5.495	74.85	5.906	0.722	0.472
Preop MBP	86.19	5.671	86.98	6.494	0.659	0.511
Preop RR	12.38	0.565	12.67	0.964	1.861	0.066
Preop Spo2	100	0	100	0	0	1

MBP: Mean blood pressure, RR: Respiratory rate, SPO2: Peripheral oxygen saturation

Table 3: Comparison of vasopressor requirement

Requirement of vasopressor	Treatment group (%)		Total (%)
	NS	Glycopyrrolate	
No	8 (15.4)	44 (84.6)	52 (50)
Yes	44 (84.6)	8 (15.4)	52 (50)
Total	52 (100)	52 (100)	104 (100)

Chi-square=49.85; *P*<0.0001

Table 4: Comparison of frequency of vasopressor requirement in both groups

Frequency of requirement of vasopressor	Treatment group (%)		Total (%)
	NS	Glycopyrrolate	
0	8 (15.4)	44 (84.6)	52 (50)
1	14 (26.9)	8 (15.4)	22 (21.2)
2	15 (28.8)	0 (0)	15 (14.4)
3	14 (26.9)	0 (0)	14 (13.5)
4	1 (1.9)	0 (0)	1 (1)
Total	52 (100)	52 (100)	104 (100)

Chi-square=56.56; *P*<0.0001

Table 5: Comparison of HR

Variables	Group				*t*-test	*P*-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
HR 1 min	72.92	6.151	73.54	7.815	0.446	0.656
HR 5 min	69.6	5.825	71.13	7.035	1.215	0.227
HR 10 min	66.81	5.402	69.17	6.183	2.078	0.04
HR 20 min	64.94	5.758	68.35	5.551	3.069	0.003
HR 30 min	65.62	5.918	67.9	4.429	2.232	0.028
HR 45 min	67.23	5.386	68.65	5.387	1.347	0.181
HR 60 min	69.13	5.194	69.85	5.062	0.707	0.481

HR: Heart rate

Table 6: Comparison of SBP

Variables	Group				*t*-test	*P*-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
SBP 1 min	100.6	7.027	103.9	7.887	2.258	0.026
SBP 5 min	90.27	7.497	99.75	6.998	6.666	<0.0001
SBP 10 min	83.71	4.816	97.6	7.754	10.969	<0.0001
SBP 20 min	84.6	5.278	94.67	7.142	8.183	<0.0001
SBP 30 min	88	6.466	94.5	8.941	4.248	<0.0001
SBP 45 min	92.25	5.884	96.13	8.765	2.653	0.009
SBP 60 min	96.9	6.763	100.73	8.975	2.456	0.016

SBP: Systolic blood pressure

Tables 8 and 9 show comparison of RR and saturation, respectively, where p value >0.05 among both the groups was statistically not significant [Graphs 8 and 9].

DISCUSSION

Hypotension is the most common side effect of spinal anesthesia. Hypotension is caused by decrease in systemic vascular resistance or cardiac output. As a result of the sympathectomy caused by spinal anesthetics, as many as one-third of patients receiving a spinal anesthetic become hypotensive with a SBP <90 mm Hg and 10–15% of patients become bradycardia. There are several reasons why hypotension occurs in spinal anesthesia. First, it may be due to decreases in systemic vascular resistance.

Second, it may be due to decreased venous return to the heart and subsequent decrease in cardiac output. Finally, if blockade of the cardioaccelerator fibers occurs, bradycardia results and there is even greater decrease in cardiac output. Blockade of cardioaccelerator fibers occurs when the dermatomal level of the sympathetic nervous system blockade is at or above the T1 level since the cardioaccelerator fibers originate from T1 to T4. When the hypotension is modest it is probably due to decreases in systemic vascular resistance. When hypotension is severe, it is believed to be due to decreases in cardiac output.[16] Hypotension may cause nausea, vomiting, unconsciousness, pulmonary aspiration, and hypoxia. Management of hypotension during spinal anesthesia includes oxygenation, fluid therapy, positional changes, pharmacotherapy, and other non-pharmacological method. In the study by Manem and Krishnamurthy[17] patients were randomly allocated into two groups of 30 each. Group G - received intramuscular

