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THE INFLUENCE OF PREMEDICATION WITH GLYCOPYRROLATE FOR SPINAL ANAESTHESIA IN PREGNANT WOMEN UNDERGOING ELECTIVE CAESAREAN SECTION

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ABSTRACT

BACKGROUND

Haemodynamic changes such as hypotension and bradycardia remain common complications associated with spinal anaesthesia in the obstetric population. If left untreated, spinal-induced hypotension and bradycardia can have detrimental effects for both mother and fetus, including maternal cardiovascular collapse and fetal acidosis. The use of glycopyrrolate for reducing haemodynamic changes after spinal anaesthesia for cesarean delivery has been investigated in multiple studies, which have shown conflicting results.

METHODS

This was a prospective observer-blinded, comparative study carried out over a period of 18 months involving 60 parturients. The study subjects were randomly allocated into 2 equal groups by simple random sampling using the shuffled closed sealed envelope technique, namely Group G & C. Group G received intravenous glycopyrrolate 0.2 mg (1 ml), while Group C received intravenous normal saline 1 ml. 0.5% hyperbaric bupivacaine was used for spinal anesthesia in both groups. Hemodynamic and block characteristics were recorded for each of the groups.

RESULTS
There was a statistically significant difference in mean pulse rate from 8 minutes to 20 minutes and at 30 minutes between the normal saline and glycopyrrolate groups ($p < 0.05\%$). Higher SBP, DBP, and MAP were seen 3 minutes and 5 minutes after induction of spinal anesthesia in the glycopyrrolate group ($p<0.05$). There was a statistically significant ($p<0.05$) difference in the total ephedrine used between the two groups. There was no significant difference in the incidence of intraoperative nausea, vomiting, and PONV. There was a significant difference in dryness of mouth in distribution between the two groups, being higher in the glycopyrrolate group ($p = 0.019$).

CONCLUSION
Pre-treatment with 0.2 mg of glycopyrrolate before administering spinal anaesthesia in pregnant women posted for elective caesarean sections decreases the incidence of hypotension before the extraction of the neonate. Glycopyrrolate also reduces the incidence of bradycardia and decreases the requirement of vasopressor, without any incidence of serious adverse side effects.

KEYWORDS: Glycopyrrolate, Spinal Anaesthesia Caesarean Sections.

INTRODUCTION

Spinal anaesthesia for CS conveys significant advantages over epidural anaesthesia as it is simple to use, with complete motor relaxation and faster onset, which allows regional anaesthesia in emergency cases, reducing the requirement for GA.[1] Traditionally, hyperbaric drugs are used for SA for CS—like hyperbaric 0.5% bupivacaine, as one can easily predict the movement of the drug in the CSF (Cerebrospinal Fluid). One of the problems with hyperbaric drugs is that they can produce very high blocks in pregnant women because of decreased volume and increased pressure of CSF, which is due to engorged epidural veins as a result of aortocaval compression.[2]

Haemodynamic changes such as hypotension and bradycardia remain common complications associated with spinal anaesthesia in the obstetric population.[3] Spinal-induced hypotension occurs due to a reduction in systemic vascular resistance,[4] with the effect being more pronounced in the obstetric population due to increased local anaesthetic sensitivity and aortocaval compression.[5] Bradycardia occurs with spinal anaesthesia for caesarean delivery due to sympathetic block, reduced venous return, and α-agonist vasopressor use. If left untreated, spinal-induced hypotension and bradycardia can have detrimental effects for both mother and fetus, including maternal cardiovascular collapse and foetal acidosis.[6,7]

Previous work has shown maternal heart rate and cardiac output to be strongly correlated; therefore, minimizing spinal-induced haemodynamic changes with anticholinergic drugs may be of interest.[5] Anticholinergics like atropine and glycopyrrolate are routinely used in anaesthesia for premedication. Atropine possesses a tertiary amine structure, allowing it to readily cross the blood-brain barrier and placenta. Glycopyrrolate, however, is an anticholinergic with a quaternary amine structure, thereby limiting its ability to cross these membranes and making it the popular choice for obstetric patients.[6]

The use of glycopyrrolate for reducing hemodynamic changes after spinal anaesthesia for cesarean delivery has been investigated in multiple studies, which have shown conflicting results. Hence, this study was conducted to determine the effect of using intravenous glycopyrrolate as a pre-medicant before administering spinal anaesthesia in pregnant women posted for elective cesarean section on the incidence of hypotension and the requirement of vasopressors. Unlike previous studies, this study included effects on both the mother and the new-born.

