TO DETERMINE EFFICACY OF GRANISETRON VERSUS PLACEBO FOR REDUCING SHIVERING IN PATIENTS UNDERGOING LOWER SEGMENT CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

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ABSTRACT

Objective: To determine the efficacy of granisetron versus placebo (saline) for reducing shivering in patients undergoing lower segment caeserian section under spinal anaesthesia.

Study Design: Comparative cross - sectional study.

Place and Duration of Study: Department of Anaesthesia, Combined Military Hospital Rawalpindi, from Apr to Sep 2019.

Methodology: Total 178 patients undergoing lower segment ceaserian section under spinal anaesthesia with age ranges from 18-40 years of American Society of Anaesthesiologists status I & II with full term pregnancy scheduled for elective caesarean section under spinal anaesthesia. Group A (n=92) received an intravenous bolus of 1 mg granisetron in a 10ml syringe and Group B (n=86) received intravenous bolus of normal saline in a 10ml syringe, drugs were administered immediately before spinal anaesthesia by anaesthetist as coded syringes. Heart rate, blood pressure, core body temperature and shivering scores were measured at 0 minutes, 30 minutes and 60 minutes, average surgery time recorded to be 60 minutes.

Results: None of the patients in group A (drug group) exhibited appreciable post spinal shivering whereas 25 (29%) in group B (placebo) had clinically significant shivering necessitated administration of other established pharmacological agents to abort shivering in order to ensure patient comfort and satisfaction with statistically significant *p*-value of <0.05.

Conclusion: Prophylactic injection granisetron was efficacious against post spinal shivering, moreover provides worth while relief of nausea and vomiting which is dilemma with most of the drugs employed for control of post spinal shivering.

Keywords: Caesarean section, Granisetron, Post spinalanaesthesia.

INTRODUCTION

Maintaining core body temperature during anaesthesia is a challenge for anaesthetist due to rapid heat loss, redistribution of body heat, effects of anaesthetic drugs and impairment of thermoregulation mechanisms by regional anaesthetic techniques. Shivering is an troublesome experience of the patient with undesirable physiologic phenomenon such as increased oxygen consumption, carbondioxide production, increased chances of myocardial ischemia, infection, bleeding, hypoxemia, lactic acidosis, increased intraocular pres-sure and intracranial pressure. Furthermore leads to misinterpretation of standard monitoring such as pulse oximetry, electrocardiography and noninvasive blood pressure thereby compromising patient management standards[1,2]. Temperature regulating mechanism is divided into three constituents, thermosensors and afferent neuronal pathway, integration of thermal inputs and effector pathways for autonomic and behavioural regulation. Nucleus raphe magnus in the medulla oblongata contains high proportion of serotonergic neurons which is part of afferent neuronal pathway and integration of thermal inputs led to hypothesis of our research concept. Serotonin (5-Hydroxytryptamine; 5-HT3), is a biological amine found in both brain and spinal cord as a major neurotransmitter. A sero-tonin 5-HT3 receptor antagonist inhibits reuptake of serotonin in the preoptic anterior hypothalamic region, which has impact on heat production and heat loss[3]. Granisetron is metabolized slowly by the liver, therefore have a longer average half life giving it advantage over odansetron, another 5-HT3 antagonist being trialed for prophylaxis of shivering after regional anaesthesia. Duration of action of granisetron is 4-9 hours eliminated by liver and kidneys. It is well tolerated drug with fewer side effects and drug interactions. It is free from sedative and extrapyramidal adverse effects[4,5].

Sussan *et al* compared granisetron with saline for prevention of shivering after regional anaesthesia in parturient undergoing caesarian section under regional anaesthesia. They reported reduced frequency of post spinal shivering in granisetron group (8%) versus the saline group (54%); *p*-value <0.05[6].

Our research was based on fact that 5-HT3 receptor antagonists have significant role in preventing post spinal shivering on account of studies conducted on various drugs of this group[7-10]. Our secondary objec-

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tive was to evaluate the efficacy in control of nausea and vomiting, in addition to determine any significant effects on parturient hemodynamic status and neonate by assessing neonatal APGAR score at 1 min and 5 min after birth.

METHODOLOGY

After approval of ethics review committee (1A/04/19) of the Combined Military Hospital Rawalpindi, consent was obtained after explaining the risks and benefits to the patients. This comparative cross - sectional study was conducted at department of Anaesthesia, Combined Military Hospital Rawalpindi, from Apr to Sep 2019.

