Comparison between Aminophylline & Neostigmine/Atropine in Post Puncture Headache of Spinal Anesthesia in Caesarian Section

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Abstract

Background: Spinal anesthesia for Caesarian sections can lead to post-puncture headache (PPH). Neostigmine/Atropine and aminophylline are potential PPH treatments. PPH results from CSF leakage causing intracranial hypotension. Pharmacological options, including Aminophylline and Neostigmine/Atropine, offer innovative approaches to PPH management.

Objectives: To compare between aminophylline and neostigmine/atropine in prevention of PPH .

Patients and methods: The study included 50 female patients (ages 18-40, ASA I and II) undergoing spinal anesthesia. They were divided into two groups: Group I received aminophylline, and Group II received neostigmine plus atropine. Data on heart rate and blood pressure were collected before and after anesthesia induction. Postoperative monitoring included pain scores until reaching a VAS score ≤ 3.

Results: The mean age of patients was 30.5 ± 8.8 years. Most patients (84%) were ASA I. Both groups had similar age distributions (P = 0.6) but slightly higher mean age in Group 1 (31.1 ± 9.9 years) compared to Group 2 (29.9 ± 7.9 years). No significant difference in ASA classification (P = 0.440). VAS scores differed significantly (P = 0.013) with neostigmine plus atropine group showing better scores. Nausea and vomiting incidence differed significantly (P = 0.018), with 40% in Group 2 and 12% in Group 1. Hemodynamic stability was similar (P = 0.203) with all Group 2 and 88% of Group 1 patients being stable.

Conclusion: Neostigmine plus atropine provides better pain relief during spinal anesthesia for cesarean sections compared to aminophylline but may increase nausea and vomiting, requiring careful consideration in clinical decisions.

Keywords: Post dural puncture headache; Aminophylline; Neostigmine; Atropine.

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Introduction

Spinal anesthesia has become a widely used technique in the field of obstetrics, particularly during Caesarian sections, owing to its rapid onset and profound sensory blockade. However, like any medical intervention, it is not without its potential complications **(Du Toit et al., 2022).** One such complication, albeit relatively infrequent, is post-puncture headache (PPH) following spinal anesthesia. PPH can significantly affect the postoperative experience of patients and, subsequently, the quality of care provided by healthcare practitioners. Therefore, the exploration of effective strategies for managing and preventing PPH is crucial to enhance the overall patient experience in obstetric anesthesia **(Baral et al., 2021).**

Two potential pharmacological treatments for the treatment of PPH are aminophylline and neostigmine/atropine. Because of its bronchodilatory effects, aminophylline, a xanthine derivative, is often used to treat respiratory problems. Its vasodilatory qualities, which may help counteract the cerebral vasoconstriction thought to be involved in the development of PPH, have heightened interest in its possible involvement in the treatment of PPH **(Kurdi et al., 2023; Fenta et al., 2021).**

Neostigmine, in contrast, is a conventional medicine used to relieve the neuromuscular blockade induced by non-depolarizing muscle relaxants. It is used in the prevention and treatment of PPH because of its potential to boost CSF production, hence reducing intracranial hypotension associated with PPH. To counteract the cholinergic effects of Neostigmine and decrease side events, atropine is given **(Shahzadi et al., 2022; Shetabi et al., 2023).**

Despite the growing interest in these medications, few studies have been conducted to directly compare the efficacy, safety, and overall impact of Aminophylline and Neostigmine/Atropine in the context of PPH after spinal anesthesia for Caesarian sections **(Akdere and Burgazli, 2011; Fenta et al., 2021; Shetabi et al., 2023; Ibrahim et al., 2021).**

To realize the relevance of studying the efficiency of Aminophylline and Neostigmine/Atropine in the treatment of PPH, one must first understand the pathophysiology of the disorder. PPH is often produced by CSF discharge from the dural puncture site made during spinal anesthesia. This discharge causes intracranial hypotension and compensatory vasodilation of cerebral arteries by reducing CSF volume in the intrathecal space. As a result, these changes contribute to the characteristic pounding headache that patients report **(Alstadhaug et al., 2020).**