METHODS

This was a prospective observer-blinded, comparative study carried out over a period of 18 months involving 60 parturient belonging to American Society of Anaesthesiologists (ASA) Physical Status Class II, aged between 18 and 35 years, height 150 and 170 cm**,** body mass index < 28 kg/m2 with singleton pregnancy who were scheduled to undergo elective caesarean section under SAB (Subarachnoid Block) were included in the study. Those having contraindications to spinal anesthesia, i.e., consent refusal, local infection, allergy to local anaesthetics, bleeding disorders, spinal deformity, severe congenital or acquired heart disease, hemorrhage, or hypovolemic shock**;** parturients with complications of pregnancy like preeclampsia, gestational diabetes, placenta praevia, and those with known sensitivity to the study drugs were excluded from the study. The study subjects were randomly allocated into 2 equal groups by simple random sampling using the shuffled closed sealed envelope technique, namely Group G & C. Group G received intravenous glycopyrrolate 0.2 mg (1 ml), while Group C received intravenous normal saline 1 ml. 0.5% hyperbaric bupivacaine was used for spinal anaesthesia in both groups.

Sensory block was tested by the pinprick method using a blunt tip 25G needle. Motor block was studied using the modified Bromage scale (0 = no paralysis, 1 = unable to raise extended leg; able to bend knees, 2 = unable to bend knee, able to flex ankle, 3 = no movement).

The following parameters were observed:

1. Hypotension: Fall of blood pressure by 20% or fall below <90 mmHg SBP (Systolic Blood Pressure) was treated using Inj. Ephedrine 6 mg and the number of times administered and the total dose required were noted.
2. Bradycardia: It is defined as heart rate < 60/ min. It was treated with Inj. Atropine 0.6 mg.
3. Incidence of nausea and vomiting till 6 hours postoperatively.
4. Incidence of dryness of mouth.
5. Time for onset of sensory block: From the time of completing the administration of the drug into the subarachnoid space till the patient develops sensory block at T_{10}.
6. Maximum sensory block: Sensory block was checked every 1 min, till the attainment of maximum sensory block, which was noted.
7. Time for maximum sensory block: From the time of complete administration of drug into the subarachnoid space till the patient develops maximum sensory blockade.
8. Time for 2 segment regression: It is the time from the maximum sensory block to regression by 2 segments.
9. Duration of sensory block: From the time of loss of sensation till the patient complains of pain at the site of surgery.
10. Time for onset of motor blockade: From the time of complete administration of drug into the subarachnoid space till the patient develops Bromage scale I motor blockade.
11. Maximum motor block: From the time of complete administration of drug into the subarachnoid space till the patient develops Bromage scale 3 motor block.
12. Time for maximum level for motor block: From the time of complete administration of drug into the subarachnoid space till the patient develops maximum motor block.
13. Duration of motor block: From the time of complete administration of drug into the subarachnoid space till the patient develops Bromage scale 0 motor blockade.
14. APGAR score at 1 minute and 5 minutes.

Statistical Analysis

Data was entered into a Microsoft Excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. The chi-square test was used as a test of significance for qualitative data. Continuous data was represented as mean and standard deviation. An independent t-test was used as a test of significance to identify the mean difference between two quantitative variables.

RESULTS

In the present study, the mean age in the IV normal saline group was 26.47 ± 3.8 years, and the IV glycopyrrolate group was 26.2 ± 3.53 years. There was no statistically significant difference in age distribution between the two groups. There was no statistically significant difference in height, weight, and BMI distribution between the two groups.