The sample size was calculated by using WHO sample size calculator. The total sample size of study was 116, by keeping level of significance 95% confidence interva l,5% error and anticipated (prevalence) frequency 8.15% was determined using 2016 study by Stone *et al*[11] but we included 178 patients to further decrease chances of bias and increase authenticity of study. All patients undergoing lower segment ceaserian section under spinal anaesthesia with age ranges from 18-40 years of ASA I & II status with full term pregnancyscheduled for elective caesarean section under regional anaesthesia, haemodynamically stable with no known co morbidswere recruited. Parturient having contraindication to regional anaesthesia, BMI> 35 kg/m^2, antepartum haemorrhage, pregnancy induced hypertension, preeclampsia, placenta previa, laboring patients were excluded from the study.

Patients were randomly allocated in two groups (group A and group B). As per study protocol, all the patients were interviewed, briefed, counseled about the procedure and informed written consent was taken. Before reporting to operation theatre, a detailed preanaesthesia assessment was carried out in all patients with necessary laboratory evaluation parameters in order to adhere with our inclusion and exclusion criteria, in addition ensure patient safety which is high priority of anaesthetic management.

On the day of surgery parturient were brought to operation theater and before initiating spinal anaesthesia standard monitoring such as pulse oximeter, non invasive blood pressure and electrocardiography via electrodes were attached and 18G IV cannula was passed under aseptic conditions. Parturient were preloaded with warm (24-26°C) 1000ml of Ringer's Lactate. Operationg room temperature was maintained at (24 -26°C) with 60% humidity. Randomization protocol was followed for drug preparation and was administered by one of the anaesthetistin form of coded syringes. Group A received 1mg intravenous bolus of granisetron prepared in 10ml of 0.9% normal saline whereas group B received 10 ml intravenous bolus of normal saline. Spinal anaesthesia was performed on patient in sitting position at L3-L4 or L4-L5 interspace after sterilization and drape, 25 G Quincke and Pencil Point needle was used, 8-10 mg of 0.5% hyperbaric bupivacaine was injected over a minute followed by positioning patient supine and placing wedge under right hip to ensure left uterine displacement. T4 sensory level block was confirmed with ethyl chloride spary and motor block was confirmed with bromage scale (0 = no block, 1 = hip block, 2 = hip and knee block, 3=hip, knee and ankle block). Patient's hemodynamic status and tympanic membrane temperature with infrared tympanic thermometer was measured at 0 minute, 30 minutes and 60 minutes. 0 min was considered at point of drug administration and average surgery time documented was 60 minutes. Patient shivering score was assessed by using validated five point scale (table-I)[12].

APGAR score (table-II) was measured at 1 minute and 5 minutes after birth which remained between 7-10 which is considered essentially normal[13].

Table-I: Patient shivering score.

Score	Definition
0	No shivering
1	Piloerection or peripheral vasoconstriction but no visible shivering
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group but not generalized
4	Shivering involving the whole body

Table-II: Neonatal APGAR Score.

Sign	0	1	2
Heart Rate	Absent	<100 beats /min	>100 beats /min
Respiratory Effort	Absent	Slow, Irregular	Good, Crying
Muscle Tone	Limp	Some Flexion of Extremities	Active Motion
Reflex Irritability	No Response	Grimace	Cough, Sneeze, or Cry
Color	Pale, Blue	Body Pink, Extremities blue	Completely Pink

Data was analysed by using SPSS-23. Frequency and percentage were calculated for qualitative data. Mean ± SD was calculated for continuous variables. Independent sample t-test and chi square test were

applied for comparison of group A and group B as required. A *p*-value ≤0.05 was considered as significant.