Previously, bed rest, water, and analgesics were often advised as first-line therapy in the management of PPH. Although these treatments give some comfort, they do not address the underlying causes of PPH, leaving patients exposed to prolonged suffering and delayed recovery **(Lins et al., 2023).**

In search of more effective PPH management strategies, pharmacological interventions have been investigated in recent years. As a potential vasodilator, aminophylline offers a novel strategy for counteracting the cerebral vasoconstriction observed in PPH. Neostigmine/Atropine, on the other hand, concentrates on enhancing CSF production in an attempt to restore normal intracranial pressure **(Panigrahi and Armstrong, 2019).**

Post-puncture headache continues to be a challenging complication of spinal anesthesia during caesarean sections, necessitating the development of effective management strategies. Aminophylline and Neostigmine/Atropine have emerged as prospective candidates for mitigating PPH, each with a unique mode of action **(Panigrahi and Armstrong, 2019; Fenta et al., 2021; Shetabi et al., 2023).**

From this point on, we are aiming to compare aminophylline and neostigmine/atropine in PPH.

Patients and methods

This prospective, randomized, comparative, single-blind clinical trial was conducted on 50 female patients aged between 40 and 50 years, presenting with American Society of Anesthesiologists (ASA) physical status classifications of I and II. The study was carried out at Qena University Hospital, spanning from August 2022 to August 2023, subsequent to receiving ethical approval from the Medical Ethics Committee within the Department of Anesthesia and Intensive Care. The study was assigned the ethical approval code: SVU-MED-AIP029-1-22-9-456, affiliated with the Qena Faculty of Medicine. Furthermore, informed written consent was diligently obtained from all participating patients.

The research enrolled a total of fifty adult patients who were scheduled to undergo spinal anesthesia utilizing bupivacaine. These patients were categorized into two distinct groups: Group I, consisting of 25 patients who received aminophylline, and Group II, encompassing 25 patients who were administered neostigmine or atropine.

Inclusion criteria for participant selection encompassed individuals aged 18 to 40 years, scheduled for cesarean section under spinal anesthesia, and categorized as ASA I or II.

Exclusion criteria were defined as follows: individuals with hypersensitivity reactions to the study medications, a documented history of alcohol or substance abuse, the presence of severe systemic disorders including cardiac, hepatic, renal, pulmonary, endocrine, neurological, or psychiatric conditions, patients who had received opioid analgesics within 24 hours prior to the surgical procedure, concurrent usage of -2 agonists, clonidine, beta-blockers, tricyclic antidepressants, MAO inhibitors, or adrenergic blockers, patients exhibiting cognitive impairment, and those classified as ASA III or IV in terms of their physical status based on ASA classification **(Li et al., 2021).**

Anesthesia management

A comprehensive medical history was obtained, and a clinical examination was conducted. Patients were positioned supine with a left lateral tilt to facilitate the surgical procedure. Comprehensive standard monitoring, which included continuous electrocardiogram (ECG) recording, non-invasive blood pressure (NIBP) measurement, and pulse oximetry, was meticulously employed throughout the study.

Intravenous (IV) access was established, and both study groups received preoperative fluid loading consisting of 10 mL/kg of Ringer's lactate solution. The administration of these fluids was executed by a qualified anesthesiologist who was not directly involved in the trial.

Subsequently, intrathecal anesthesia was administered to patients while they were seated, employing a 2.5 mL injection of hyperbaric 0.5% bupivacaine at the L3–L4 lumbar level.

For Group 1, aminophylline, dissolved in 100 mL of normal saline for intravenous infusion, was administered over a minimum period of 30 minutes once daily for two consecutive days. The recorded outcomes were then subjected to comparative analysis, as previously reported by **(Kroon, 2007).**

In Group 2, a slow intravenous injection was performed, delivering 20 µg/kg of neostigmine and 10 µg/kg of atropine dissolved in 20 mL of 0.9% saline. This intervention was executed over a 5-minute duration and was repeated every 8 hours. The treatment regimen continued until patients achieved a Visual Analog Scale (VAS) pain score of ≤3 or for a maximum duration of 72 hours, as per the methodology outlined by **(Adeyinka and Kondamudi, 2023).**

Intraoperative and postoperative data acquisition encompassed the measurement of heart rate, systolic blood pressure (BP), diastolic BP, and mean arterial BP. These measurements were conducted at specific time points, which included just prior to the administration of intrathecal blocks, at the baseline, immediately preceding and following anesthesia induction. Subsequently, in the postoperative period, the monitoring process persisted, and the Visual Analog Scale (VAS) pain scores were documented until the attainment of a VAS score ≤ 3, with ongoing comprehensive patient surveillance.