In the present study, there was a statistically significant difference in mean pulse rate from 8 minutes to 20 minutes and at 30 minutes between the normal saline and glycopyrrolate groups ($p < 0.05\%$) with heart rate found to be higher in the glycopyrrolate group. The highest mean heart rate was found to be 115.57/min at a 5-minute interval after giving glycopyrrolate. Heart rate remains significantly higher in group G up to 20 minutes. At other intervals there was no significant difference in mean pulse rate between the two groups.

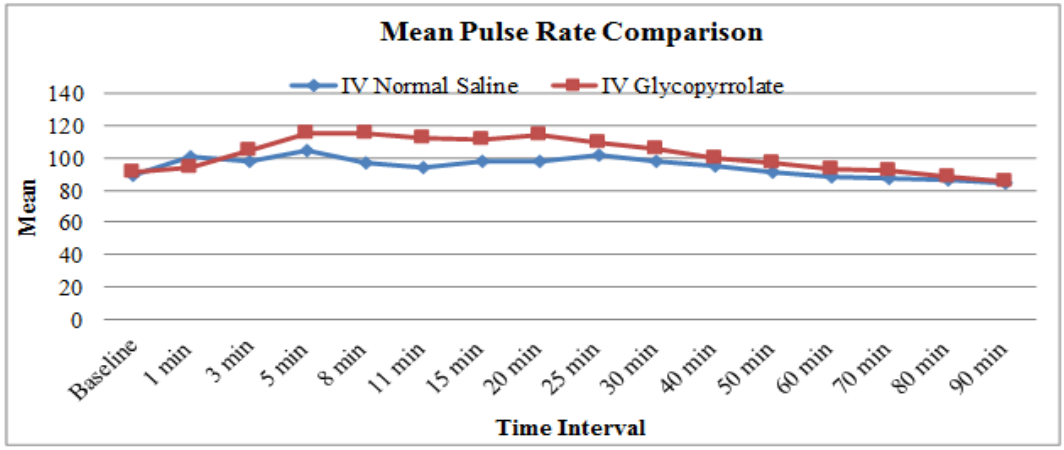

Figure 1: Line Diagram Showing Mean Pulse Rate Comparison between Two Groups at Different Time Intervals

There was no statistically significant difference in the incidence of bradycardia between the two groups at any intervals ($p>0.05$). None of the patients in the study had cardiac arrest.

In the present study, higher SBP was found in the glycopyrrolate group at 3-minute and 5-minute intervals post spinal anaesthesia induction. The lowest mean SBP was found in group C at the 5-minute interval. There was statistically significant difference in mean SBP at 3 minute and 5 minute between two groups ($p<0.05$). At other intervals there was no significant difference in mean SBP between the two groups.

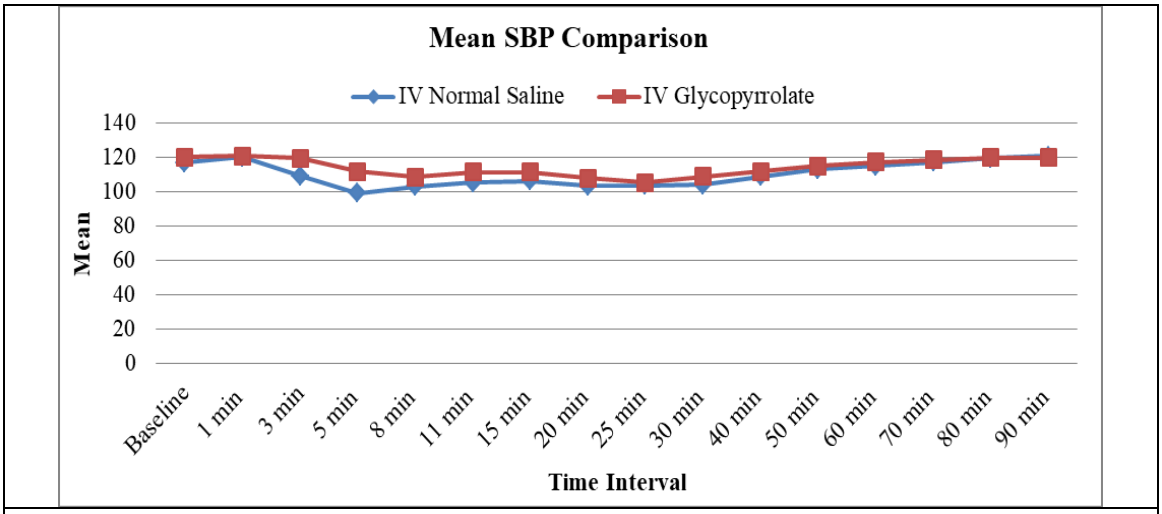

Figure 2: Line Diagram Showing Mean SBP Comparison between Two Groups at Different Time Intervals

