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A Prospective, Randomised, Comparative, Study of Oral Gabapentin, Theophylline and Caffeine in The Treatment of Post Dural Puncture Headache In Patient of LSCS Under Spinal Anaesthesia

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Abstract

Aim and objectives: To evaluate the effect of oral Gabapentin, Theophylline and Caffeine in the treatment of post dural puncture headache in patient of lower segment caesarian section under spinal anesthesia.

Materials and Methods: One hundred twenty ASA grade I and II patients with PDPH, who were undergone elective and emergency lower segment caesarean section under spinal anesthesia were studied in the Department of Anaesthesiology, S.S Medical College Rewa (M.P.) from December 2015 to Oct. 2017. The patients were divided into Group G (n=30, were given Tab Gabapentin 300 mg BD orally), Group T (n=30, were given Tab Theophylline 250 mg BD orally), Group C (n=30, were given Tab Caffeine 300 mg BD orally) and Group P (n=30, were given placebo Tab B-complex BD orally). VAS score for severity of headache were observed and recorded before the administration of drugs and after the administration of drugs at 6, 12, 24, 48 and 72 hours.

Result: Gabapentin, Theophylline and Caffeine were effective in relieving the PDPH in patients of LSCS done under spinal anaesthesia. No significant effects on haemodynamic parameters were observed with all the study drugs. Recurrence of PDPH was significantly high with caffeine treatment. No serious untoward effects or complications of study drugs were observed in the study.

Conclusion: The study conclude that Gabapentin, Theophylline and Caffeine were effective in relieving the PDPH in patients of LSCS done under spinal anaesthesia and recurrence of PDPH was significantly high with caffeine treatment.

Keywords: PDPH, Spinal anaesthesia, Gabapentin, Theophylline, caffeine and VAS score.

Introduction

Childbirth is life changing experience for a mother. It is associated with profound physical, social and psychological effects on her. The increasing use of regional technique for labour analgesia and operative delivery is associated with post dural puncture headaches (PDPH).[1]

Post dural puncture headache described as severe, 'searing and spreading like hot metal' distributed over the frontal and occipital areas radiating to neck and shoulders. Other symptoms include nausea, vomiting, hearing loss, tinnitus, vertigo, dizziness, paraesthesia over the scalp, upper and lower limb pain, visual

disturbances and cranial nerves palsies. Pain is exacerbated by head movement and more in upright posture and relieved by lying down. An increase in severity of headache on standing is the hallmark of PDPH[2].

PDPH is thought to be caused by CSF leakage through the dural puncture at greater rate than its production leading to a fall in CSF pressure [3].This causes headache by 2 mechanisms. One is the sagging of the intracranial structures in the upright position; with traction on the meanings, cranial nerves and upper cervical nerves causing frontal occipital and cervical pain. The second mechanism is compensatory vasodilation in response to the low intracranial pressure which again causes headache[4].The upright position worsens the headache by further decreasing the intracranial pressure and also by increasing the rate of loss of CSF through the dural puncture.

Gabapentin, a structural analogue of gamma amino butyric acid (GABA) is an antiepileptic drug and is widely used as a medication to relieve pain, especially neuropathic pain. It does not bind with plasma protein and is not metabolized in humans. After a single oral dose of 300 mg, mean maximum plasma concentration is attained in 2-3 hrs [5].

Theophyllinea methylxanthine derivative having phosphodiesterase inhibiting activity leading to the relaxation of bronchial smooth muscles (bronchodilation) as well as cerebral vasoconstriction. Vasoconstriction through blocking of adenosine receptor along with induction of CSF production by stimulating Na^+-K^+ Pumps are the mechanism of relief in PDPH.[6]

Caffeine is a central nervous system stimulant that amongst other properties produces cerebral vasoconstriction. It is available in an oral and i.v. form. The oral form is well absorbed with peak levels reached in 30 min. Caffeine crosses blood- brain barrier and the long half-life of 3-7.5 allows for infrequent dosing schedules. The dose now recommended for the treatment of PDPH is 300-500 mg of oral or i.v. caffeine once or twice daily.