Statistical analysis

Version 26 of the Statistical Package for the Social Sciences (SPSS) software was employed for analysis. Quantitative variables were illustrated as mean ± SD, while qualitative variables were represented using counts and percentages. To determine significance, unpaired t-tests were applied to quantitative data, while Chi-square was utilized in qualitative data. A P-value ≤ 0.05 was statistically significant.

Results

Demographic and Clinical Characteristics of Patients: A cohort of fifty female patients undergoing lumbar puncture for cesarean section participated in this study, with ages ranging from 18 to 46 years. The mean age of the cohort was 30.5 ± 8.8 years. Notably, the majority of patients, comprising 84% of the total, exhibited an American Society of Anesthesiologists (ASA) classification of I, as depicted in (**Table.1** and **Fig.1**).

Table 1. Patients' demographic and clinical features (n=50)

Parameters		**Number**	**Percentage %**
Age (years)	18-30	29	58 %
	31-46	21	42 %
	Mean ± SD	30.52 ± 8.832	
	Median (range)	29 (18-46)	
ASA	I	42	84 %
	II	8	16 %

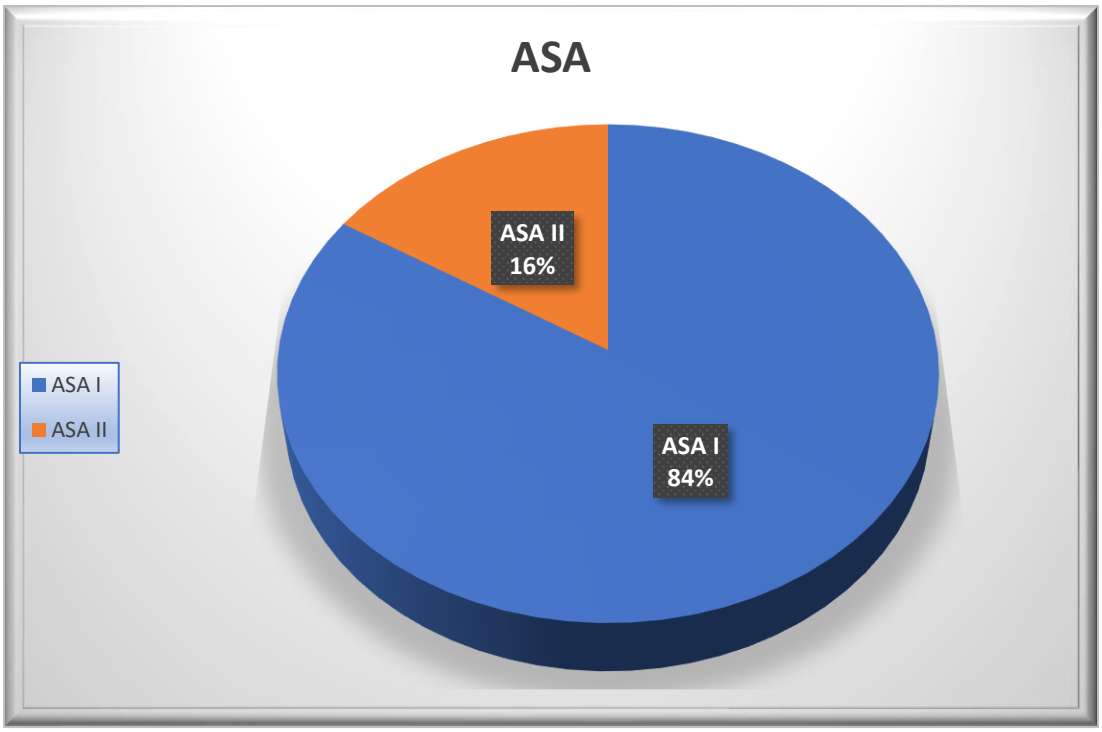

Fig.1. ASA classification among the studied females

A comparative analysis revealed no statistically significant difference in age distribution between the two groups (P = 0.6), although group 1 exhibited a slightly higher mean age of 31.1 ± 9.9 years compared to 29.9 ± 7.9 years in group 2.