In the present study, higher DBP was seen 3 minutes after induction of spinal anaesthesia in the glycopyrrolate group ($p<0.05$). There was a statistically significant difference in mean DBP at 3-minute intervals between the two groups. At other intervals, there was no significant difference in mean DBP between the two groups.

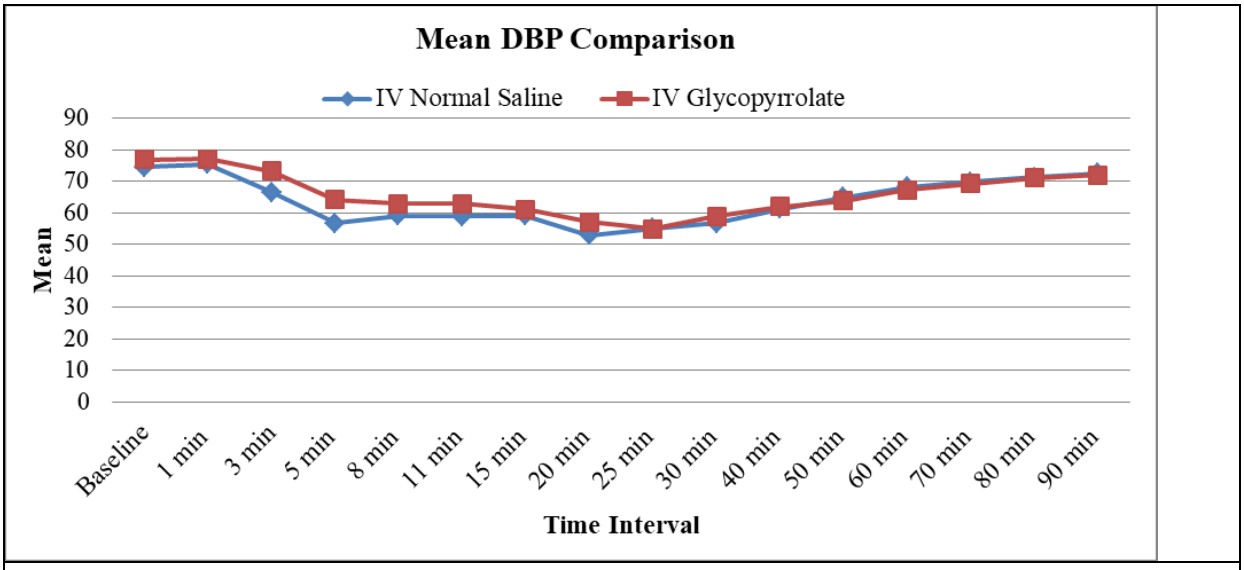

Figure 3: Bar Diagram Showing Mean DBP Comparison between Two Groups at Different Time Intervals

In the present study, there was a higher mean MAP of 88.71 and 80.09 in the glycopyrrolate group at 3-minute and 5-minute intervals, respectively, post spinal anaesthesia induction. Hence, there was a statistically significant difference ($p<0.05$) in mean MAP at 3 minutes and 5 minutes between the two groups. At other intervals there was no significant difference in mean MAP between the two groups.

