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Original Article

Efficacy of Nalbuphine in Restraining Oxytocin-Induced Discomfort During Operative Delivery

Munnaza Andleeb, Ayisha Raja*, Fatima Sharif, Kaukab Majeed, Kaswar Sajjad Ansari***, Syeda Surayya Jabeen******

Department of Obstetrics and Gynecology, Combined Military Hospital, Quetta/National University of Medical Sciences (NUMS) Pakistan, *Department of Obstetrics and Gynecology, Combined Military Hospital, Milir/National University of Medical Sciences (NUMS) Pakistan, **Department of Anesthesia, Combined Military Hospital, Quetta/National University of Medical Sciences (NUMS) Pakistan, ***Department of Medicine, Combined Military Hospital, Quetta/National University of Medical Sciences (NUMS) Pakistan, ****Department of Obstetrics and Gynecology, Combined Military Hospital, Kohat/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To measure the intensity of pain caused by bolus of Oxytocin during cesarean delivery and efficacy of Nalbuphine to control it.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Obstetrics and Gynecology, Combined Military Hospital Quetta, Pakistan from May to October 2023.

Methodology: This Quasi-experimental study was conducted in CMH Quetta for a duration of six months (May-October 2023). The ethical board of hospital granted permission (ERC#CMH QTA-IERB/09/2023). Total 150 patients were included in the study after application of inclusion and exclusion criteria. Patients were divided into two groups marked as: Group-S (n=75) and Group-N (n=75). The Group-S patients did not receive Nalbuphine and Group-N patients received Nalbuphine. The primary outcome was frequency of side effects in both groups and secondary outcome was patient's satisfaction.

Results: The frequency of adverse effects in Group-S was higher than the Group-N patients. The most frequent side effect was chest pain with the frequency of 16(21.3%) in Group-S patients and 2(2.7%) in Group-N patients with p value of <0.001. The patient satisfaction was better in Group-N patients. The frequency of patient satisfaction was 72(96.0%) in Group-N patients and 47(62.7%) in Group-S patients with *p*-value <0.001.

Conclusion: Nalbuphine can mitigate discomfort due to Oxytocin bolus in parturient undergoing cesarean section under Centro-axial anesthesia.

Keywords: Anesthesia, Cesarean section, Nalbuphine, Spinal, Oxytocin.

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INTRODUCTION

Oxytocin is a neuropeptide synthesized in paraventricular hypothalamus and housed in posterior pituitary for release when required. It predominantly enhances contractions of uterus during labor and ejection of milk during lactation.[1] It has subtle anti-diuretic effect.[2] Since it is peptide in nature therefore it cannot be administered orally as gastric acidity and intestinal juices denature it. The preferred route of administration of synthetic Oxytocin is intravenous; however, its intramuscular and intranasal routes have been used effectively. Oxytocin has quick onset of action (two minutes) and short half-life (fifteen minutes) after intravenous administration. Syntocinon is synthetic preparation of Oxytocin which is widely available and extensively used as adjuvant to various obstetric procedures.[3] The commonly known side effects of Oxytocin are epigastric pain, vomiting, nausea, tachycardia, dyspnea, hypotension and headache.[4] The hemodynamic instability of Oxytocin is due to vasodilatation.[5] The intravenous boluses of high doses of Oxytocin (10 international units) have been associated with myocardial ischemia, right ventricular strain pattern, flushing and chest pain.[6]

Apart from the known side effects it is our observation that patients feel chest discomfort and tightness, shoulder/arm pain, suffocation and garlic taste after administration of Oxytocin. The intra-operative stress can consequently lead to post-partum depression in gravid ladies.[7] There are reports of post-traumatic stress disorder after cesarean delivery.[8] Thus, the side effects of Oxytocin can have lasting effects in scenario of operative delivery.

There is a local study by waseem,[9] *et al.*, which has compared bolus dose versus intravenous infusion of Oxytocin for prevention of epigastric pain associated with it. This study aimed to learn adverse

Correspondence: Dr Munnaza Andleeb, Department of Obstetrics and Gynecology, Combined Military Hospital, Quetta Pakistan
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effect profile of Oxytocin, counter discomfort associated with it and analyze the experience.