Caffeine may relieve PDPH because of its ability to increase cerebral vascular resistance, decrease cerebral CBF, and decrease cerebral blood volume.[7]

The aim of this study is to evaluate the effect of oral Gabapentin, Theophylline and Caffeine in the treatment of post dural puncture headache in patient of lower segment caesarian section under spinal anesthesia.

Material And Method

120 patients of ASA grade I &II scheduled for elective and emergency lower segment caesarean section under spinal anesthesia in the Department of Anesthesiology, S.S Medical College Rewa(M.P.) after getting written informed consent from the patients. The enrollment of patients were done in between Dec. 2015 to Oct. 2017. The patients were enrolled based on following:

Inclusion Criteria

1. Elective and emergency LSCS.
2. Patient of ASA grade I & II.
3. Patient of age group 18-40 years, pregnant female, undergoing elective or emergency lower segment caesarean section, under spinal anesthesia.

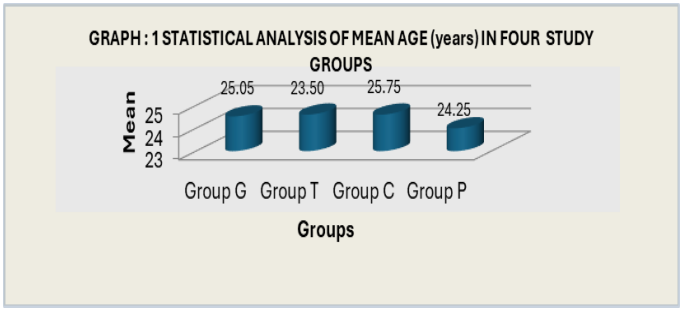
Statistical Analysis

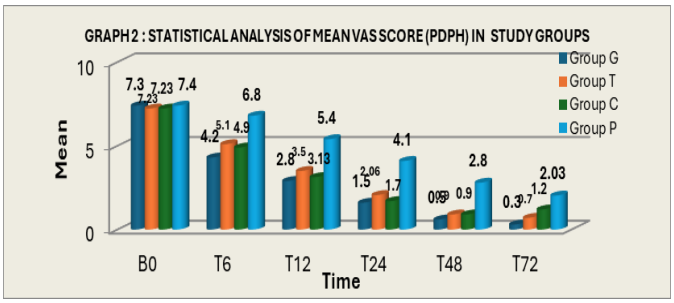
The observations recorded in all the groups were tabulated and statistical analysis was carried out by using appropriate statistical software SPSS 17. Student ‘t' test for inter group comparison was used.P-value >0.05 was taken to be statistically insignificant & P-value <0.05 was taken as statistically significant whereas P-value <0.01 taken to be statistically highly significant.

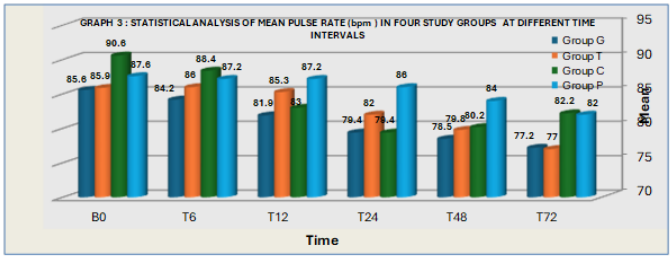
Observations And Results

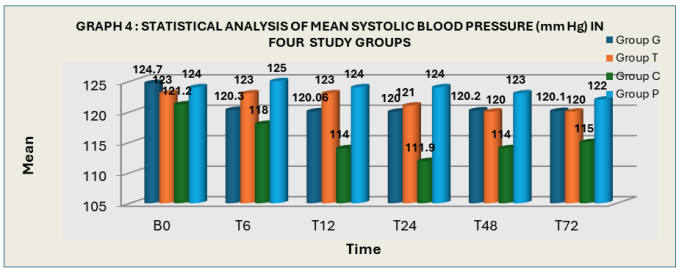
Table 1: Grouping of Patients According To The Study Drugs