Similarly, there was no statistically significant distinction between the two groups concerning ASA classification (P = 0.440), with 88% of group 1 and 80% of group 2 patients classified as ASA I, as detailed in (**Table.2** and **Fig.2**).

Table 2. Relation between interventions and demographic features of the studied patients

Parameters		**Group 1 (n=25)**		**Group 2 (n=25)**		**P value**
		Number	**%**	**Number**	**%**	
ASA	**I**	22	88%	20	80%	**0.440**[(1)]
	II	3	12%	5	20%	
		Mean ± SD		**Mean ± SD**		**0.636**[(2)]
Age (years)		31.12 ± 9.838		29.92 7.858		

[(1)]chi-square test-[(2)] student t-test

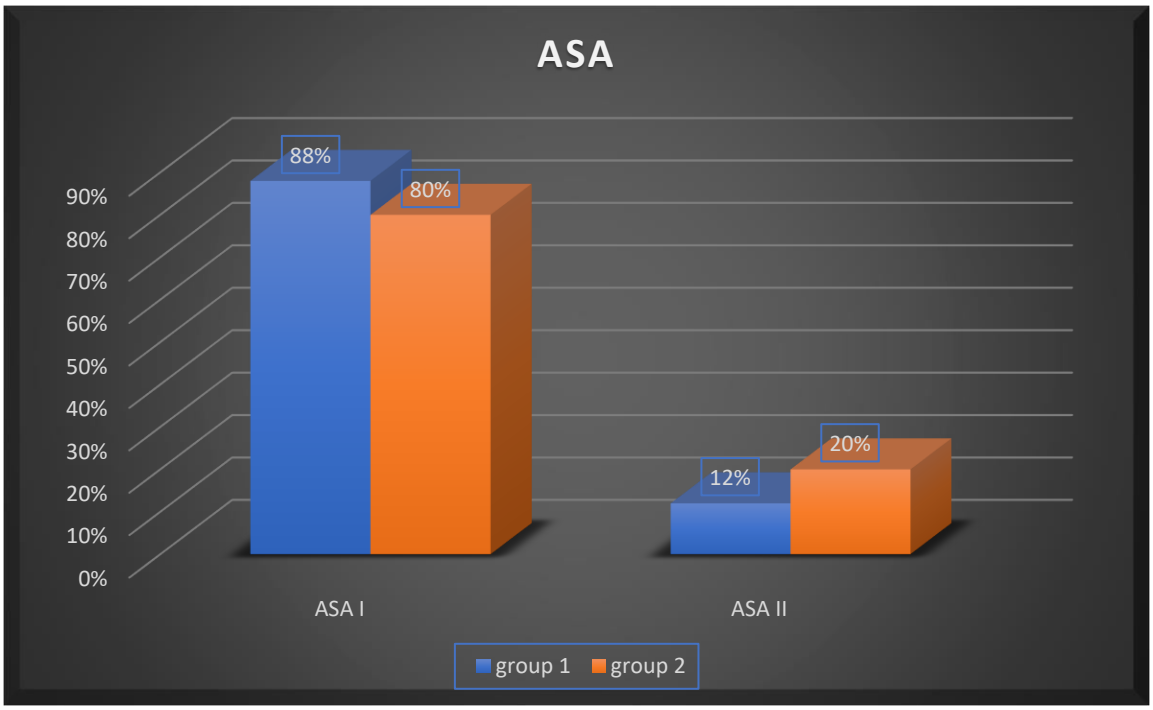

Fig.2. ASA classification among the two groups

A statistically significant difference was observed between the two groups in terms of Visual Analog Scale (VAS) scores (P = 0.013). Notably, patients treated with neostigmine plus atropine exhibited superior VAS scores after one and two days compared to those receiving aminophylline. Among patients treated with aminophylline, 68% did not achieve VAS scores ≤ 3, while only 32% in the neostigmine plus atropine group failed to attain this threshold, as presented in **(Table.3** and **Fig.3**).