Table 7: Comparison of DBP

Variables	Group				t-test	P-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
DBP 1 min	66.71	3.907	70.42	5.403	4.014	<0.0001
DBP 5 min	58.31	6.821	67.83	5.956	7.58	<0.0001
DBP 10 min	52.29	5.482	64.77	6.345	10.733	<0.0001
DBP 20 min	52.38	5.221	62.29	6.539	8.535	<0.0001
DBP 30 min	55.08	6.312	60.94	7.8	4.215	<0.0001
DBP 45 min	58.96	6.417	62.29	8.069	2.327	0.022
DBP 60 min	62.46	5.758	65.08	7.211	2.044	0.044

DBP: Diastolic blood pressure

Table 8: Comparison of RR

Variables	Group				t-test	P-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
RR 1 min	12.21	0.457	12.4	0.869	1.412	0.161
RR 5 min	13	0.686	13.19	0.864	1.257	0.212
RR 10 min	13.29	0.915	13.21	1.016	0.406	0.686
RR 20 min	12.71	0.893	12.88	0.9	0.984	0.327
RR 30 min	12.88	0.832	12.87	0.991	0.107	0.915
RR 45 min	13	0.863	12.92	1.082	0.401	0.689
RR 60 min	12.94	0.916	13.04	0.885	0.544	0.587

RR: Respiratory rate

Table 9: Comparison of saturation

| Variables	Group				t-test	P-value
	NS		Glycopyrrolate			
	Mean	SD	Mean	SD		
SPO2 1 min	99.98	0.139	99.9	0.298	1.689	0.094
SPO2 5 min	99.83	0.382	99.92	0.269	1.484	0.141
SPO2 10 min	99.85	0.364	99.88	0.323	0.57	0.57
SPO2 20 min	99.67	0.474	99.83	0.382	1.823	0.071
SPO2 30 min	99.75	0.437	99.83	0.382	0.955	0.342
SPO2 45 min	99.81	0.398	99.81	0.398	0	1
SPO2 60 min	99.65	0.653	99.85	0.364	1.854	0.067

SPO2: Saturation of peripheral oxygen
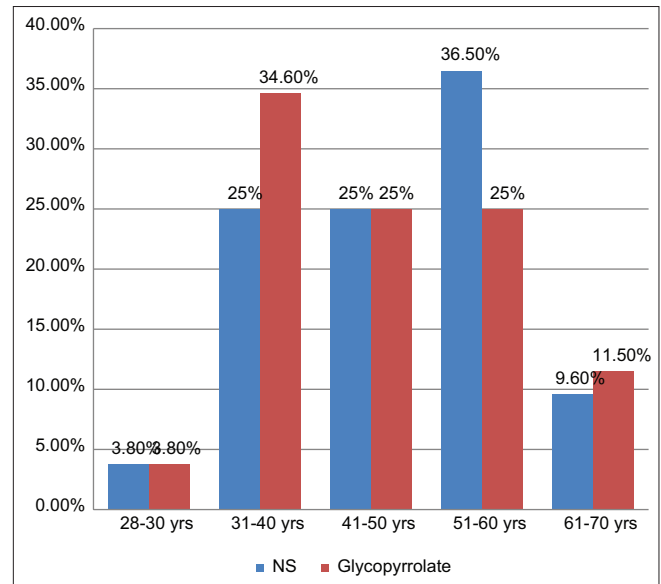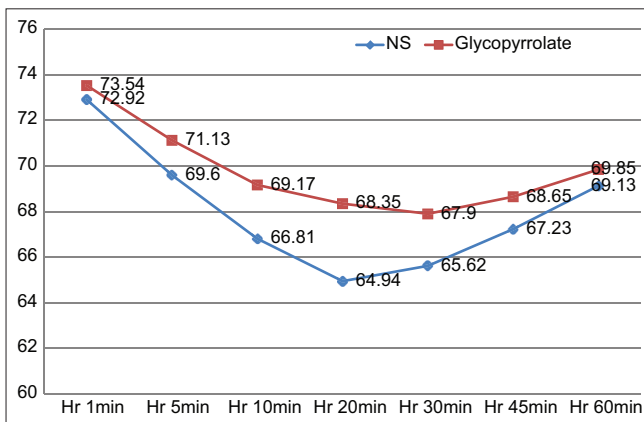