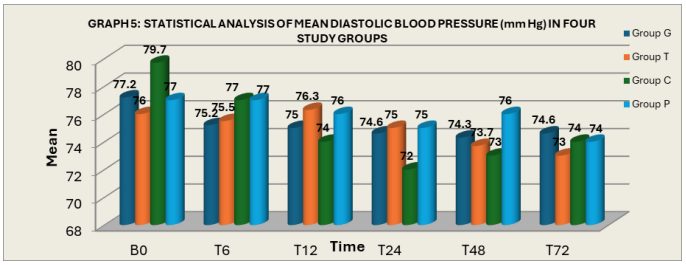
Group G (n=30)	Patients who received Tab Gabapentin 300 mg BD orally for 1 day
Group T (n=30)	Patients who received Tab Theophylline 250 mg BD orally for 1 day
Group C(n=30)	Patients who received Tab Caffeine 300 mg BD orally for 1day
Group P (n=30)	Patients who received placebo (Tab. B-complex) orally BD for 1 day

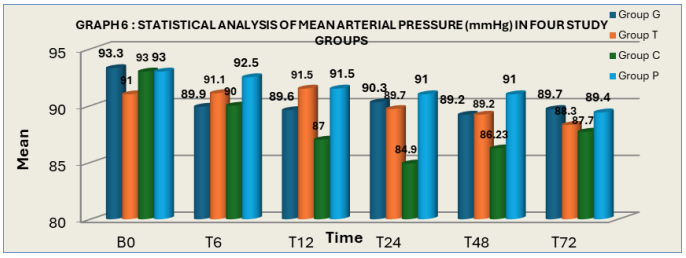












Discussion

PDPH is a complication of spinal anesthesia, more often seen in parturients, because of their risk factors of young age and female gender. The PDPH is mainly dependent on the size and type of needle. Before starting treatment, confirmation of diagnosis is essential because 5-16% of headaches after dural puncture are not PDPH. [5]

The characteristic manifestation of PDPH is its postural component; it increases with sitting or standing and improves with supine position. The pain occurs in the temporal, frontal, or occipital regions bilaterally and can be associated with backache, nausea, neck stiffness, cranial nerve signs, and localized muscle spasms. A history of dural puncture and postural component of the headache are important in diagnosis[8]. The most accepted mechanism for induction of headache is leakage of cerebrospinal fluid through dural hole resulting in cerebral vasodilatation, increased arterio-venous pressure gradient, dural traction and compression of cranial

contents from loss of the cranial fluid cushion. It is important to differentiate PDPH from other causes as tension headache, migraine headache, drug withdrawal, preeclampsia, meningitis, and subarachnoid hemorrhage.[8]

Current treatment for PDPH involves complete bed rest, hydration, analgesics, oral or intravenous caffeine [7], theophylline[6],sumatriptan[9], ACTH, corticosteroids, gabapentin, and epidural patch.

Many studies have been done in past for the treatment of PDPH with the use of different drugs like oral or intravenous caffeine[7], theophylline[6], sumatriptan[9], ACTH, corticosteroids, gabapentin, and epidural patch etc., but none of the studies has compared gabapentin, theophylline and caffeine so far for treatment of PDPH.

Demographic Data

As shown in Graph no. 1 the mean of all the four groups with the majority of patients belonging to the age group of 18-40 years was 25.28±0.30 with even distribution of age in each group as 25.05±2.84, 23.50±2.69, 25.75±3.23 and 24.25±30 years in group G, T, C and P respectively(P>0.05). Thus, all the groups were comparable with respect to demographic data.