Table 3. Outcome among the two groups

Parameters		**Group 1 (I.V aminophylline) (n=25)**		**Group 2 (I.V neostigmine/atropine) (n=25)**		**P value**
		Number	%	Number	%	
Dose at which VAS score achieved ≤ 3	Not achieved	17	68%	8	32%	**0.001***
	1st	2	8%	0	0%	
	2nd	6	24%	1	4%	
	3rd			5	10%	
	4th			4	16%	
	5th			3	12%	
	6th			2	8%	
	7th			2	8%	
VAS scores achieved ≤ 3	1st day	2	8%	10	40%	**0.013***
	2nd day	6	24%	7	28%	
	Not achieved	17	68%	8	32%	
Nausea and vomiting	Yes	3	12%	10	40%	**0.018***
	No	22	88%	13	52%	

	Nausea only	0	0%	2	8%	
Hemodynamics	Stable	22	88%	25	100%	**0.203**
	Tachycardia	2	8%	0	0%	
	Transient desaturation	1	4%	0	0%	

* chi-square test-#student t-test; ASA: American society of anesthesiologist; VAS: Visual analogue scale

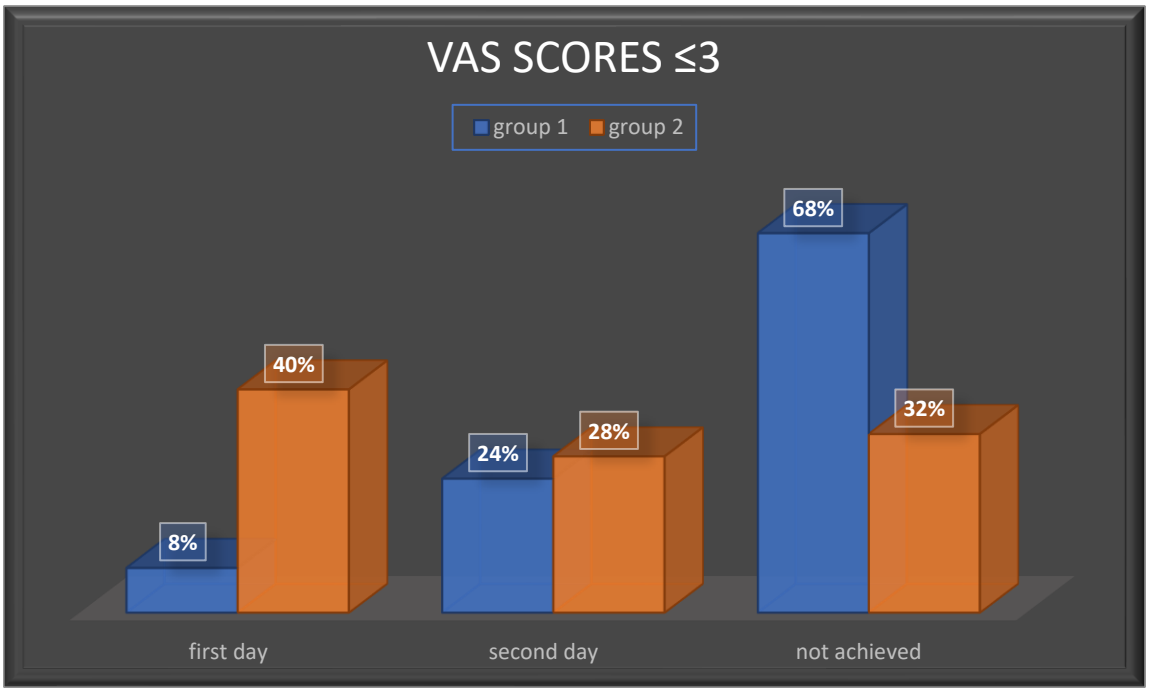

Fig.3. VAS scores ≤ 3 among the two groups

There was no statistically significant difference between the two groups concerning the incidence of nausea and vomiting (P = 0.018). Specifically, 40% of patients in group 2 experienced nausea and vomiting, whereas only 12% of patients in group 1 reported these symptoms, as shown in (**Fig. 4**).

