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Original Article

Comparison between Addition of Neostigmine and Atropine to Standard Post-Dural Puncture Headache Regimen Versus Standard Regimen Alone

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ABSTRACT

Objective: To compare the treatment efficacy of adding neostigmine and atropine to standard treatment regimen versus standard regimen alone for post-dural puncture headache (PDPH) in patients after caesarian section delivery.
Study Design: Randomized controlled trial (IRCT: 72737).
Place and Duration of Study: Anesthesia Department, Combined Military Hospital, Kharian Pakistan, from Jun to Nov 2023.
Methodology: Patients in the standard regimen received the institute followed conservative management. Patients in the modified regimen (Group-A) received the same protocol and drugs of the standard regimen (Group-B) as well as IV neostigmine 20 mcg/kg and atropine 10 mcg/kg in 20 ml.
Results: Median pain scores 6 hours post-intervention were 3.00 (IQR=0.00) in Group-A versus 6.00 (IQR=0.00) in Group-B (p<0.001). Re-assessment of pain scores at 12 hours post-intervention showed median scores of 2.00 (IQR=0.00) in Group-A versus 5.00 (IQR=1.00) in Group-B (p<0.001). At 24 hours post-procedure, median scores were 2.00 (IQR=0.00) in Group-A versus 5.00 (IQR=0.00) in Group-B (p<0.001). Median scores at 48- and 72-hours post-intervention were 1.00 (IQR=0.00) and 1.00 (IQR=0.00) in Group-A versus 4.00 (IQR=0.00) and 3.00 (IQR=0.00) in Group-B (p<0.001).
Conclusion: We conclude that neostigmine/atropine as adjunct to standard therapy of post-dural puncture headache (PDPH) offer superior pain relief and early resolution of associated symptoms of neck stiffness and nausea.

Keywords: Atropine, Caesarian, Neostigmine, Post-dural Puncture Headache.

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INTRODUCTION

Caesarian deliveries are one the most common surgical interventions, with the incidence increasing to around 20% in the last 10 years, half a million caesarian deliveries are done in the UK alone.[1,2] The incidence of complications after the procedure are also on the rise.[3]

Post-dural puncture headache (PDPH) is a common complication seen in 3 to 9% of patients who undergo caesarian delivery.[4] The mechanism implicated is dural puncture and subsequent consistent leak of cerebrospinal fluid (CSF) at the site of spinal puncture leading to changes in CSF pressure causing traction of the meninges in the brain with cerebral vessel vasodilation as an indirect response to decreased CSF pressure.[5] This causes the classical headache of PDPH radiating to the lateral and back side of the head aggravated on sitting or standing associated with nausea, vomiting and photophobia in many cases.[6]

There have been many conventional and standard therapies proposed for the treatment of PDPH but no treatment regimen has gained universal acceptance as the first-line method when it comes to regimens other than a blood patch.[7] However, blood patch requires expertise with chances of dural puncture again in the non-expert hand.[8] Therefore, intravenous, and oral treatment options are first exhausted before a blood patch may offer as the last resort for treatment.

In recent years, the role of neostigmine with atropine has been proposed as a superior method in alleviation of PDPH.[9,10] The mechanism proposed is the anti-inflammatory role of neostigmine at the level of the choroid plexus since it doesn't cross the blood brain barrier and the central effects of atropine on attenuating the dilated cerebral blood vessels in the brain. Even though the proposed mechanism has merit theoretically, studies on it are scarce and lacking especially in our demographic setup, which is why we carried out this study.

METHODOLOGY

This randomized controlled trial was carried out at the Department of Anesthesia, Combined Military Hospital Kharian, Pakistan, from Jun to Nov 2023 after

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approval from the Ethical Review Board (vide letter no. 23). This study was also registered at Iranian registry of clinical trials (IRCT) (vide trial no 72737). Combined Military Hospital Kharian is a 700-bedded tertiary care facility catering to a vast number of patients.

