

Theophylline versus NSAID in the Treatment of Postdural Puncture Headache in Obstetric Patients

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ABSTRACT

Objective: To determine the effectiveness of oral Theophylline compared to Non-Steroidal Anti-Inflammatory Drugs in the management of postdural puncture headache in obstetric patients.

Study Design: Quasi-experimental Study.

Place and Duration of Study: Anaesthesia Department, Combined Military Hospital, Kharian Pakistan, from Apr to Sep 2018.

Methodology: Our study enrolled 60 pregnant women suffering from postdural puncture headache. They were divided into two groups, NSAID-Group (Group-A) who received 30mg of Ketorolac in three divided doses in 24 hours and Theophylline-Group (Group-B) who received 750mg of oral Theophylline in three divided doses in 24 hours after which effects of both drugs were noted.

Results: Pregnant women were enrolled in NSAID-Group and in Theophylline Group. Mean baseline Visual Analogue Scale score was 7.500 ± 0.97 in NSAID-Group and 7.33 ± 0.92 in Theophylline Group. Mean weight was 66.86 ± 5.25 kg in NSAID-Group and 67.16 ± 7.01 Kg in Theophylline-Group. In NSAID-Group efficacy was noted in 7(23.3%) patients as compared to 25(83.3%) patients in Theophylline-Group, ($p < 0.001$).

Conclusion: Theophylline when given orally in the management of postdural puncture headache proved to be a superior alternative to NSAID medication.

Keywords: Efficacy, NSAID, Oral Theophylline and Postdural puncture headache.

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INTRODUCTION

Postdural puncture headache (PDPH) is an important complication of neuraxial anaesthesia. Obstetric anaesthetists are frequently confronted by this cumbersome complication, and it is incapacitating and distressing for the patient.¹ Karl August Bier known as father of spinal anaesthesia, first reported the subarachnoid route for local anaesthetics in 1898, noting that it was excessive loss of cerebrospinal fluid (CSF) which caused the headache.² The headache is mostly occipital, frontal, or generalized, sometimes radiating to the back of neck or shoulders. Valsalva manoeuvres like coughing and straining exacerbate it by raising intra cranial pressure causing nausea, tinnitus, stiff neck, photophobia, and dizziness along with visual disturbances and auditory disturbances.³ Dural taps due to unintended breach of dural membrane occur during labour epidural for painless delivery with use of large bore 18 or 16G spinal needles, with the incidence of headache between 1.5%

to 11.2%.⁴ Onset of Headache usually happens within 72 hours of the dural tap but the experience of the provider reduces the risk by 1.02 per year increase in practise.⁵ The first-line treatment of PDPH is mostly done by pharmacotherapy as it is more effective, as shown by a study which demonstrated that the efficacy of NSAID was 14.3%⁶ while another showed the efficacy of Theophylline being beneficial in 90% cases of postdural puncture headache.⁷ No comparative study on these two pharmacological treatments has been found so far in Pakistani population. As the results of international studies cannot be applied on our people due to dissimilar genetics and confounding factors, thus rationale behind this study is to compare the efficacy of parenteral NSAID versus enteral Theophylline in the treatment of post-dural puncture headache in obstetrics patients in our local population to determine if either treatment reduces the incidence of post-dural puncture headache in our population.

METHODOLOGY

The quasi-experimental study was carried out at Department of Anaesthesia, CMH, Kharian Pakistan, from April to September 2018, after gaining

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permission from Hospital Ethical Committee (IERB No CMH/18/724). Sample size was calculated with WHO sample size calculator taking percentage of PDPH with P1 (NSAID Group) 14.5% and 90%6 with P2 (Theophylline-Group).

Inclusion Criteria: Pregnant women aged 18-35 years were included who underwent caesarean section and developed postdural puncture headache.

Exclusion Criteria: Patients with chronic headache, psychiatric problems, pre-eclampsia, and history of convulsions were excluded.

