

## Evaluation of Pre-emptive Intramuscular Glycopyrrolate in Prevention of Spinal Anesthesia Induced Hypotension in Elective Cesarean Sections

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### Abstract

**Context:** Spinal anesthesia induced hypotension in parturients undergoing Cesarean section can be detrimental to both foetus and mother. Prophylactic administration of vasopressors helps in preventing hypotension thereby maintaining the uteroplacental blood flow. **Aims:** The main objective of this study is to determine whether prophylactic intramuscular Glycopyrrolate administration reduces the incidence and severity of hypotension associated with spinal anesthesia in parturients. **Settings and Design:** Randomized double blinded prospective study. **Methods and Material:** Sixty parturients scheduled for elective LSCS under spinal anesthesia were randomly allocated into two groups of 30 each, Group G who received intramuscular glycopyrrolate 0.2 mg (1 ml) and Group S who received intramuscular saline (1 ml), 15 minutes prior to subarachnoid block. Incidence and severity of hypotension, heart rate and blood pressure changes, incidence of nausea and vomiting were observed. **Statistical analysis used:** Chi-square test was used for qualitative data and for Continuous data, mean and standard deviation. SPSS 22 software was used. **Results:** Thirteen out of thirty parturients (43.3%) had hypotension in glycopyrrolate group whereas 22 out of 30 parturients (73%) developed hypotension in saline group with a p value of 0.018. The median dose of vasopressor requirement was less in glycopyrrolate group when compared to saline group (0 vs 6 mg). **Conclusions:** Pre-emptive treatment with intramuscular glycopyrrolate reduces the incidence and severity of hypotension in parturients undergoing Cesarean sections under spinal anesthesia.

**Keywords:** Glycopyrrolate; Hypotension; Subarachnoid block.

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### Introduction

Subarachnoid block (SAB) given for parturients undergoing Lower segment Cesarean section (LSCS) has been associated with marked hypotension due to higher level of sympathetic blockade

achieved. Its incidence has been reported as high as 40-70% [1]. Maternal hypotension is associated with severe distress to the mother in the form of nausea & vomiting, dizziness etc. Also, it can lead to placental hypoperfusion that can cause adverse neonatal outcomes [2]. Traditional intravenous (IV) crystalloid Preloading or Co-loading might help

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in decreasing the severity of this hypotension but cannot completely prevent its incidence [3].

Sympathomimetics are usually administered "Reactively" i.e. administration of drugs after the appearance of hypotension. A more logical approach is "Proactive" i.e. giving vasopressors pre-emptively to prevent the occurrence of hypotension following subarachnoid block. This Pre-emptive or Proactive approach has reduced the incidence and severity of spinal anesthesia induced hypotension in many studies conducted worldwide [4,5,6,7].

Glycopyrrolate, an anti-cholinergic, has been successfully used in preventing spinal anesthesia induced hypotension in the elderly population undergoing lower abdominal and lower limb surgeries [8].

Glycopyrrolate was also studied in pregnant population for prevention of subarachnoid block induced bradycardia, intra-operative and post-operative nausea and vomiting etc. Its use in parturients has been documented to be safe without any fetal effects because of its inability to cross placental barrier [9,10,11].

Very few studies were available which investigated the use of "intravenous" Glycopyrrolate for prevention of spinal anesthesia induced hypotension in Cesarean sections, but have reported that there was abrupt tachycardia [11]. So we aimed to study, the efficacy of Pre-emptive "intramuscular" administration of glycopyrrolate in prevention of hypotension associated with subarachnoid block in patients undergoing lower segment Cesarean sections. Glycopyrrolate was administered intramuscularly to avoid abrupt increase in heart rate (HR) & to gradually counteract the hypotensive episodes during the subarachnoid block. We have also evaluated the severity of hypotension following subarachnoid block by calculating the total dose of rescue vasopressors used. Also, we evaluated incidence of bradycardia, nausea & vomiting and also reactive heart rate and blood pressure changes following administration of glycopyrrolate.

### Objectives of the study

*Primary objective:* To determine if prophylactic intramuscular glycopyrrolate administration reduces the incidence and severity of hypotension associated with spinal anesthesia in parturients by assessing the incidence of hypotension and calculating the total dose of rescue vasopressor used.

### Secondary objectives

1. Hemodynamic alterations like incidence of bradycardia, Maximal Heart rate achieved.
2. Postoperative complications like Nausea and vomiting.
3. Drug related side-effects like dry mouth, dizziness etc.
4. Other peri-operative adverse events were also be evaluated.

### Materials and Methods

*Study design:* This is a randomised double blinded prospective study.

*Source of data:* 60 parturients who underwent elective lower segment Cesarean sections under spinal anesthesia at tertiary care centre, Tamaka, Kolar, during the period of October 2016 to April 2018.