Inclusion Criteria: Female patients of any age with post-dural puncture headache diagnosed according to the International Headache Society Criteria presenting to the anesthesia clinic 48-72 hours after caesarian delivery.[5,12]

Exclusion Criteria: Patients with allergy to either atropine, neostigmine, paracetamol and/or ibuprofen, those with known history of migraine, cluster headache, those on anti-depressants, those with any neurological disease, and those with major respiratory and cardiac disease were excluded.

Sample size was calculated using World Health Organisation calculator keeping the population proportion requiring blood patch for severe post dural puncture headache (PDPH) in the standard regimen versus modified regimen groups being 15.9% versus 0%.[11] Minimum sample size calculated was 42 when comparing the two proportions. We included a total of 130 patients using non-probability consecutive sampling, which were divided into two groups of 65 each via lottery method (Figure).

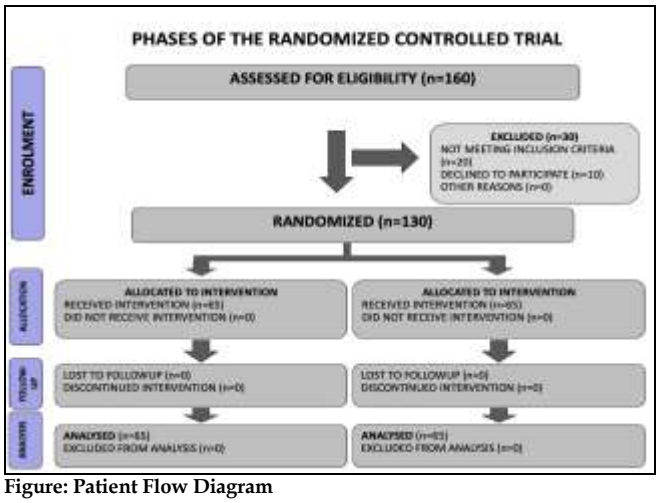

Figure: Patient Flow Diagram

The study method included all patients as per the inclusion criteria furnished. The patients were randomized into the modified treatment group (Group-A, n=65) and the standard treatment group (Group-B, n=65) after randomization. The method of randomization was non-probability consecutive sampling via lottery method. This was a double-blind study and once the patients were divided into the two groups, the anesthetist on duty doing the intervention in both groups received pre-made infusions and solutions prepared by an independent anesthesia resident unaware of the study protocol or variables to be observed through sealed envelopes with instructions on the preparation of the regimen to be given. All patients with pain threshold more than >5 on the visual analog scale (VAS) were scheduled to receive one of the regimens as per the sampling method. All the patients were attached standard monitoring that included non-invasive blood pressure, heart rate, respiratory rate, and oxygen saturation.

Patients in the standard regimen (Group-B) received the institute followed conservative management of IV Paracetamol 15mg/kg, IV Ibuprofen 5 mg/kg, IV Ondansetron 4 mg, IV Omeprazole 40 mg, Ringer lactate at 1.5 ml/kg/hr and caffeine 135 mg. The regimen was followed at 8-hourly intervals till the time pain on visual analog scale was <3. Patients in the modified regimen (Group-A) received the same protocol and drugs of the standard regimen as well as IV neostigmine 20 mcg/kg and atropine 10 mcg/kg in 20 ml in the same 8 hourly intervals till the time pain threshold on the visual analog scale was <3. Patients with VAS <3 before 72 hours were still given 20 ml of 0.9% normal saline to maintain blinding.

Primary variables measured was pain threshold on visual analog scale (VAS) at 6,12,24,48, and 72 hours after the start of treatment. Secondary variables observed need for blood patch, improvement in neck stiffness, nausea and vomiting and treatment associated side effects.[13] All statistical calculations were performed using Statistical Package for Social Sciences 26. Demographic data were statistically described in terms of mean ± standard deviation, frequencies, and percentages when appropriate. Mann Whitney-U test was used to compare median values. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 130 patients were studied divided into the modified regimen group (Group-A, n=65) and standard regimen groups (Group-B, n=65). Mean age of patients in the Group-A was 27.83±2.42 years versus 27.91±2.32 years in Group-B. Mean weight of patients in the groups was 74.40±4.10 kg for Group-A and 74.55±4.00 kg for the standard regimen group. Mean onset of headache in both groups varied from

40.62±8.05 mean hours in the modified regimen group versus 42.26±8.55 hours in the standard regimen group (Table-I).