Graph 1: Demographic data: Age (years)
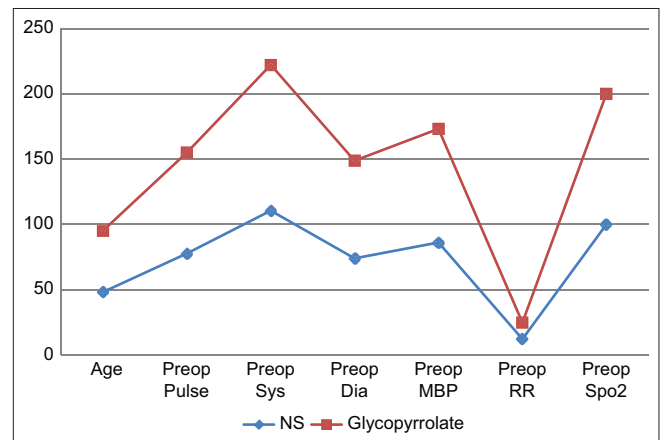
Graph 2: Comparison of preoperative vital parameters
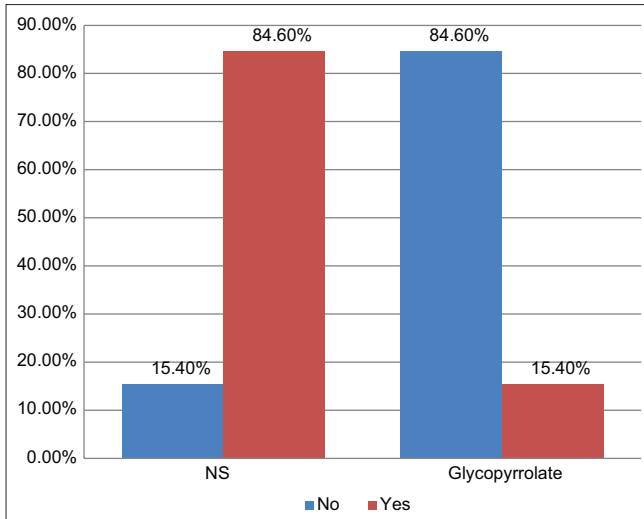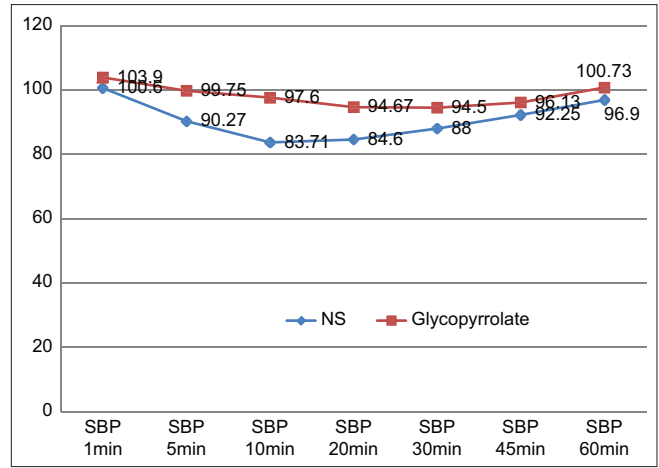
Graph 3: Comparison of vasopressor requirement
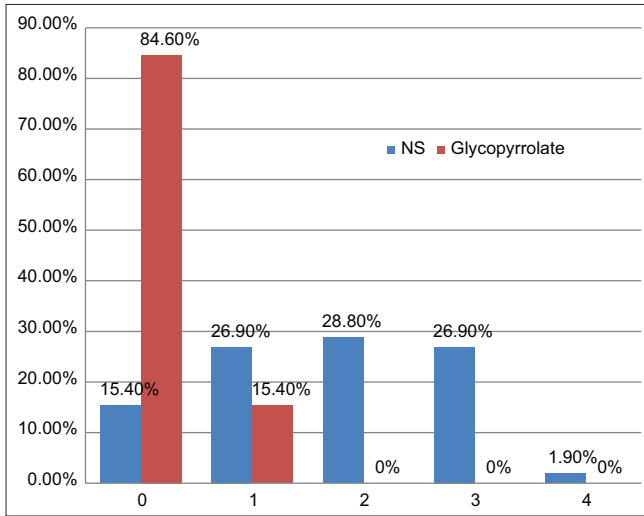
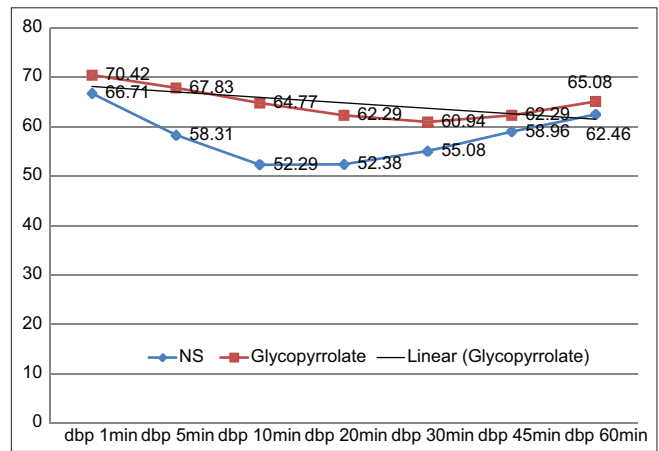**Graph 4: Comparison of frequency of vasopressor requirement in both groups**