RESULTS

A total of 178 females were included of ASA status I & II (table-IV), mean age of patients was 28.76 ± 4.67 years range from 18-40 years. Data was divided in to two groups group A (drug group) and group B (Placebo), 92 (51.7%) patients was in group A and 86 (48.3%) in group B). Mean age of group A was 28.77 ± 4.50 and group B was 28.74 ± 4.88 (*p*=0.969). Mean time duration was 61.91 ± 5.55 minutes in group A and in group B was 62.21 ± 5.17 minutes (*p*=0.488). Mean heart rate at 0 minute was 103.44 ± 17.97, in group A was 106.87 ± 20.166 and in group B was 99.77 ± 14.515 (*p*=0.007). Mean of heart rate at 30 minutes was 95.52 ± 13.47, in group A was 95.43 ± 13.937 and group B was 95.62 ± 13.046 (*p*=0.929). Mean of heart rate at 60 minutes was 89.28 ± 12.14, mean of group A was 87.48 ± 9.383 and in group B was 91.21 ± 14.34 (*p*=0.04). Mean tympanic membrane temperature at 0 minutes, 30 minutes and 60 minutes was 37.783 ± 0.41, 37.65 ± 0.53 and 37.40 ± 0.55 respectively. In group A the mean tympanic membrane temperature at 0 minutes, 30 minutes and 60 minutes was 37.724 ± 0.36, 37.778 ± 0.47 and 37.546 ± 0.49 respectively and in group B mean of tympanic membrane temp at 0 minutes, 30 minutes and 60 minutes was 37.845 ± 0.464, 37.524 ± 0.56, 37.524 ± 0.56 and there *p*-values were 0.051, 0.001 and 0.001 respectively. Mean of shivering score at 0 minute of group A was 0.91 ± 0.58 and group B was 0.71 ± 0.65 (*p*=0.029), mean of shivering score at 30 minutes of group A was 0.13 ± 0.03 and in group B was 0.94 ± 0.62 (*p*=0.001), mean of shivering score at 60 minutes of group A was 0.2 ± 0.14 and in group B was 1.31 ± 1.21 (*p*=0.001). Shivering score was higher in group B and was statically significant as depicted in (table-III & fig-1). 29.06% (n=25) patients in Group B were given Inj Tramadol Hydrochloride in order to relieve significant shivering whereas none of the parturient augmented with any other pharmacological therapy for shivering prophylaxis. Systolic and diastolic blood pressure was higher in group B at 30 minutes interpreting a signficant statistical difference.

Table-III: Comparison of monitored parameters among group A (Granisetron) & group B (Placebo).

	Group A (n=92)	Group B (n=86)	*p*-value
Age	28.77 ± 4.50	28.74 ± 4.88	0.969
Time duration	61.63 ± 5.88	62.21 ± 5.17	0.488
Heart Rateat 0 minute	106.87 ± 20.166	99.77 ± 14.515	0.007
Heart Rate at 30 minutes	95.43 ± 13.937	95.62 ± 13.046	0.929
Heart Rate at 60 minutes	87.48 ± 9.383	91.21 ± 14.34	0.04
Tympanic membrane temperature at 0 minute	37.724 ± 0.36	37.845 ± 0.464	0.051
Tympanic membrane temperature at 30 minutes	37.778 ± 0.47	37.524 ± 0.56	0.001
Tympanic membrane temperature at 60 minutes	37.546 ± 0.49	37.524 ± 0.56	0.001
Shivering score at 0 minute	0.91 ± 0.58	0.71 ± 0.65	0.029
Shivering score at 30 minutes	0.13 ± 0.03	0.94 ±0.62	0.001
Shivering score at 60 minutes	0.2 ± 0.14	1.31 ± 1.21	0.001
Systolic BP at 0 minute	128.33 ± 15.93	129.08 ± 12.48	0.726
Diastolic BP at 0 minute	78.08 ± 13.11	77.24 ± 10.18	0.634
Systolic BP at 30 minutes	113 ± 14.20	118.26 ± 13.94	0.013
Diastolic BP at 30 minutes	65 ± 12.06	69.06 ± 9.84	0.015
Systolic BP at 60 minutes	110.15 ± 13.47	112.67 ± 8.5	0.140
Diastolic BP at 60 minutes	62.94 ± 12.71	64.26 ± 5.84	0.379

(Table-III & fig-1) Incidence of nausea and vomiting recorded to be 9 (10.46%) in group B requiring emesis mangement.

Table IV: Distribution of patients according to ASA status (n=178).

ASA	Group A (n=92)	Group B (n=86)	Total (n=178)
	n (%)	n (%)	n (%)
I	72 (78.3)	72 (83.7)	144 (80.89)
II	20 (21.7)	14 (16.3)	34 (19.10)

DISCUSSION

Data analysis of research interpreted statistically significant efficacy of granisetron in management of shivering encountered after commencement of regional anaesthesia, moreover provided an added benefit of prevention from nausea and vomiting was achieved. There was no incidence of shivering in granisetron group however 25 (29%) patients in placebo (normal saline) group required administration of 50 mg intra-

venous bolus of tramadol hydrochloride for effective control of shivering and 9 (10.4%) patients presented with complaint of nausea and vomiting which was treated with 10 mg intravenous bolus of metoclopramide[14,15].