### Method of collection of data

*Inclusion criteria:* Parturients belonging to ASA physical status I and II, aged between 18-35 years with a Body Mass Index between 19-30 Kg/m<sup>2</sup>, scheduled for elective LSCS.

*Exclusion criteria:* Patients suffering from cardiac (Arrhythmias, heart blocks, bradycardia) and pulmonary diseases, gross spinal abnormality, localised skin sepsis, haemorrhagic diathesis, neurological diseases, pre-existing hypertension (Systolic blood pressure >140 mmHg, Diastolic blood pressure >90 mmHg), uncooperative or refusing for spinal anesthesia were excluded from the study.

### Sampling procedure

After obtaining written informed consent, 60 patients were randomly divided into two groups of 30 each. Randomization was done by computer generated random number table.

*Group G:* Intramuscular Glycopyrrolate 0.2 mg (1 ml)

*Group S:* Intramuscular 0.9% Normal saline (1 ml)

Pre-anaesthetic evaluation for all parturients was done one day prior to surgery. Patients were kept fasting as per the standard NPO guidelines i.e, 6 hours for solids and 3 hours for clear fluids. Premedication included Tab. Pantoprazole 40 mg and Tab. Metoclopramide 10 mg, three hours prior to surgery. On arrival to the operation theatre, patient's blood pressure and heart rate (HR) were recorded thrice

at three-minute intervals, while lying comfortably on the bed before venipuncture. The mean of these three readings was recorded as the baseline value for the maternal Mean arterial pressure (MAP) and HR. Monitoring included non-invasive blood pressure (NIBP), continuous electrocardiography (ECG), and pulse oximetry. A wide bore 18G intravenous (i.v) cannula was inserted after skin infiltration with local anaesthetic. Based on computer generated random number table, patient's group was identified and the study drug/control drug was given intramuscularly by the consultant anaesthesiologist without the observer (who acquired the data) being aware of the drug given. Within the next 15 minutes patient was positioned for spinal anesthesia. Under all aseptic precautions after positioning the patient in left lateral decubitus position, using 25G Quincke's spinal needle, Lumbar puncture was performed at L3-L4 interspace through a midline approach, 10 mg of hyperbaric bupivacaine was injected into the intrathecal space and patient was made supine, with 15 degrees left lateral tilt. The time of intramuscular injection was considered as time zero and the following parameters were observed.

*Parameters observed*

Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO<sub>2</sub> were recorded every two minutes for ten minutes and then every five minutes thereafter.

*Clinically significant Hypotension* was defined as decrease in MAP by > 25% from the base line.

*Rescue vasopressor* to treat hypotension included i.v ephedrine 6 mg boluses. The total amount of vasopressor required was also noted.

The percentage change in MAP and HR was calculated from the difference between the baseline and the lowest recorded values.

*% change in MAP* = (Baseline MAP-lowest recorded MAP)/Baseline MAP ×100.

*% change in HR* = (Baseline HR-lowest recorded HR)/Baseline HR ×100.

*Bradycardia* (HR<50 bpm) was treated with i.v. atropine 0.6 mg.

*Sample size*

The number of patients enrolled in our study were calculated prospectively. Assuming 80% incidence of hypotension in the untreated control group, a 30% reduction in incidence of hypotension in the control group was considered statistically significant.

*Sample Size Estimation Formula*

Sample Size calculated using the formula:

$$\frac{2\sigma^2 [Z_{\alpha} + Z_{(1-\beta)}]^2}{(m_1 - m_2)^2}$$

**Results**

*Statistical evaluation of data or parameters were done as follows:*

Data was analysed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test or Fischer's exact test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

*Graphical representation of data:* MS Excel and MS word was used to obtain various types of graphs such as bar diagram and line diagram.

*p value* (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

*Statistical software:* MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyse data.

A total of 60 patients were analysed with 30 patients in Group G who received intramuscular Glycopyrrolate pre-treatment and 30 patients in Group S who received saline (placebo).

Study subjects in both the groups were comparable to each other with respect to age, weight, height, body mass index and surgical duration as depicted in Table 1.

**Table 1:** Demographic data

	Group G		Group S		p Value
	Mean	SD	Mean	SD	
Age (yrs)	26.0	3.1	24.9	3.6	0.195
Weight (Kg)	70.8	11.2	65.8	10.4	0.080
Height (cms)	156.5	5.9	152.2	5.9	0.007*
BMI (Kg/m <sup>2</sup> )	28.9	4.0	28.4	3.8	0.604
Duration of surgery (minutes)	50.8	10.1	49.6	10.4	0.653

(Group G: Glycopyrrolate, Group S: Saline, SD - Standard deviation)

There was no clinically or statistically significant difference between both the groups regarding the level of subarachnoid block achieved as shown in Table 2.