Graph 5: Comparison of heart rate

Graph 6: Comparison of systolic blood pressure

Graph 7: Comparison of diastolic blood pressure
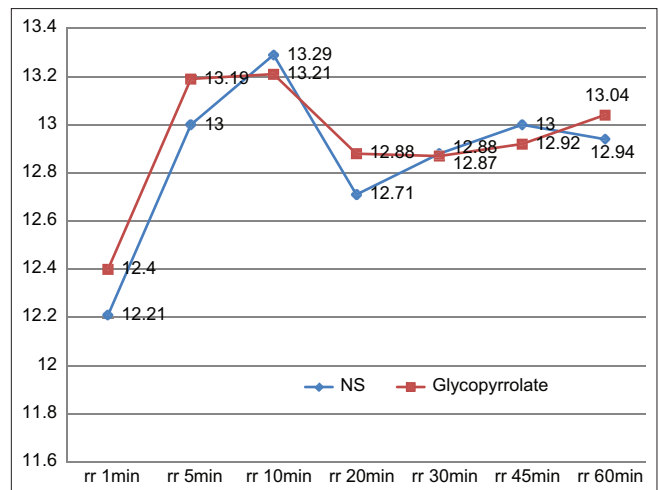

Graph 8: Comparison of respiratory rate

0.2 mg glycopyrrolate and Group S - received 1ml saline, 15 min before spinal anesthesia. 13 out of 30 patients had hypotension in G group. Whereas, 22 out of 30 patients developed hypotension in saline group with $P = 0.018$. Median dose of rescue vasopressor used in G group was 0 mg and in saline group was 6 mg. This difference in total dose of rescue vasopressor used between two groups was statistically significant with $P = 0.008$. In the study by
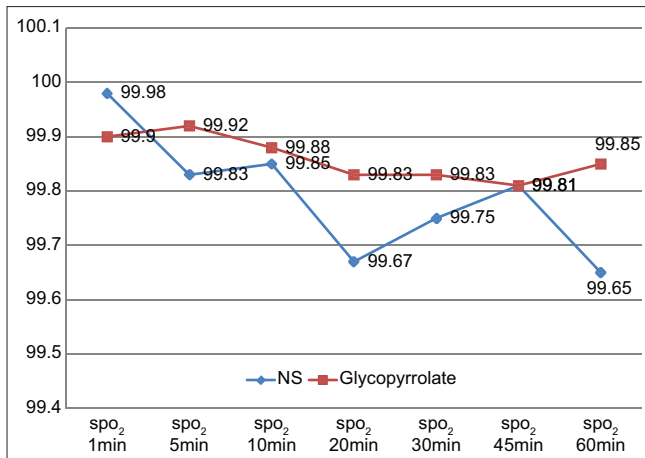
Graph 9: Comparison of saturation

Hwang *et al.*,[18] 66 patients were randomly divided into two groups. They received either glycopyrrolate 0.2 mg (Group G) or normal saline (Group S) intramuscularly, 15 min before spinal anesthesia. They found that, 23 out of 33 (70.0%) patients in Group S, experienced hypotension compared with 9 of 33 (27.3%) patients in group G (Difference = 42.7%; 95% CI 18.4–60.2; $P = 0.0001$). The median amount of vasopressor (ephedrine) required was 5 mg in Group S compared with 0mg in group G (difference = 5.0 mg; 95% CI: 2.7–7.3 $P = 0.0001$). In the study by Kee *et al.*,[19] 104 patients randomly received intravenous glycopyrrolate 4 ug/kg or saline placebo. The primary outcome, the cardiac output, 5 min after spinal injection was greater in the glycopyrrolate group. Both cardiac output and HR were greater over time in the glycopyrrolate group versus the control group (both the $P < 0.001$) but there was no difference in stroke volume over time ($P = 0.95$) and decrease in vasopressor dose when glycopyrrolate given before a phenylephrine infusion. In the study by Ure *et al.*,[20] a total of 50 patients were randomly divided in two groups of 25 each. In the glycopyrrolate group, ten patients developed nausea and vomiting compared with 17 of 25 in the placebo group. Patients in the group pretreated with glycopyrrolate reported a reduction in the frequency ($P = 0.02$) and severity ($P = 0.03$) of nausea. Incidence of hypotension was similar in each group but significantly higher total doses of vasopressor (ephedrine) were given to the placebo group ($P = 0.02$). In the study by Chamchad *et al.*,[21] patients were randomly allocated into two groups of 35 each. Group G received 0.4 mg glycopyrrolate and Group S received equal volume of saline and they found that none of the 35 patients who were given glycopyrrolate and 6 of the 35 (17%) patients who received saline experienced bradycardia ($P = 0.02476$, Fisher's exact test) In the study by Yentis[1] patients were allocated by computer generated random number in blocks of 40 to receive either glycopyrrolate 4 ug/kg made up 2 ml by 0.9% sodium chloride (group G) or 2 ml of 0.9%