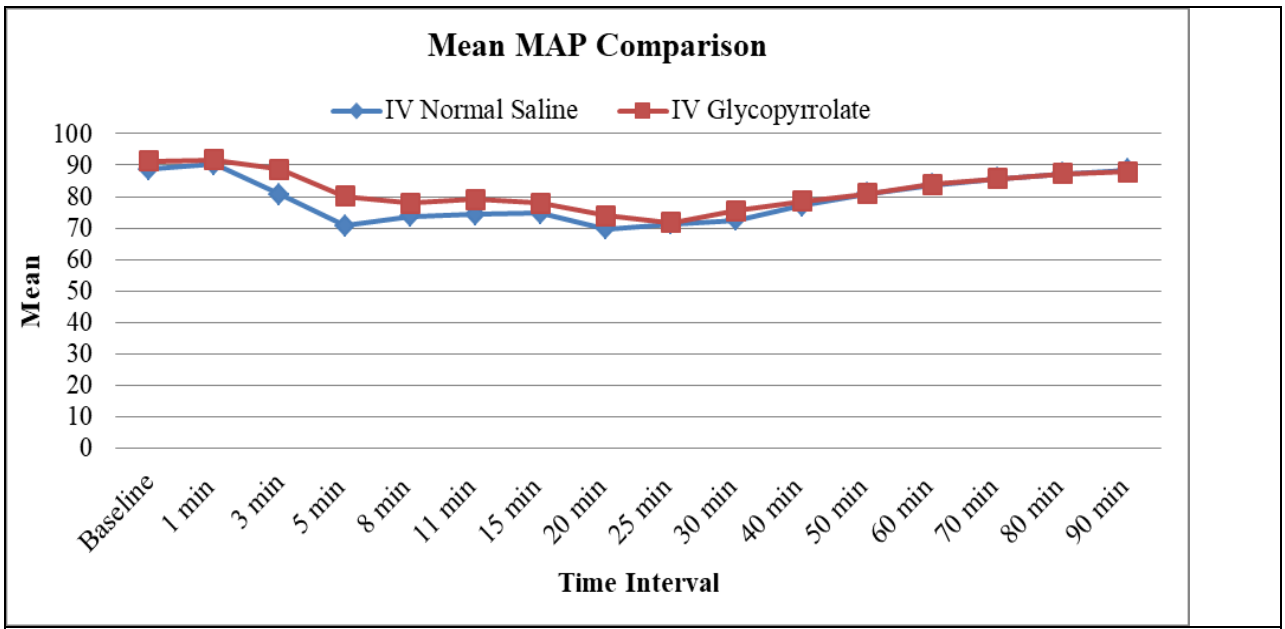

Figure 4: Line Diagram Showing Mean MAP (mm Hg) Comparison between Two Groups at Different Time Intervals

In the present study, there was hypotension in the IV normal saline group at 3 minutes, 5 minutes, and 20 minutes and 30-minute intervals. Hence, there was a statistically significant incidence of

hypotension in the normal saline group at 3-minute, 20-minute, and 30-minute intervals. At other intervals, there was no significant difference in the incidence of hypotension distribution between the two groups.

In the present study, the mean total ephedrine used in the IV normal saline group was 12.96 ± 5.66 mg, and the IV glycopyrrolate group was 8.7 ± 3.63 mg. There was a statistically significant ($p<0.05$) difference in the total ephedrine used between the two groups.

In the present study, the IV normal saline group had a 20% incidence of intraoperative nausea and vomiting, 10% had an incidence of PONV, and 13.33% had an incidence of dryness of mouth.

While in the IV glycopyrrolate group, 10% of subjects had an incidence of intraoperative nausea and vomiting, 3.33% had an incidence of PONV, and 40% had an incidence of dryness of mouth.

There was no significant difference in the incidence of intraoperative nausea, vomiting, and PONV. There was a significant difference in the dryness of mouth in distribution between the two groups, being higher in the glycopyrrolate group.