Table-I: Demographic Characteristics and Onset of Headache in Study Groups (n=130)

Variable	Group-A (n=65) Mean±SD	Group-B (n=65) Mean±SD
Mean age (years)	27.83±2.42	27.91±2.32
Mean weight (kg)	74.40±4.16	74.55±4.08
Onset of headache (hours)	40.62±8.00	42.26±8.55

When the primary outcome variables were seen, median pain score on the VAS showed significant differences in the two groups post-intervention. Median pain scores 6 hours post-intervention were 3.00 (IQR=0.00) in Group-A versus 6.00 (IQR=0.00) in Group-B (p<0.001). Re-assessment of pain scores at 12 hours post-intervention showed median scores of 2.00 (IQR=0.00) in Group-A versus 5.00 (IQR=1.00) in Group-B (p<0.001). At 24 hours post-procedure, median scores were 2.00 (IQR=0.00) in Group-A versus 5.00 (IQR=0.00) in Group-B (p<0.001). Median scores at 48- and 72-hours post-intervention were 1.00 (IQR=0.00) and 1.00 (IQR=0.00) in Group-A versus 4.00 (IQR=0.00) and 3.00 (IQR=0.00) in Group-B (p<0.001), which can be seen in Table-II.

Table-II: Median Pain Scores on Visual Analog Scale Post-Intervention (n=130)

Median Pain Scores on Visual Analog Scale	Group-A (n=65) Median (IQR)	Group-B (n=65) Median (IQR)	*p*-value
Before intervention	9.00 (IQR=1.00)	9.00 (IQR=0.00)	-
6 hours after intervention	3.00 (IQR=0.00)	6.00 (IQR=0.00)	<0.001
12 hours after intervention	2.00 (IQR=0.00)	5.00 (IQR=1.00)	<0.001
24 hours after intervention	2.00 (IQR=0.00)	5.00 (IQR=0.00)	<0.001
48 hours after intervention	1.00 (IQR=0.00)	4.00 (IQR=0.00)	<0.001
72 hours after intervention	1.00 (IQR=0.00)	3.00 (IQR=0.00)	<0.001

While assessing the secondary outcome variables, it was seen that the need for blood patch was only required in 01(1.5%) patient after treatment in the modified regimen (Group-A) versus 10(15.4%) patients requiring blood patch after treatment with the standard regimen (Group-B) for 72 hours. When associated primary complaints were followed up before and after treatment, it was seen that the incidence of neck stiffness and nausea was reported by 63(96.9%) and 53(81.5%) patients in Group-a and Group-B respectively before start of therapy which regressed to 00(0%) and 01(1.5%) patient with the complaint after the end of treatment. In the standard regimen group (Group-A), the same complaints were reported in 61(93.8%) and 52(80%) patients before therapy which regressed to 05(7.7%) and 03(4.6%) patients still reporting the complaints after the end of therapy (Table-III). Adverse effects frequency of treatment regimens is summarized in Table-IV.