sodium chloride (Group S). Intraoperative HR increased by a greater amount in Group G than in Group S ($P = 0.002$). In the study by Patel *et al.*,[22] a total of 311 patients were included in the study; 153 received glycopyrrolate and 158 placebo. The maximal HR achieved in the glycopyrrolate group was significantly higher when compared to control (MD, 15.85 bpm [5.40–26.31]; $P < 0.0001$); however, the incidence of bradycardia was not statistically different. The vasopressor (phenylephrine) dose required was significantly reduced with glycopyrrolate group. This study was planned to evaluate for prevention of spinal induce hypotension and bradycardia by giving prophylaxis intravenous 4 ug/kg glycopyrrolate and reduce the need of vasopressor and observe hemodynamic changes. Study sample population was randomly divided into two groups (each group, $n = 52$) in which the observation were recorded and statistically evaluated. Patient in either group received an intravenous access with 18 gauge intravenous cannula. Preload of 15 ml/kg ringer's lactate solution was given over 10 min. Patients received either glycopyrrolate 4 mcg/kg (group G) made up to 2 ml with 0.9% sodium chloride or 2 ml 0.9% sodium chloride (group S). Subarachnoid space was then located using a 26-gauge Quinke spinal needle and 0.5% hyperbaric bupivacaine 3.0 ml injected intrathecally. Our study found that glycopyrrolate group was more hemodynamically stable than control group. There was significant reduction in spinal induce hypotension in group G with $P < 0.0001$ of SBP at 5 min (90.27 vs. 99.75), 10 min (83.71 vs. 97.6), 20 min (84.6 vs. 94.67), and at 30 min (88 vs. 94.5). Similar statistical difference was also observed in DBP at 1 min (66.71 vs. 70.42), 5 min (58.31 vs. 67.83), 10 min (52.29 vs. 64.77), 20 min (52.38 vs. 62.29), 30 min (55.08 vs. 60.94) and of mean arterial pressure at 5 min (68.98 vs. 78.52), 10 min (62.83 vs. 75.9), 20 min (63.13 vs. 73.13), and 30 min (65.98 vs. 72.23) after spinal anesthesia. Our study also showed that glycopyrrolate prevent spinal induce bradycardia after 10 min of spinal anesthesia. It was also statistically significant with *P*-value at 10 min = 0.04 and at 20 min = 0.003. Our study also showed statistically significant result in that there was reduced need of vasopressor in the glycopyrrolate group, 8 (15.4%) out of 52 patients, whereas 44 (84.6%) out of 52 patients in the Group NS required vasopressor (Chi-square = 49.85; $P < 0.0001$). 14 (26.9%) patients in Group NS required vasopressor only once whereas 8 (15.4%) patients in the glycopyrrolate group required the vasopressor once. 15 (28.8%) patients of Group NS required vasopressor twice whereas none of the patients needed vasopressor for the 2nd time in Group G. 14 patients (26.9%) of Group NS required vasopressor thrice and 1 (1.9%) patient required vasopressor for the 4th time in group NS. (Chi-square = 56.56; $P < 0.0001$). Group NS patients required more vasopressor than glycopyrrolate group (Group G) to maintain hemodynamic stability. Thus,

we can conclude that glycopyrrolate reduce the incidence of hypotension in comparison to control group.

CONCLUSION

Our study concluded that intravenous glycopyrrolate before spinal anesthesia prevents spinal induce hypotension and bradycardia and also reduce requirement of vasopressor for treatment of hypotension. Our study demonstrated that intravenous glycopyrrolate when used before spinal anesthesia, provided the most acceptable intraoperative hemodynamic stability.

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