Base line demographics (age, base line VAS score and weight) were recorded. Written, informed consent was taken from each participant of study. It was ensured that there was no breach in confidentiality and all risks explained vigilantly. All patients underwent spinal anaesthesia and had American Society of Anaesthesiologists (ASA) classification one

Postdural Puncture Headache was described as headache greater than 5 on VAS after spinal anaesthesia and efficacy was present if there was no headache (VAS=0) 14 hours after treatment. The participants were randomly selected by balloting (Figure). The person doing balloting was kept blind. There were 30 participants in each study Group. In NSAID Group, Ketorolac (Toradol) 10mg three times per day was prescribed while Theophylline tablet 250 mg was prescribed three times a day in Theophylline Group. Patients were assessed at 1 hour, 8 hours and 14 hours and VAS score was calculated to compute efficacy as per operational definition. Efficacy from both Groups was noted by the researcher on a self-designed data collection tool.

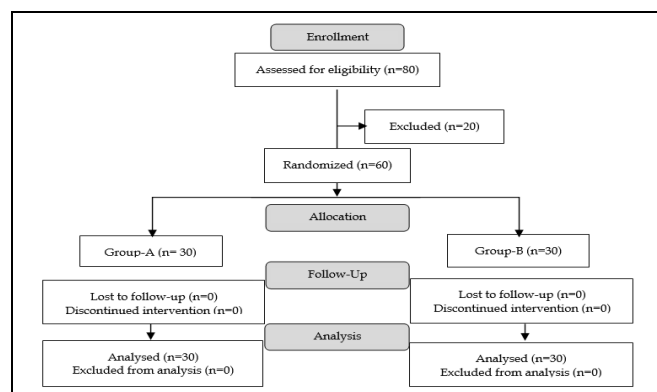


Figure: Patient Flow Diagram (n= 60)

Data was studied with Statistical Package for the Social Sciences (SPSS) version 22.0. Mean±SD was calculated for weight, age, and base line VAS score.

Frequency and percentage were computed for ASA grade and efficacy. Chi-square test was employed for inferential statistics, keeping $p \leq 0.05$ as indicative.

RESULTS

Age range in this study was from 18 to 35 years with mean age of 28.833 ± 2.57 years in NSAID Group and 29.766 ± 2.59 years in Theophylline Group. Mean Baseline VAS score was 7.500 ± 0.97 in NSAID Group and 7.333 ± 0.92 in Theophylline Group. Mean weight was 66.866 ± 5.25 Kg in NSAID Group and 67.166 ± 7.01 Kg in Theophylline Group as indicated in Table-I. There were 25(83.3%) ASA I patients in Group A and 24(80%) in Group B. There were 5(16.7%) ASA II IN GROUP A and 6(20%) ASAII in Group B shown in Table-II. In NSAID Group efficacy was appreciated in 7(23.3%) subjects as compared to 25(83.3%) subjects in Theophylline Group, ($p < 0.001$) as presented in Table-III. Association of efficacy with respect to age, baseline VAS, ASA grade and weight are shown in Table-IV.

Table-I: Descriptive Statistics of the Patients (n=60)

Demographics	NSAID Group (n=30)	Theophylline Group (n=30)
Age (years)	28.833±2.57	29.766±2.59
Baseline VAS score	7.500±0.97	7.333±0.92
Weight (Kg)	66.866±5.25	67.166±7.01

Table-II: Distribution of American Society of Anesthesiologists Classification Grade in Study Groups (n=60)

ASA grade	NSAID Group (n=30)	Theophylline Group (n=30)
I	25(83.3%)	24(80%)
II	5(16.7%)	6(20%)

Table-III: Comparison of Efficacy in Study Groups (n=60)

Efficacy	NSAID Group n=30	Theophylline Group n=30	p-value
Yes	7(23.3%)	25(83.3%)	<0.001
No	23(76.7%)	5(16.7%)	

DISCUSSION

As no comparative study on these two pharmacological treatments has been conducted in the Pakistani population so far, this study aimed to compare the efficacy of parenteral NSAIDs versus enteral Theophylline in treating post-dural puncture headache in obstetric patients to determine if either treatment reduces the incidence of post-dural puncture headache. While PDPH is self-limiting in most cases, symptomatic treatment is often needed to