VAS Score (PDPH)

Mean (±SD) headache scores on visual analog scale showed highly significant (p<0.01) scores in group G, group T and group C as compared to group P at all the points of observations.

According to observation the mean (±SD) VAS in group P (placebo group) at baseline was 7.4±1.16 which then progressively decreased till 72h as shown by values at 6h(6.8±1.4), 12h(5.4±1.5), 24h(4.1±1.3), 48h(2.8±1.4) and 72h(2.03±1.6). These values were lower than the baseline values and were statistically highly significant (p=0.001).

In group G, the mean (±SD) VAS at baseline was 7.4±1.4 highly significant (p<0.001) decrease in VAS was observed till 72h after treatment as shown by values 6h(4.3±1.7), 12h(2.9±1.3), 24h(1.6±1.1), 48h(0.6±0.89) and 72h(0.3±0.7). These values were lower than the baseline values statistically highly significant(p=0.001).

In group T, the mean (±SD) VAS at baseline was 7.23±1.7 A highly significant (p<0.001) decrease in VAS was observed till 72h after treatment as shown by values 6h(5.1±2.2), 12h(3.5±1.7), 24h(2.06±1.4), 48h(0.9±1.2) and 72h(0.7±0.1.3).

In group C, the mean (±SD) VAS at baseline was 7.23±1.2 A highly significant (p<0.001) decrease in VAS was observed till 72h after treatment as shown by values 6h(4.9±1.6), 12h(3.13±1.93), 24h(1.7±2.1), 48h(0.9±1.4) and 72h(1.2.±1.7).

On intergroup statistical analysis of group G with T, group G with C and group t with C at different time intervals the mean VAS were statistically not significant throughout the study period (p> 0.05). On comparing group G with group P, group T with P and group C with P mean VAS score werestatistically highly significant throughout study period (p=0.001).Compared to other study group VAS score were high throughout the study period in group P as the treatment was not given in the placebo group.

- Gabapentin, a structural analogueof gamma amino butyric acid (GABA) is an antiepileptic drug and is widely used as a medication to relieve pain, especially neuropathic pain. Gabapentin has been reported to be effective in the treatment of PDPH, Possibly through its GABAergic actions, combined with other mechanisms such as calcium channel blockade. [10]
- Theophyllinea methylxanthine derivative having phosphodiesterase inhibiting activity leading to the

relaxation of bronchial smooth muscles (bronchodilation) as well as cerebral vasoconstriction. Vasoconstriction through blocking of adenosine receptor along with induction of CSF production by stimulating Na^+-K^+ Pumps are the mechanism of relief in PDPH.[6]

- Caffeine is a central nervous system stimulant that amongst other properties produces cerebral vasoconstriction. Caffeine may relieve PDPH because of its ability to increase cerebral vascular resistance, decrease cerebral CBF, and decrease cerebral blood volum.

When compared to various studies, our findings were similar to following authors:

Erol D D [10]conducted a study to investigate the analgesic and antiemetic efficacy of gabapentin or ergotamine/caffeine (cafergot), in addition to conservative treatment consisting of bed rest and adequate fluid intake, for the treatment of PDPH. They observed that the VAS scores on days 2, 3 and 4, and the emesis score on days 3 and 4 were significantly low ($p<0.05$) in the gabapentin group than cafergot group.

Nofal W H et al [8] conducted a study in parturients undergoing cesarean section under spinal anesthesia aiming to prophylactically gabapentin reduce the incidence, severity, and duration of PDPH complication. They observed that pre-operative administration of 600 mg of gabapentin significantly delayed the onset and reduces severity (mean VAS) and duration of PDPH($p<0.05$).However, the dose of gabapentin chosen for our study was based on the studies that mentioned that a single oral dose of either 300 mg or 600 mg given to mother before cesarean section baby appeared to have no effect on breastfeeding initiation or baby well being.