	Group					**Chi Square**
	IV Normal Saline		**IV Glycopyrrolate**			
	N	**%**	**N**		**%**	
Incidence of intra-operative nausea vomiting	Yes	6	20.00%	3	10.00%	p = 0.278
Incidence of PONV	Yes	3	10.00%	1	3.33%	p = 0.301
Incidence of dryness of mouth	Yes	4	13.33%	12	40.00%	p = 0.019*

Table 1: Incidence of Intra-Operative Nausea, Vomiting, PONV and Dryness of Mouth Distribution between Two Groups

In the present study, the mean time for the onset of sensory block in the IV normal saline group was 48.5 ± 18.11 seconds, and in the IV glycopyrrolate group, it was 53.67 ± 16.97 seconds. The mean time for the onset of sensory block in the IV normal saline group was 48.5 ± 18.11 seconds, and in the IV glycopyrrolate group, it was 53.67 ± 16.97 seconds. The mean duration of sensory block in the IV normal saline group was 155 ± 33.17 minutes, and in the IV glycopyrrolate group, it was 170.83 ± 28.83 minutes. The mean time for the onset of motor block in the IV normal saline group was 36.83 ± 12.63 seconds, and in the IV glycopyrrolate group, it was 40.17 ± 14.23 seconds. The mean time for maximum motor block in the IV normal saline group was 78.67 ± 17.76 seconds, and in the IV glycopyrrolate group, it was 84.17 ± 17.67 seconds. The mean duration of motor block in the IV normal saline group was 175.17 ± 33.82 minutes, and in the IV glycopyrrolate group, it was 190.83 ± 27.2 minutes. Thus, there was no statistically significant difference between the two groups with respect to the block characteristics.

In the present study, the mean time of delivery of the baby in IV normal saline was 6.83 ± 0.69 minutes, and in the IV glycopyrrolate group, it was 6.85 ± 0.63 minutes. There was no significant difference in time of delivery of baby (min) distribution between the two groups. The mean APGAR score at 1 min in the IV normal saline group was 7.87 ± 0.35, and in the IV glycopyrrolate group, it was 7.90 ± 0.31. The mean APGAR score at 5 min in IV normal saline group was 9.13 ± 0.35, and in the IV glycopyrrolate group, it was 9.13 ± 0.35. There was no significant difference in APGAR score at 1 and 5 minutes between the two groups.

	Group				**P-Value**
	IV Normal Saline		**IV Glycopyrrolate**		
	Mean	**SD**	**Mean**	**SD**	
Time for onset of sensory block (sec)	48.50	18.11	53.67	16.97	0.259
	Group				P-Value
	IV Normal Saline		IV Glycopyrrolate		
	Mean	SD	Mean	SD	
Time for maximum sensory block (sec)	96.83	23.87	101.50	20.56	0.420
	Group				P-Value
	IV Normal Saline		IV Glycopyrrolate		
	Mean	SD	Mean	SD	
Duration of sensory block (min)	155.00	33.17	170.83	28.83	0.053
	Group				P-Value
	IV Normal Saline		IV Glycopyrrolate		
	Mean	SD	Mean	SD	
Time for onset of motor block (sec)	36.83	12.63	40.17	14.23	0.341
	Group				P-Value
	IV Normal Saline		IV Glycopyrrolate		
	Mean	SD	Mean	SD	
Time for maximum motor block (sec)	78.67	17.76	84.17	17.67	0.234
	Group				P-Value
	IV Normal Saline		IV Glycopyrrolate		
	Mean	SD	Mean	SD	
Duration of motor block (min)	175.17	33.82	190.83	27.20	0.053

Table 2: Block Characteristics

DISCUSSION

Previous studies have shown maternal heart rate and cardiac output to be strongly correlated; therefore, minimizing spinal-induced hemodynamic changes with anticholinergic drugs may be of interest.[8,9] Since atropine crosses the placental barrier leading to foetal tachycardia, use of glycopyrrolate as pre-medicant maybe a better choice in prevention of spinal-anaesthesia induced hypotension in caesarean sections. Hence, our study was conducted to see if glycopyrrolate used as a pre-medicant has any advantage in reducing the incidence of spinal-induced hypotension by maintaining the maternal heart rate and also preventing spinal-induced maternal bradycardia.

All parturients in the two groups (n=60) were comparable with respect to age, gender, body weight, height, BMI, and duration of surgery. There was no statistical difference between the groups regarding the demographic criteria. The mean height of the parturients in group G was 158.77 cm and 159.37 cm in group C; hence, 2 ml of hyperbaric bupivacaine 0.5% was used for spinal anaesthesia in our study.