Table-IV: Association of Efficacy with Study Parameters (n=60)

Parameters	Efficacy	Group A	Group B	p-value
Age				
Age Group 18-27 years	Yes	4(19%)	22(84.6%)	<0.001
	No	17(81%)	4(15.4%)	
Age Group 28-35 years	Yes	0(0%)	1(50%)	<0.121
	No	4(100%)	1(50%)	
Baseline VAS Score				
For 6-8	Yes	7(26.9%)	24(85.7%)	<0.001
	No	19(73.1%)	4(14.3%)	
For >8	Yes	0(0%)	1(50%)	<0.121
	No	4(100%)	1(50%)	
ASA Score				
ASA I	Yes	7(28%)	20(83.3%)	<0.001
	No	18(72%)	4(16.7%)	
ASA II	Yes	0(0%)	5(83.3%)	<0.005
	No	5(100%)	1(16.7%)	
Weight				
Weight ≤ 70 Kg	Yes	6(25%)	16(84.2%)	<0.001
	No	18(75%)	3(15.8%)	
Weight > 70 Kg	Yes	1(16.7%)	9(81.8%)	<0.009
	No	5(83.3%)	2(18.2%)	

alleviate symptoms but the medications and interventions in practice in vogue have many undesirous effects. According to Monro Kellie Burrows doctrine there is vasodilatation of cerebral venous sinuses as a compensatory mechanism in reaction to CSF leakage leading to intracranial hypotension and consequently PDPH.⁸ One study suggested that some patients have reduced levels of neuropeptide called substance P, which is a neuropeptide found in intracranial CSF, which predisposes these individuals to more neurogenic inflammation and a greater possibility of PDPH.⁹ Another study advocated the use of Epidural blood patch for PDPH with a success degree of 80-97% percent¹⁰ however, blood patch is an invasive intervention which requires patients' cooperation, and it can prove detrimental if infection or accidental subarachnoid injection happens. Subcutaneous injection of sumatriptan is successful in mitigating PDPH within 6 hours¹¹ while other authors have reported that intravenous infusion of adreno cortico trophic hormone in two cases was also successful in alleviating PDPH¹² however, both the above-mentioned pharmacological agents are not cost effective, and their controlled trials are still required on larger scale. Oral intake of Caffeine (oral dosage, 300 mg)¹³ also showed marked reduction of PDPH in a study Group in addition to aminophylline infusion when compared to placebo.¹⁴ Akdere *et al.*

studied intravenous Theophylline in PDPH¹⁵ and agreed with other authors who also favored infusion of Theophylline as it reduced visual analog score.¹⁶ The aim of our study was to focus on noninvasive manner of alleviating PDPH. Theophylline is methylxanthine derivative. The mode of action is blockade of adenosine receptors. This results in vasoconstriction of cerebral vasculature and reduction in venous engorgement decreasing intracranial blood flow and thus mitigates PDPH. Methylxanthines also act on sodium-potassium ATPase to enhance CSF production resolving symptomatology of PDPH. Methylxanthine derivatives are helpful in improvement of symptoms.¹⁷ Their principal mode of action is preventing the compensatory vasodilation of cerebral vessels which occurs in reaction to depleted CSF volume. The review of above-mentioned modalities advocates the use of a pharmacological agent which is easy to administer with least undesirous effects. Theophylline showed efficacy of 83.3% while NSAID Group efficacy was only seen in 7(23.3%) patients ($p=0.001$). A study by Mahoori *et al.* showed the efficacy of Acetaminophen was low as compared to aminophylline in the treatment of postdural puncture headache¹⁸ along with another study which indicated beneficial effect of Theophylline in resolving PDPH as compared to placebo, however this study was considered as pilot study due to limited sample size.

CONCLUSION

We determined that oral Theophylline is superior to NSAIDs in treatment of postdural puncture headache. The advantages of rapid onset and long duration of action also make oral Theophylline a better choice.

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Conflict of Interest: None.

Authors' Contribution

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

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

MAQ & KM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

UK & HI: 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

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of any part of the work are appropriately investigated and resolved.

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