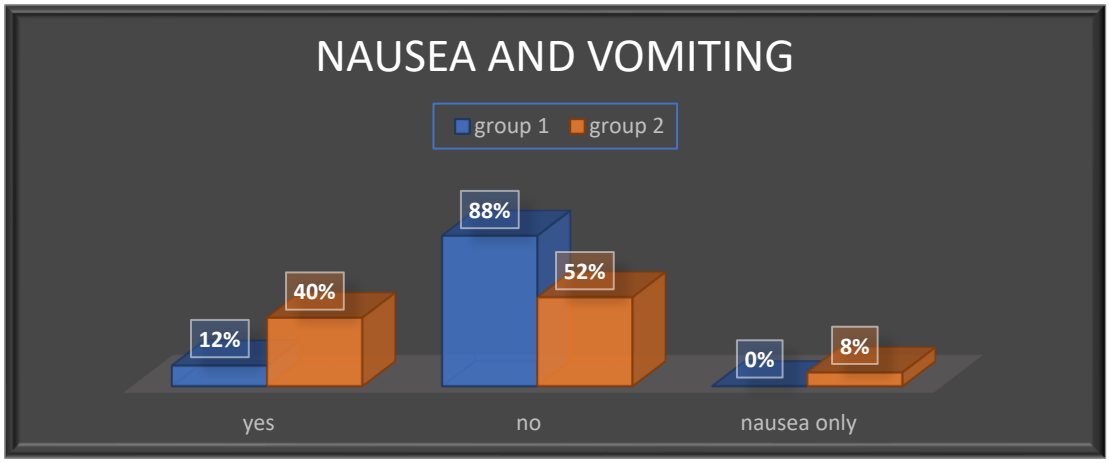

Fig.4.Nausea and vomiting among the two groups

No significant difference was detected between the two groups in terms of hemodynamic stability (P = 0.203). All patients in group 2 were hemodynamically stable, compared to 88% of patients in group 1, as illustrated in (**Fig.5**).