Effect on Haemodynamics

There was significantly higher mean SBP in the glycopyrrolate group in comparison to the control group at the 3rd minute (119.53 +/- 13 mmHg vs. 109.17 +/- 15.79 mmHg, respectively, p value = 0.007) and the 5th minute (111.87 +/- 20.78 mmHg vs. 99.07 +/- 19.23 mmHg, respectively, p value = 0.016). At other intervals there was no significant difference in mean SBP between the two groups. A similar observation was made by Ure D et al.,[8] and Biswas BN et al.,[9] where the authors found that the fall in SBP in the saline group was greater compared to the glycopyrrolate group before the extraction of the fetus. In contrast, in the study done by Quiney NF et al.,[10] the authors found an increased incidence of hypotension in the glycopyrrolate group immediately after giving spinal anaesthesia before uterine incision compared to the saline group, possibly because of the higher dose of 2.5 ml of hyperbaric bupivacaine used, unlike 2 ml in our study.

There was significantly higher mean DBP in group G in comparison to group C at the 3rd minute (73.30 +/- 10.23 mmHg vs. 66.47 +/- 13.18 mmHg, respectively, p value = 0.029). At other intervals there was no significant difference in mean DBP between the two groups. There was significantly higher MAP in group G in comparison to group C at 3rd minute (88.71+/-10.68 mmHg vs. 80.70+/-13.78 mmHg respectively, p value=0.015) and 5th minute (80.09+/-17.69 mmHg vs. 70.80+/-15.26 mmHg respectively, p value=0.033). At other intervals there was no significant difference in mean MAP between the two groups. However, in the study conducted by Rucklidge MWM et al.,[11] there was no statistically significant difference in the MAP in both groups, which does not compare with our study. However, the authors have not specified the readings of MAP at various time intervals. Their study was combined spinal-epidural anaesthesia for caesarean sections in women with relative bradycardia, unlike only spinal anaesthesia in our study.

In our study, there was a significantly higher incidence of hypotension seen in group C at the 3rd minute (group C-20%, group G-3.33% respectively, p value=0.04), 5th minute (group C-33.33%, group G-13.33% respectively, p=0.043), 20th minute (group C-30%, group G-6.67% respectively, p value=0.020), and 30th minute (group C-26.67, group G-6.67% respectively, p value=0.038) intervals compared to group G. At other intervals, there was no significant difference in the incidence of hypotension distribution between the two groups. Quiney N F et al.,[10] reported that in the glycopyrrolate group, there was a three-fold increase in the incidence of hypotension during the period until uterine incision, although there was no difference thereafter in both the groups. Yentis SM et al.,[12] also found a higher percentage of fall in blood pressure in both glycopyrrolate (35%) and saline (20%), with p value = 0.13. However, the sample size in both studies was very small for comparison. Maternal cardiac output and utero-placental blood flow are closely related, and glycopyrrolate will be advantageous in clinical situations where there is a compromise of utero-placental blood flow by maintaining the blood pressure.

In the present study, the mean total ephedrine used (mg) in the IV normal saline group was 12.96 ± 5.66 mg, and in the IV glycopyrrolate group was 8.7 ± 3.63 mg. There was a significant difference in total ephedrine used between the two groups with p value=0.006). Quiney NF et al.,[10] found a significantly lesser use of ephedrine in the glycopyrrolate group compared to the control group (39.7 mg +/- 15 vs. 61.5 mg +/- 23.3 respectively, p value=0.001), which is similar to our study. Ure D et al.,[8] also found that there was significantly lesser total ephedrine used in glycopyrrolate group (6 mg) compared with saline group (15 mg), p value=0.02 In contrast, studies conducted by Yentis SM et al.,[12] Rucklidge MWM et al.,[11] and Chamchad D et al.,[13] did not find any difference in the total ephedrine requirement in both groups. In the former two studies, a combined spinal epidural technique was used, and in the latter, glycopyrrolate 0.4 mg was used instead of 0.2 mg in our study.