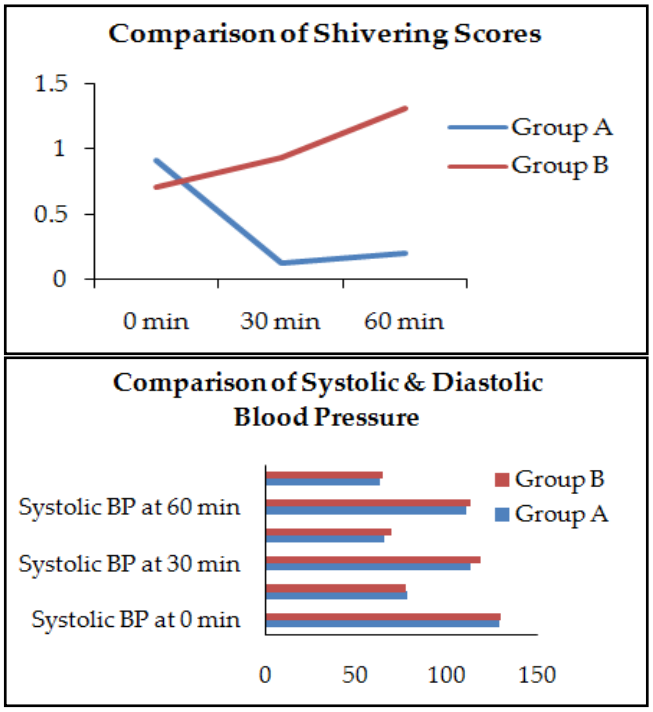

Figure: Trends of shivering scores & blood pressure in group A (n=92) and group B (n=86).

Zhou *et al* conducted a meta – analysis that included 14 randomized controlled trials that demonstrated significant efficacy of 5-HT3 receptor antagonists in control of shivering after regional anaesthesia in comparison to placebo[16]. Moreover potency was comparable to meperidine with added advantage of prevention of nausea, vomiting and lack of respiratory depression which is a major concern with meperidine administration[17]. Sajedi *et al* illustrated that granisetron is as beneficial as tramadol hydrochloride in preventing post operative shivering in patients undergoing elective orthopedic surgery under general anaesthesia but tramadol has troublesome effects of nausea, vomiting and dizziness resultantly lead to less patient satisfaction and delay in early ambulation[18].

Sagir *et al* compared prophylactic ketamine and granisetron for control of shivering during regional anaesthesia but hallucinations associated with ketamine limits its use in parturient[19]. Aldaba and Amir in there study demonstrated that 1mg intravenous bolus of granisetron attenuated decrease in systolic and diastolic blood pressure which is evident after spinal block, these findings are consistent with our study as systolic and diastolic blood pressure was higher in group B at 30 minutes of analysis and difference was statistically significant[20].

Therefore, peculiar thing about our research project was that a single agent is cure for nausea, vomiting and shivering after regional anaesthesia all of which are concerns for an anaesthetist in parturient management and satisfaction undergoing caesarean section under regional anaesthesia.

LIMITATION OF STUDY

Our study had limitation that it was not multicentred as procurement of drug was difficult due to cost and limited availability. Moreover shivering grade was assessed subjectively on basis of shivering grades only which could have led to inaccurate human perception.

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CONCLUSION

Prophylactic administration of granisetron 1mg intravenously effectively prevents shivering in parturient undergoing lower segment caesarean section, furthermore provides beneficial relief of nausea and vomiting which is dilemma with most of the drugs employed for control of post spinal shivering and parturient undergoing caesarean section. Another advantage of granisetron is availability of sustained release formulations in form of FDA approved transdermal patches which can provide relief from metabolic over burden due shivering manifested after regional anaesthesia, nausea and vomiting for longer period post operatively.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Kabade DS, Venkatesh, Karthik, Kumar. Comparative study of granisetron versus pethidine for the prevention of perioperative shivering under spinal Anesthesia. Karnataka Anesthesia J 2016; 2(1): 14-18.
2. Sun J, Zheng Z, Li Y, Zou L, Li G, Wang X, et al. Nalbuphine versus dexmedetomidine for treatment of combined spinal-epidural post-anesthetic shivering in pregnant women undergoing cesarean section. J Intl Med Res 2019; 47(9): 4442-53.
3. Block M, Sinner B, Gottlicher M, Simon E, Martin E, Motsch J. Involvement of serotonergic pathways in postanesthetic cold