METHODOLOGY

This study was conducted in Combined Military Hospital Quetta, Pakistan. This Quasi-experimental study spanned over six months from May to October 2023. The ethical board of hospital granted permission study (ERC#CMH QTA-IERB/09/2023). The sample size calculation was done by keeping power of test 90%, significance level 7%, anticipated patient population who develop pain with Nalbuphine P1(2%),[10] and anticipated patient population who develop pain without Nalbuphine P2 (12%).[11] The sample size came out to be 135, so we included 150 patients in the study. The sample was collected by non-probability purposive sampling. The patients who met inclusion and exclusion criteria were included and after randomization patients were grouped together as Group-S (n=75) and Group-N (n=75) as shown in Figure.

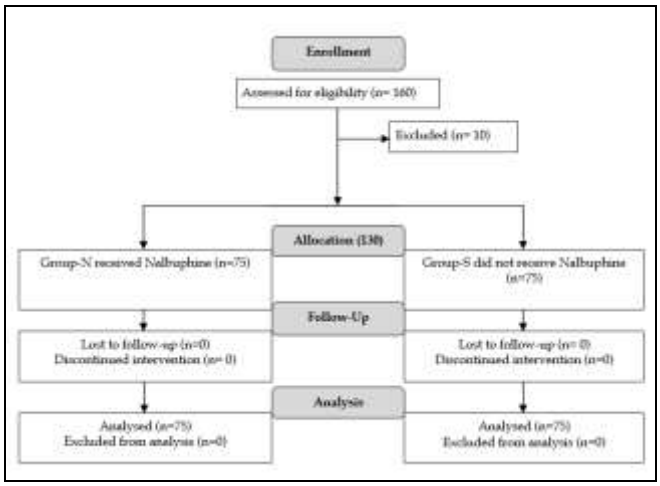

Figure: Phases of Study

Inclusion criteria: Parturients at term (36-40 weeks of gestation) with age limit from 20 years to 40 years having ASA physical status II undergoing cesarean section under spinal anesthesia were included.

Exclusion criteria: Following patients were excluded from the study : Parturients before term with ASA status III or IV who have gestational diabetes, hypertensive disorders, neuropsychiatric .disorders, Anemia (Hemoglobin<10), allergic to opioids, not wiling for spinal anesthesia, undergoing emergency cesarean section and have bled greater than 500ml during operative delivery were excluded.

Patients were grouped together after application of exclusion and inclusion criteria. The Informed consent was taken from all patients participating in the study and intention of study was explained to them. The groups were marked as: Group-S and Group-N. The Group-S patients did not receive Nalbuphine and Group-N patients received Nalbuphine.

Patients were examined thoroughly and then assessed in pre-anesthesia assessment clinic. On day of operation, all the patients were shifted to Operation Theater. Standard monitoring was attached and intravascular access was gained with 16 gauge intravenous cannula (B.Braun) in all patients. All patients were premedicated with injection Ondansetron (8mg) and Dexamethasone (8mg) and given standard spinal anesthesia in sitting position. The 1.5 milliliter volume of hyperbaric Bupivacaine (0.75%, Abocaine spinal, Hogwarth parmaceticals) was given at L3-L4 interspace with 27 gauge spinal needle (Quinke). After subarachnoid block, all patients were immediately laid supine with wedge under right hip. The lactated ringer with 1000ug of Phenylephrine was co-loaded after spinal and manually titrated to prevent spinal induced hypotension. The surgery was started after 5 minutes after having confirmed level of block (T4) and Bromage 113.

In Group-S patients 10 international units of injection Syntocinon (Syntomax) were given after delivery of anterior shoulder followed by slow intravenous infusion of 7 international units of Syntocinon per hour12. In Group-N patients 10 international units of Syntocinon were given after delivery of anterior shoulder. Injection Nalbuphine 0.75mg per kg was given immediately after clamping of the cord and it was followed by slow intravenous infusion of 7 international units of Syntocinon per hour12. Both Group-S and Group-N patients were observed for adverse effects after that. Following parameters were noted: Age, BMI, gestational age, parity, presence or absence chest pain, epigastric pain, shoulder pain, arm pain and headache. The record of other side effects along with post-operative patient's satisfaction was made. The primary outcome was frequency of side effects in both groups and secondary outcome was patient's satisfaction. The loss of sense of coldness to Ethyl chloride spray at T4 dermatome showed T4 level of spinal block. Unable to move knees and feet after spinal anesthesia signified Bromage 1 score. The painful event was recorded if the intensity

of pain was significant quantified with the help of visual analog score (VAS). A visual analog score of 4-10 was considered significant.