Alireza M et al [11] conducted a study to compare the effect of pregabalin, gabapentin and acetaminophen in patients who suffered from PDPH. Headache was evaluated using visual analog scale (VAS). They found that VAS score was significantly lower in Pregabalin group and gabapentin group compared to acetaminophen group($p=0.001$). They observed that both pregabalin and gabapentin were useful and safe in management of PDPH.

Erol D D [12] conducted a study to investigate the efficacy and tolerability of administration of gabapentin in patients of PDPH. Patients were divided into two groups, gabapentin group received 300 mg three times a day and same dose was repeated for 4 days. Other group received a placebo. The VAS scores at 1-4 days were significantly lower ($p< 0.05$) in the gabapentin group compared to placebo.

Haemodynamic Parameters

Pulse Rate (PR)

According to present study observation the mean (±SD) HR (bpm) at baseline was 85.6 ± 13.8 bpm in group G. The maximum decrease in heart rate (81.9± 9.1) was seen at 12 h after administration of study drugs. Heart rate progressively decreases further in the study period which was highly significant ($p=0.00$).In group T the mean (±SD) HR (bpm) at baseline was 85.9 ± 12.18 bpm. Heart rate progressively decreases further in the study period which was highly significant ($p=0.00$).In group C the mean (±SD) HR (bpm) at baseline was 90.6 ± 9.5 bpm. Heart rate progressively decreases further in the study period which was highly significant ($p=0.00$).In group P the mean (±SD) HR (bpm) at baseline was 87.6 ± 11.9 bpm. There was decrease in heart rate progressively throughout the study period which was highly significant ($p=0.00$).On intergroup statistical analysis of mean HR of Group G and T at different time intervals, there was no significant difference in pulse rate throughout the study period after drug

administration(P>0.05).On comparing Group G with Group C at different time intervals, there was no significant difference in pulse rate throughout the study period after drug administration(P> 0.05). On comparing Group G with Group P at different time intervals, there was highly significant difference in pulse rate seen at 24h after drug administration (p= 0.00). Significant difference in pulse rate seen at 12, 48 and 72 h.

While on comparing Group T with Group C, Group T with Group P and Group C with Group P at different time intervals, there was no significant difference in pulse rate seen after drug administration(p> 0.05).

Systolic Blood Pressure (SBP)

In the present study, as shown in the mean (±SD) SBP (mmHg) at baseline was 124.7± 13.7 mm Hg in the group G, which decreased to 120.3±12.5 mm Hg at 6h after administration of study drug, which was highly significant(p=0.00). While in group C the mean (±SD) SBP (mmHg) at baseline was 121.2± 10.4 mm Hg there was highly significant difference in SBP after administration of drugs(p=0.00). In group T and group P the mean (±SD) SBP (mmHg) at baseline was 123± 11 mm Hg and 124±12 respectively and there was no significant difference in SBP after administration of drugs(p>0.05).

In inter-group statistical analysis, the fall in systolic blood pressure was highly significant on comparison of group G with group C, group T with group C and group C with group P at 12, 24, 48 and 72h after treatment(p=0.00). While on comparing group G with group T, group G with group P and group T with group P the fall in systolic blood pressure was not significant after administration of study drug(p>0.05).

Diastolic Blood Pressure (DBP) In the present study, the mean (±SD) DBP (mmHg) at baseline was 77.2±9.1 mm Hg in the group G which decreased to 74.6±4.2 mm Hg at 72h after administration of study drug, the fall in DBP was significant(p≤0.05).In group T the mean (±SD) DBP (mmHg) at baseline was 76± 7.5 mm Hg which decreased to 73± 3.9 mm Hg at 72h after administration of study drug the fall in DBP was significant at 48h and 72h (p≤0.05).In group C the mean (±SD) DBP (mmHg) at baseline was 79.7± 9.6 mm Hg which decreased to 74±5.5 mm Hg at 72h after administration of study drug the fall in DBP was significant at 24, 48 and 72h(p≤0.05).In group P the mean (±SD) DBP (mmHg) at baseline was 77± 7.7 mm Hg which decreased to 74± 5.4 mm Hg at 72h after administration of study drug the fall in DBP was significant at 24h and 72h (p≤0.05).In inter-group statistical analysis, the fall in diastolic blood pressure was insignificant in inter-group comparison of group G with group T(p>0.05), group G with group C (p>0.05), group G with group P, group T with group C, group T with group P and group C with group P(p>0.05).