defence: Dolasetron prevent shivering. J Thermal Biol 2002; 27(2): 159-66
4. Abdel-Ghaffar HS, Moeen SM. Prophylactic granisetron for post-spinal anesthesia shivering in cesarean section: A randomized controlled clinical study. Acta Anaesthesiol Scand 2018; 63(3): 381-88.
5. Joshi SS, Atora A, George. Comparison of Intravenous butarphanol, odansetron and tramadol for shivering during regional anaesthesia: A propspective randomized double – blind study. Anaesth Pain Inten Care 2013; 17(1): 33-39.
6. Mohammadi SS, Jabbarzadeh, Movafegh. Efficacy of granisetron on prevention of shivering, nausea and vomiting during cesarean delivery under spinal anesthesia: A randomized double-blinded clinical trial. J Obs Anaesth Crit Care 2015; 5(1): 22-26.
7. Varshney KR, Garg, Kapoor, Jheetay S. The role of ramosetron in the prevention of post-spinal shivering in obstetric patients. A prospective randomized double blind study. Romanian J Anaesth Inten Care 2019; 26(1): 37-43.
8. Kim MS, Kim DW, Woo SH, Yon JH, Lee S. Effect of ramosetron on shivering during spinal anaesthesia. Korean J Anesthesiol 2010; 58(3): 256-59.
9. Nallam SR, Cherukuru K, Sateesh G. Efficacy of intravenous ondansetron for prevention of post-spinal shivering during lower segment cesarean section: a double-blinded randomized trial. Anesth Essays Res 2017; 11(2): 508–13.
10. Shin HJ, Choi ES, Lee GW, DO SH. Effects of preoperative serotonin-receptor-antagonist administration in spinal anesthesia-induced hypotension: a randomized, double-blind comparison study of ramosetronand ondansetron. Reg Anesth Pain Med 2015; 40(5): 583-88.
11. Luggya ST, Kabuye NR, Mijumbi C, Tindimwebwa BJ, Kintu A. (2016) Prevalence, associated factors and treatment of post spinal shivering in a Sub-Saharan tertiary hospital: a prospective observational study. BMC Anesthesiol 2016; 16(1): 100.
12. Jain A, Gray, Slisz, Haymore, Badjatia, Kulstad. Shivering treatments for targeted temperature management: a review. J Neuro Sci Nurs 2017; 50(2): 63-67.
13. Kliegman MR. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier 2016; (94): 794-98.
14. Mishriky MB, Habib S. Metoclopramide for nausea and vomiting prophylaxis during and after Caesarean delivery: a systematic review and meta-analysis. Br J Anaesth 2012; 108(3): 374–83.
15. Vyas V, Gupta R, Dubey P. Comparative efficacy and safety of intravenous clonidine and tramadol for control of postspinal anesthesia shivering. Anesth Essays Res 2018; 12(3): 663-68.
16. Zhou C, Zhu Y, Bao Z, Wang X, Liu Q. Efficacy of ondansetron for spinal anesthesia during cesarean section: a meta-analysis of randomized trials. J Int Med Res 2018; 46(2): 654–62.
17. Jayaraj A, Balachander, Kuppusamy K, Arusamy Rai, Siddiqui. Comparison of meperidine, tramadol and fentanyl for post-spinal shivering prevention during cesarean delivery: A double-blind randomized controlled trial. J Obs Gyna Res 2019; 45(11): 2202-08.
18. Sajedi P, Moseli A, Efficacy of Granisetron in Preventing Post anesthetic Shivering. Acta Anaesth Taiwanica 2008; 46(4): 166-70.
19. Sagir O, Gulhas, Toprak, Yucel. Control of shive-ring during regional anaesthesia: prophylactic ketamine and granisetron. Acta Anaesthesiologica Scandinavica, 2006; 51(1): 44-49.
20. Aldaba AA, Amir MY. Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: A double-blind, prospective randomized controlled study. J Anaesthesiol Clin Pharmacol 2015; 31(3): 329-32.