**Table 2:** Level of block achieved comparison between two groups

		Group G (n=30)		Group S (n=30)	
		Count	%	Count	%
Level of Block	T4	17	56.7%	13	43.3%
	T5	8	26.7%	13	43.3%
	T6	5	16.7%	4	13.3%

( $\chi^2 = 1.835$ ,  $df = 2$ ,  $p = 0.400$ )

Patients in Glycopyrrolate group though had a 43.3% incidence of hypotension, this was very much less compared to saline group (73.3%). With a p value of 0.018, there was a statistically significant difference between both the groups with respect to incidence of hypotension as shown in Table 3.

**Table 3:** Incidence of Hypotension

		Group G (n=30)		Group S (n=30)		p value
		Count	%	Count	%	
Incidence of Hypotension	Yes	13	43.3%	22	73.3%	0.018*
	No	17	56.7%	8	26.7%	

Table 4. shows the severity of hypotension in both the groups. Median dose of Rescue Vasopressor used in Glycopyrrolate 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 (p value 0.008).

There was no statistically significant difference in incidence of complications such as bradycardia, tachycardia and reactive hypertension, percentage change in heart rate and mean arterial pressure, incidence of nausea and vomiting in both the groups (Tables 5,6,7).

**Table 4:** Total dose of Rescue Vasopressor Used comparison between two groups

Group		Total dose of Rescue Vasopressor Used					p value
		Mean	Standard Deviation	Median	Maximum	Minimum	
Glycopyrrolate		4.1	5.4	0	18	0	0.008*
	Saline	9.6	8.6	6	30	0	

**Table 5:** Comparison of complications between two groups

		Group G (n=30)		Group S (n=30)		p value
		Count	%	Count	%	
Bradycardia	Yes	1	3.3%	1	3.3%	1.000
	No	29	96.7%	29	96.7%	
Tachycardia	Yes	5	16.7%	7	23.3%	0.519
	No	25	83.3%	23	76.7%	
Reactive Hypertension	Yes	1	3.3%	0	0.0%	0.313
	No	29	96.7%	30	100.0%	
	No	17	56.7%	8	26.7%	

**Table 6:** Percentage change in MAP and Heart rate comparison between two groups

	Group G		Group S		p value
	Mean	SD	Mean	SD	
Percentage Change MAP	23.9	9.9	28.9	9.9	0.653
Percentage Change HR	12.6	8.7	17.1	11.7	0.055

(Group G: Glycopyrrolate, Group S: Saline, SD - Standard deviation)

**Table 7:** Nausea or Vomiting comparison between two groups

		Group G (n=30)		Group S (n=30)	
		Count	%	Count	%
Nausea or Vomiting	Absent	30	100.0%	27	90.0%
	Nausea	0	0.0%	2	6.7%
	Vomiting	0	0.0%	1	3.3%

( $\chi^2 = 3.158$ ,  $df = 2$ ,  $p = 0.206$ )

## Discussion

Post spinal hypotension is the most commonly encountered adverse effect of spinal anesthesia. It is of critical importance, especially so in obstetric scenario, as it can potentially cause decreased uterine perfusion and consequently endanger the unborn child [1].

Glycopyrrolate is a quaternary ammonium compound which is commonly used in anesthetic practice as an anti-sialagogue, to treat bradycardia (vagolytic action) and also is a part of reversal agent for neuromuscular blockade (antimuscarinic action). In a study conducted by Hwang J et al., glycopyrrolate proved to be a potent agent, when given prophylactically via intramuscular route, to prevent post spinal hypotension in elderly patients receiving spinal anesthesia for elective lower limb orthopedic surgeries [8].

Taking that study's findings into consideration and changing the study population, this prospective, randomized double blind study was undertaken to study the efficacy of prophylactic intramuscular glycopyrrolate as a potential preventive agent against spinal anesthesia induced hypotension in elective Cesarean sections.

In our study, the mean age, weight, Height and BMI were comparable between both the groups. Also, the surgical duration was more or less similar in both the groups.

The level of sympathetic block achieved after spinal anesthesia was statistically not significant between the two groups. Clinically it was obvious that higher level of block was achieved in more patients who received glycopyrrolate, thereby negating the probability that higher level of block could have influenced the incidence of hypotension. Based on these data, it can be inferred that both the groups, glycopyrrolate and saline, had similar patient characteristics, block characteristics and duration of surgery.

Thirteen out of thirty patients who received intramuscular glycopyrrolate 15 minutes prior to subarachnoid block developed hypotension. This constitutes to 43.3% incidence of hypotension in Glycopyrrolate group. On the contrary, 22 patients out of 30 patients who were in the control group, i.e. who received saline injection, had developed episodes of hypotension requiring treatment with vasopressors. This constitutes to an astonishing 73.3% incidence of hypotension in saline group. There was a clinically as well as statistically significant difference in the incidence

of hypotension between the two groups with a *p* value showing 0.018.