Data was recorded on Statistical Package of Social Science (SPSS) version 26. The frequency and percentage of adverse effects were recorded along with other qualitative variables. The mean and standard deviation was computed for quantitative variables. Chi square test (for qualitative variables), and independent samples t-test (for normally distributed quantitative data) were applied and p-value of ≤0.05 was considered as statistically significan.

RESULTS

The primary outcome was frequency of side effects in both groups and secondary outcome was patient's satisfaction The demographic profile of the study groups was similar with mean age of Group-S to be 27.80±5.18 years and 29.27±4.45 years in Group-N. The body mass index (BMI) was also comparable in parturients of both study groups with mean BMI of 28.60±2.89 Kg/m_2 in Group-N and 28.97±2.59Kg/m_2 in Group-S. The mean gestational age in Group-N was 37.92±1.11 weeks and 38.41±1.18 weeks in Group-S. There were 2(2.7%) primigravida in Group-N and 6 primigravida in Group-S. There were 17(22.7%) para one, 32(42.7%) para two, 15(20.0%) para three, 7(9.3%) para four and 2(2.7%) para five in Nalbuphine group. Similarly, there were 25(33.3%) para one, 25(33.3%) para two, 25(33.3%) para three and 4(5.3%) para four in group Syntocinon group. There was no para five in Syntocinon group. When compared with respect to age, BMI, Gestational age and parity in both groups was computed as 0.236, 0.887, 0.037 and 0.151respectively which shows that both groups had similar demographics as presented in Table-I.

The frequency adverse effects in Group-S were higher than the Group-N patients as shown in Table-II. The most frequent side effect was chest pain with the frequency of 16(21.3%) in Group-S patients and 2(2.7%) in Group-N patients with *p*-value of <0.001. The epigastric pain was 12(16.0%) in Group-S patients and 1(1.3%) on Group-N patients shoulder pain was 2(2.7%) in Group-S patients while none of Group-N patients developed shoulder pain (*p*-value<0.001). Arm pain, nausea/vomiting headache was not observed in any Group-N patients while their frequency was 2(2.7%), 1(1.3%) and 5(6.7) in Group-S patients with *p*-value0.248, 0.05 and 0.05 respectively.

2(2.7%) patients developed feeling of suffocation in both study groups (*p*-value 0.69). The frequency of hemodynamic instability was also analogous in both study groups with frequency of 2(2.7%) versus 3(4.0%) in Group-N versus Group-S (*p*-value <0.50).

Table-I: Adverse Effects of Oxytocin Bolus in Study Groups (n=150)

Adverse effect(s)		Group-N n=75 Frequency (%)	Group-S n=75 Frequency (%)	*p*-value
Chest Pain	Yes	2(2.7)	16(21.3)	<0.001
	No	73(97.3)	59(78.7)	
Epigastric Pain	Yes	1(1.3)	12(16.0)	<0.001
	No	74(98.7)	63(84)	
Shoulder Pain	Yes	0(0)	2(2.7)	<0.248
	No	75(100)	73(97.3)	
Arm Pain	Yes	0(0)	2(2.7)	<0.248
	No	75(100)	73(97.3)	
Nausea, Vomiting	Yes	0(0)	1(1.3)	<0.50
	No	75(100)	74(98.7)	
Suffocation	Yes	2(2.7)	2(2.7)	<0.69
	No	73(97.3)	73(97.3)	
Abnormal Taste Sensation	Yes	1(1.3)	2(2.7)	<0.50
	No	74(98.7)	73(97.3)	
Headache	Yes	0(0)	5(6.7)	<0.029
	No	75(100)	70(93.3)	
Hemodynamic Instability	Yes	2(2.7)	3(4.0)	<0.50
	No	73(97.3)	72(96.0)	

Table-II: Demographic Characteristics of Study Groups (n=150)

		Group-N n=75 Mean±SD	Group-S n=75 Mean±SD	*p*-value
Age (years)		29.27±4.45	27.80±5.18	0.236
BMI (Kg/m_2)		28.60±2.89	28.97±2.59	0.887
Gestational Age (weeks)		37.92±1.11	38.41±1.18	0.037
		Frequency (%)	Frequency (%)	
Parity	0	2(2.7)	6(8.0)	0.151
	1	17(22.7)	25(33.3)	
	2	32(42.7)	25(33.3)	
	3	15(20.0)	25(33.3)	
	4	7(9.3)	4(5.3)	
	5	2(2.7)	0(0)	

The patient satisfaction was better in Group-N patients. The frequency of patient satisfaction was 72(96.0%) in Group-N patients and 47(62.7%) in Group-S patients with *p*-value<0.001. Only 3(4.0%) patients showed dissatisfaction in Group-N. However, 28(37.3%) Group-S patients were dissatisfied with *p*-value <0.001 (Table-III).