Table-III: Secondary Outcomes associated with Post-Dural Puncture Headache (n=130)

Variable	Group-A (n=65) n(%)	Group-B (n=65) n(%)
Need for blood patch	01(1.5%)	10(15.4%)
Neck stiffness		
Before intervention	63(96.9%)	61(93.8%)
72 hours after intervention	00(0.0%)	05(7.7%)
Nausea and vomiting		
Before intervention	53(81.5%)	52(80.0%)
72 hours after intervention	01(1.5%)	03(4.6%)

Table-IV: Treatment-associated Side Effects (n=130)

Variable	Group-A (n=65) n(%)	Group-B (n=65) n(%)
Diarrhea	00(0%)	00(0%)
Abdominal cramps	00(0%)	00(0%)
Muscle cramps	12(18.5%)	00(0%)
Muscle twitches	05(7.7%)	00(0%)
Bronchospasm	00(0%)	00(0%)
Bladder hyperactivity	07(10.8%)	00(0%)

DISCUSSION

The study was carried out in a tertiary care setup that receives a major bulk of obstetric cases from all over the country. The study aimed at finding more suitable, tolera nbble, and improved regimens to the already available arsenal for treating PDPH. Even though blood patch offers the most effective method to treat PDPH according to available literature, we have found that our patient population becomes very reluctant to go through a similar invasive procedure after going through the ordeal of spinal anesthesia before.[14,15] Psychological fear of blood insertion in the epidural space is a cause for majority of the patients unwilling to go for blood patch as first line treatment modality.[16] Hence, other methods need to be perfected which have shown to provide early benefit in these patients since PDPH causes significant discomfort for the post-caesarian mother resulting in late mobilization, prolonged stay, delayed breast feeding and overall resource burden in an already bottlenecked and burdened medical system.

The study was designed to test the role of neostigmine and atropine in ameliorating the pain and presenting complaints associated with PDPH. A similar study was carried out by Mahmoud *et al.*, which concluded a significant early improvement in the visual analogue pain (VAS) score for post post-dural puncture headache (PDPH).[11] The results of this

study were consistent with our results, in both the VAS scale mean regression as well as reducing neck stiffness and incidence of nausea in groups taking the modified regimen versus the standard regimen.

When talking about amelioration and improvement in neck stiffness, nausea and photophobia associated in our study groups, the modified regimen group was superior providing relief in almost 99% of patients with neck stiffness and almost all with nausea as well. This can be attributed to the anti-emetic effect of atropine.[17] Similarly, the same was observed in a study carried out by Ibrahim *et al.,* and Nair *et al.,* showed a marked decline in primary symptoms of nausea, vomiting and neck stiffness.[9,18]

All the primary and secondary variables studied were consistent with a recent study done by Makram *et al.,* confirming and aligning our results with theirs when using the neostigmine/atropine combination.[19] When talking about the adverse effect profile, the side effects seen were all due to the cholinergic effects neostigmine. However, since the dose was diluted and given slowly, the side effects were mild, well tolerated and resolved spontaneously requiring no medical treatment in the subjects. The study recommends the use of neostigmine/atropine as adjunct to the standard regimen for treatment of PDPH. Based on the present results, we can propose several recommendations for the future research. Because this study was carried out in a single medical center, it is highly recommended to perform multi-center trials with a larger number of patients. This will help to validate our findings across different clinical settings and populations. Moreover, the future studies should make a direct comparison of the neostigmine and atropine regimen with other standard treatments, such as intravenous caffeine or the epidural blood patch. Such comparisons are very necessary to evaluate the overall effectiveness, safety, and patient satisfaction. Finally, further investigations are required to determine the optimal dosage that gives maximum pain relief with minimum side effects, and it is advised to observe the patients for a longer time period beyond 72 hours to ensure there is no late recurrence of the headache symptoms.

LIMITATIONS OF STUDY

The main limitation of our study is that we did not follow-up our study participants for long-term side effects or benefits of the modified treatment. Our sample size was also small. Given the importance of the study topic, it is recommended that larger cohorts be included at different centres across the country to maximize the generalizability of findings.

CONCLUSION

We conclude that neostigmine/atropine as adjunct to standard therapy of post-dural puncture headache (PDPH) offer superior pain relief and early resolution of associated symptoms of neck stiffness and nausea.

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Authors' Contribution

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

QAB & SW: Data acquisition, data analysis, critical review, approval of the final version to be published.

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

BHKD & HNM: 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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