These results were quite similar to study done by Hwang J et al. in elderly population undergoing lower limb orthopedic surgeries under spinal anesthesia, which showed that Glycopyrrolate could minimize the incidence of hypotension when given prophylactically [8].

But there was a study done by Ure D et al., in which it has been observed that there was similar incidence of hypotension in both the groups but the severity of hypotension was less in glycopyrrolate group [12]. Similar observations were recorded in the studies done by Yentis et al. and Rucklidge et al., who concluded that there was statistically no significant difference in the incidence of hypotension with glycopyrrolate pretreatment in pregnant patients undergoing LSCS under spinal anaesthesia.

In our study, the Median dose of rescue vasopressor used for treatment of hypotensive episodes was used as surrogate marker for assessing the severity of hypotension. Lesser the vasopressor requirement, lesser the severity of hypotension. Mean dose of rescue vasopressor used in Glycopyrrolate group was  $4.1 \pm 5.4$  mg and  $9.6 \pm 8.6$  mg in saline group. Median dose used was calculated to be 0 mg in glycopyrrolate group versus 6 mg in saline group. This difference in total rescue vasopressors used between the two groups was statistically significant with a *p* value of 0.008. Our study results have reinforced the results of many previous studies that, prophylactic glycopyrrolate administration reduces the requirement of vasopressors after subarachnoid block, thereby reducing the severity of hypotension. Similar results were observed in study by Hwang J et al., though the study population was elderly [8]. Ure D et al. conducted their study in parturients and have concluded that the severity of hypotension was less in parturients who were administered prophylactic glycopyrrolate [12].

On the contrary, studies conducted by Yentis SM et al. and Rucklidge MW et al. showed that severity of hypotension, as assessed by requirement of ephedrine boluses, was similar in patients treated with Glycopyrrolate and saline [10,11].

A meta-analysis conducted by Selina D Patel et al., taking into consideration 5 Randomized control trials (RCTs), showed that though the reduction in the incidence of hypotension was not significant with pre-emptive glycopyrrolate treatment before subarachnoid block, there was a "modest reduction" in severity of hypotension

in patients who received glycopyrrolate. They suggested that larger study populations and further research is required to recommend routine prophylaxis with Glycopyrrolate [13].

One patient out of 30 patients (3.3%) who received intramuscular Glycopyrrolate had an episode of bradycardia. This patient was a 23-year-old female with gestational diabetes mellitus and gestational polyhydramnios, who developed sudden bradycardia immediately after turning the patient supine. It was promptly treated with i.v Atropine 0.6 mg. A probable diagnosis of aorticaval compression was made and immediate left lateral uterine tilt was given with Manual Left Uterine displacement, though a wedge was placed under patient's right hip as a standard practice [14].

These findings observed in our study were in contrast to a study conducted by Chamchad et al. who observed that prophylactic administration of Glycopyrrolate to parturients undergoing LSCS under spinal anesthesia had lower incidence of spinal anesthesia induced bradycardia when compared to placebo group [9].

None of the patients who received glycopyrrolate had any episodes of nausea and or vomiting. Two out of 30 patients (6.7%) in saline group complained of nausea alone and one patient (3.3%) had an episode of vomiting. Though the no. of patients who developed nausea and vomiting were less in number to conclude that glycopyrrolate was associated with lesser incidence of nausea and vomiting, results obtained from other studies have shown that Glycopyrrolate administration reduces the incidence and severity of peri operative nausea and vomiting in pregnant females undergoing lower segment cesarean sections under spinal anesthesia [15].

#### *Limitations of the study*

This was a small, single centered study. Further studies with larger study population can provide enough data to draw conclusions. Also, the timing of administration of i.m glycopyrrolate in emergency cesarean sections could be a problem considering the urgency to deliver the baby. One of the most common adverse effects of glycopyrrolate administration, that is dryness of mouth has not been evidenced in any of the patients in this study [16].

#### **Conclusion**

Pre-emptive use of intramuscular Glycopyrrolate causes lesser incidence and severity of hypotension

in parturients undergoing elective lower segment Cesarean sections under subarachnoid block.

As abrupt tachycardia was not observed when glycopyrrolate was administered through intramuscular route, it can be concluded that intramuscular glycopyrrolate provides stable heart rate than intravenous administration.

Prophylactic intramuscular Glycopyrrolate provides better hemodynamic stability after spinal anesthesia in parturients undergoing elective lower segment Cesarean sections, without any major adverse effects.

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#### **Key Messages**

Glycopyrrolate pretreatment helps in reducing the incidence and severity of hypotension following spinal anesthesia in parturients undergoing elective Cesarean sections, providing stable hemodynamics without any major adverse events. Intramuscular route reduces the incidence of abrupt tachycardia.

*Conflict of Interest:* Nil

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