In our study, there was a statistically significant difference in mean pulse rate at the 8th minute and 11th minute. 15th minute, 20th minute (p value ranging between 0.001-0.002), and 30th minute (p value=0.029) between group G and group C after administering spinal anaesthesia. Heart rate was found to be significantly higher in the glycopyrrolate group at these time intervals. At other intervals, there was no significant difference in mean pulse rate between the two groups. Ure D et al.,[8] Yentis SM et al.,[12] and Chamchad D et al.,[13] found that the glycopyrrolate group had a significantly higher increase in the intraoperative heart rate, which is similar to our observation. However, Rucklidge MWM et al.,[11] found no difference in the heart rate between the groups.

There was no significant difference in the incidence of bradycardia between the two groups at any interval. There were 2 patients with bradycardia at the 3rd minute and 11th minute, respectively, in group C who responded to treatment with inj atropine 0.6 mg IV. There was no incidence of bradycardia in group G. Jain R et al.,[14] found a significant increase in the incidence of bradycardia in the patients receiving saline compared to patients receiving glycopyrrolate (p value = 0.03). However, in their study, 2.5 ml of hyperbaric bupivacaine was used, unlike 2 ml in our study. Since maintenance of heart rate is important for maintaining the cardiac output, use of glycopyrrolate as a pre-medicant will maintain the cardiac output and in turn maintain the utero-placental perfusion. This was also shown by the study conducted by Yoon HJ et al.[15]

Incidence of Side Effects

Intra-operative nausea and vomiting was seen in 20% and 10% of the subjects in group C and group G, respectively (p value=0.278). PONV was seen in 10% and 3.33% of the subjects in group C and group G, respectively (p value = 0.301). There was no significant difference in the incidence of intraoperative nausea, vomiting, and PONV. Yentis SM et al.,[13] and Rucklidge MWM et al.,[14] found no difference in the incidence of nausea and vomiting between the subjects in the glycopyrrolate group and the saline group, which is similar to our study. Ure D et al.,[8] found that there were fewer episodes and lesser severity of nausea in the glycopyrrolate group, which is similar to our study, which found some reduction in the incidence of nausea, vomiting, and PONV, though it was statistically insignificant. Biswas BN et al.,[9] also found a significantly lower incidence of nausea and vomiting in the glycopyrrolate group.

There was 13.33% and 40% in the incidence of dryness of mouth in group C and group G, respectively (p value=0.001). Hence, there was a significantly higher incidence of dryness of mouth in patients receiving glycopyrrolate in group G. Yentis SM et al.,[12] and Jain R et al.,[14] also found that there was a significantly higher incidence of dryness of mouth in patients who received glycopyrrolate. Rucklidge MWM et al.,[11] found no difference in the dryness of the mouth among the groups, which could be attributed to the lower dose of glycopyrrolate (0.13 mg) used. Patel SD et al.,[16] in a meta-analysis, concluded that there is a significant increase in the incidence of dryness of mouth in glycopyrrolate groups, which is similar to our study.

Effect on New Born

In our study, the mean APGAR score at the 1st minute in group C was 7.87 ± 0.35, and in group G it was 7.90 ± 0.31 (p value = 0.694). There was no significant difference in APGAR score at 1 minute between the two groups. Similarly mean APGAR score at 5th minute in group C was 9.13 ± 0.35 and in group G was 9.13 ± 0.35 (p value=1). There was no significant difference in APGAR score at the 5th minute between the two groups**.** Ure D et al.,[8] found that there was no significant difference in APGAR score between the groups, which is similar to our study. Biswas BN et al.,[9] also found no difference between the groups.

Block Characteristics

The use of glycopyrrolate as a pre-medicant did not affect the block characteristics of spinal anaesthesia in the present study. Chamchad D et al.,[13] found that there was a 0.8 dermatomal difference with a higher ascent in the saline group, though not accompanied by increased hypotension. Ure D et al.,[8] found a similar time taken for sensory block in both groups, which is similar to our study.

CONCLUSIONS

Pre-treatment with 0.2 mg of glycopyrrolate before administering spinal anaesthesia in pregnant women posted for elective caesarean sections decreases the incidence of hypotension before the extraction of the neonate. Glycopyrrolate also reduces the incidence of bradycardia and decreases the requirement of vasopressor, without any incidence of serious adverse side effects.

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