Mean Arterial Pressure (MAP)

In the present study, the mean (±SD) MAP (mmHg) at baseline was 93.3±10.1 mm Hg in the group G which decreased to 89.7± 3.9 mm Hg at 72h after administration of study drug, the fall in MAP was highly significant(p=0.00). In group T the mean (±SD) MAP (mmHg) at baseline was 91± 8.2 mm Hg which decreased to 88.3± 3.8 mm Hg at 72h after administration of study drug, the fall in MAP was significant(p≤0.05. In group C the mean (±SD) MAP (mmHg) at baseline was 93± 9.3 mm Hg which decreased to 87.7± 4.6 mm Hg at 72h after administration of study drug, there was highly significant difference in fall of MAP(p=0.00).In group P the mean (±SD) MAP (mmHg) at baseline was 93± 8.9 mm Hg which decreased to 89.4± 5.3 mm Hg at 72h after administration of study drug, the fall in MAP was not significant(p>0.05).In inter-group statistical analysis, the fall in mean arterial pressure was highly significant at 12,

24 and 48h after administration of study drug on comparison of group C with group P(p=0.00), on comparison of group T with group C fall in mean arterial pressure was highly significant at 12, 24 and 48h (p≤0.05), while it was not significant on comparison of group G with group T, group G with group P, group T with group P(p>0.05).

When compared to various studies, our findings were similar to following authors:

Ragab A and Noman K conducted a study to evaluate the efficacy and safety of caffeine for prevention of PDPH in young adult patients received spinal anaesthesia. They observed the MAP and HR were significantly lower in caffeine group compared to other group during the whole postoperative recording period(p<0.05).

Erol D D conducted a study to investigate the efficacy and tolerability of administration of gabapentin in patients of PDPH. He observed the mean SBP, mean DBP and mean HR were not different between the two groups at any of the monitored points of time. No other author mentioned about haemodynamic parameters in there study.

Side-Effects And Complications

In the present study 3.33%, 6.65% and 16.65% of patients complained of nausea/vomiting in group T, C and P respectively, where as 3.33%, 6.65%,19.98% and 39.96% of patients complained of recurrence of headache in group G, T, C and P respectively.

When compared to various studies, our findings were similar to following authors:

William R et al conducted a study to evaluate effect of oral caffeine on postpartum patients with postdural puncture headache. They observed two patients in the study complained of mild and transient flushing and jitteriness and few patients felt recurrence of headache after completion of treatment.

Sen J and Sen Bconducted a study to evaluate the efficacy of theophylline for the management of postdural puncture headache (PDPH) in patients after spinal anaesthesia.They observed there were recurrence of headache after completion of treatment was higher in conservative group than theophylline group.

Ragab A and Noman K conducted a study to evaluate the efficacy and safety of caffeine for prevention of PDPH in young adult patients received spinal anaesthesia. They observed there were recurrence of headache after completion of treatment with intravenous caffeine. In another study **Nofal W H et al** found incidence of sedation in gabapentin group.

Conclusion

Following conclusions are drawn from the present study:

- Gabapentin, Theophylline and Caffeine were effective in relieving the PDPH in patients of LSCS done under spinal anaesthesia.
- No significant effects on haemodynamic parameters were observed with all the study drugs. • Recurrence of PDPH was significantly high with caffeine treatment.
- No serious untoward effects or complications of study drugs were observed in the study.

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