Table-III: Patient Satisfaction (n=150)

	Group-N n=75 n (%)	Group-S n=75 n (%)	*p*-value
Satisfied	72(96.0%)	47(62.7%)	<0.001
Unsatisfied	3(4.0%)	28(37.3)	

DISCUSSION

The frequency of side effects was high (50.66%) in Group-S participants with chest discomfort to be the most frequent 16(21.3%) side effect and vomiting to be least frequent (1.33%). One patient started crying after injection Syntocinon and explained that pain was gripping along with chest heaviness. However, there were no associated electrocardiogram changes.

The inclusion and exclusion criteria were deliberated carefully to remove the possible confounding factors and prevent bias. The infusion of Phenylephrine was manually adjusted to prevent hypotension and bradycardia.[14] The hypotension and bradycardia also lead to nausea, vomiting and suffocation,[15] that's the reason why preclusion of hypotension and bradycardia was ensured in both group participants. However, any episode of hypotension after bolus of Syntocinon was attributed to Syntocinon bolus and recorded as side effect of Syntocinon. Ondansetron attenuates spinal hypotension and improves patient's hemodynamics,[16] when given as premedication for cesarean section.[17]

The gravity of adverse effects of Syntocinon on hemodynamic profile of gravid patients undergoing operative delivery was brought to attention when a patient developed profound hypotension which resulted in cardiac arrest.[18] keeping in view the above incidence, Bolton *et al*., recommended low dose (five international units) slow intravenous infusion of Syntocinon for cesarean in healthy patients. For gravid ladies with cardiac pathologies, they suggested to restrain the dose even further.[19] In our setup, relatively high dose of uterotonic drug is given. According our standing operating procedure, a dose of 10 international unit of Syntocinon in given to all patients. The timing of dosage is meticulously synchronized with clamping of cord and good communication between obstetrician and anesthesiologist is maintained at this step. The bolus dose is followed by maintenance infusion of Syntocinon in lactated Ringer at a rate of 7 international units per hour for 6 hours.

There is scarcity of local literature on optimal dosage of syntocinon. There is significant disparity between the dosage regime of national and international practices. Some international studies suggest 1 to 320 international units, and some suggest 5 units of Syntocinon to be optimal to exert its uterotonic effects. However, there is relatively constant adverse effect profile of Syntocinon even with smaller dose (5 units).[21]

Nalbuphine is synthetic opioid being used for analgesia for last forty years and it exhibits analgesic efficiency is equivalent to standard opioid morphine without causing overt respiratory depression.[22] Nalbuphine also attenuates hemodynamic response of gravid females under general anesthesia due to inherent cardiac stability.[22] The injection Nalbuphine immediately relieved pain (2.75 minutes) in our patients and they stopped complaining of pain and associated symptoms. There is no local or international study to support the use of Nalbuphine in gravid ladies undergoing surgery under Centro-axial anesthesia may be since little attention has been paid to Syntocinon related side effects. Schoppmann et recommended use of Nalbuphine for labor pain in gravid ladies who had brief second stage of labor.[23] We kept the dose of Nalbuphine low that is 0.07 milligram per kg as this dose of nalbuphine is not associated with respiratory depression or psychomimetic side effects.

Nalbuphine is mostly reserved for moderate to severe pain. The chest pain in parturients of our study groups was moderate to severe in nature which showed that Nalbuphine was a logical choice. The paucity of literature signifies the need of more studies on this subject. A single injection of nalbuphine was sufficient to relieve syntocinon induced pain which posed discomfort to a substantial number of our study participants. The patients who still complained of chest pain were those who felt uncomfortable soon after injection of Syntocinon. After nalbuphine they seemed comfortable with VAS<4. Therefore, it is safe to suggest that nalbuphine can be used to attenuate Syntocinon related side effects in patients and increase patient satisfaction.

LIMITATIONS OF STUDY

We used Nalbuphine as short acting opioids are not available in our setups. We might need to reconsider our protocols and practices of after availability of short acting opioids Fentanyl and Remi Fentanyl.

CONCLUSION

The findings of this study show that Nalbuphine can mitigate discomfort due to Oxytocin bolus in patients undergoing cesarean section under centro-axial anesthesia.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & AR: Conception, study design, drafting the manuscript, approval of the final version to be published.

FS & KM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

KSA & SSJ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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