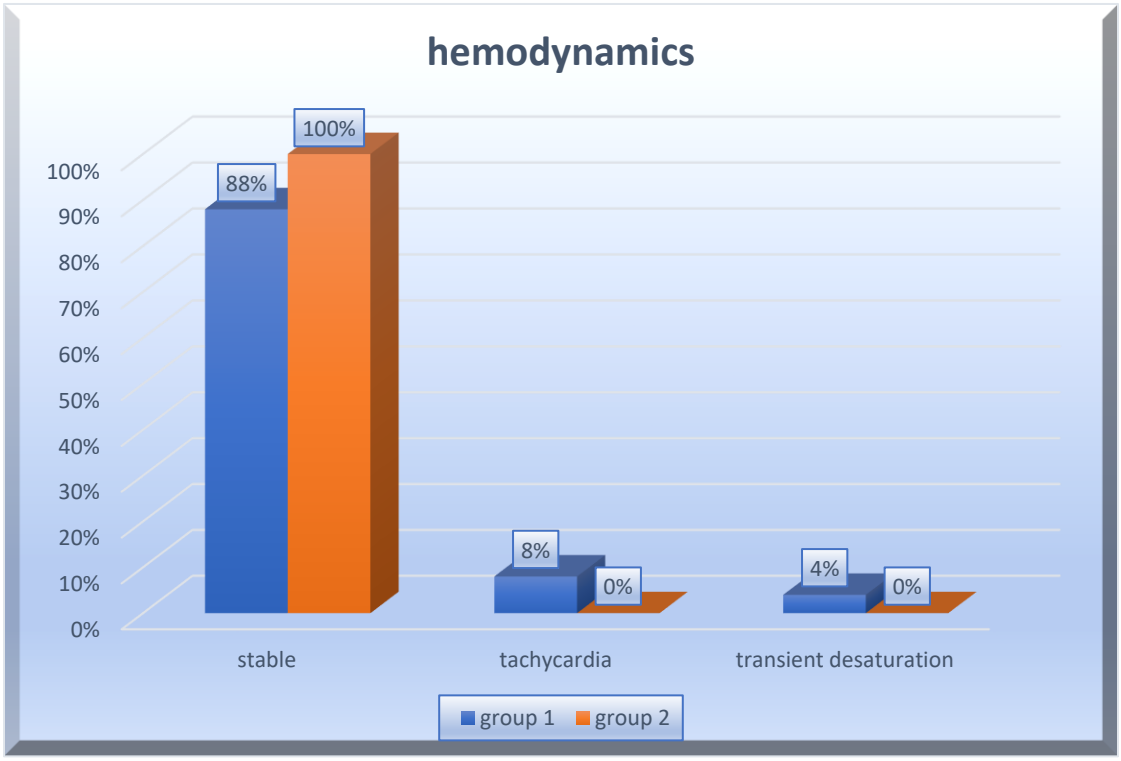

Fig.5.hemodynamics among the two groups

Discussion

In the medical research, the comparison of distinct patient cohorts offers several notable advantages in mitigating the occurrence of Post-Dural Puncture Headache (PDPH). Our study, characterized by a single-blinded design, was undertaken to assess the relative efficacy of aminophylline and neostigmine-atropine in the context of PDPH arising from spinal anesthesia during cesarean section procedures.

In our study, hemodynamic parameters displayed no statistically significant variance between the two treatment groups (P=0.203). Group 2 exhibited 100% hemodynamic stability, in contrast to 88% in Group 1. **Safaan et al. (2021)** conducted a prospective randomized controlled clinical study involving 75 pregnant female patients aged 20 to 40 years, with a body weight range of 60 to 100 kg and ASA physical status II, undergoing elective cesarean section. These patients were randomly allocated to three distinct groups. Group A received an intravenous dose of 250 mg of aminophylline immediately post-infant delivery, while Group B received intravenous neostigmine at a rate of 20 µg/kg, accompanied by atropine at 10 µg/kg, also administered immediately post-infant delivery. Group C received three capsules of gabapentin, each containing 300 mg, with the first administered two hours before spinal

anesthesia, the second six hours post-cesarean section, and the third following a 14-hour interval. The findings of this study unveiled a significant increase in heart rate (HR) post-aminophylline administration in Group A. Nevertheless, insignificant differences in HR and mean arterial blood pressure were observed among the three groups when considering the pre- and post-drug administration changes, in line with our own study results.

Also, **Wu et al. (2018)** conducted an independent investigation involving 126 patients diagnosed with PDPH across five medical facilities in China. Of these patients, 62 were allocated to the aminophylline group, while the remaining 64 were assigned to the placebo group. The median age of participants was 37 years, with 76.2% being female. Their results indicated no statistically significant difference in the incidence of adverse events between the two groups.

Regarding the efficacy in preventing PDPH, a statistically significant difference emerged in VAS scores between the two groups (P = 0.013). Neostigmine plus atropine exhibited superior VAS scores after one and two days compared to aminophylline. Among aminophylline-treated patients, 68% failed to achieve VAS scores ≤ 3, in contrast to 32% among those treated with neostigmine plus atropine.

In contrast to our findings, **Safaan et al. (2021)** investigated 75 pregnant female patients aged 20 to 40 years, with weights ranging from 60 to 100 kg, classified as ASA II, undergoing elective cesarean section. These patients were randomly assigned to three groups, each consisting of 25 individuals. Group A received an intravenous injection of 250 mg aminophylline immediately after infant delivery, while Group B received an intravenous infusion of neostigmine at a rate of 20 µg/kg along with atropine at 10 µg/kg, administered immediately post-infant delivery. Group C was administered three capsules of gabapentin, each containing 300 mg. Their findings indicated a significantly lower incidence of PDPH in Group A (8%) compared to Group B (40%) and Group C (24%). Additionally, the onset of PDPH was notably delayed in Group C compared to both Group A and Group B, with no significant difference in onset between Group A and Group B.

In a study by **Wu et al. (2018)** involving 126 PDPH patients, those administered aminophylline exhibited substantially lower mean VAS scores 8 hours post-treatment (5.3 vs. 2.9, p < 0.001). Aminophylline-treated patients were also significantly more likely to report improvements on the Patient Global Impression of Change (PGIC) scale, with 39.1% showing improvement compared to 72.6% in the aminophylline group.

Also**, Abdelaal et al. (2018)** conducted a comparative investigation of neostigmine and atropine (n = 41) versus a saline placebo (n = 44) in managing PDPH, with 85 patients receiving conservative treatment involving hydration and analgesics. VAS scores were significantly lower (P < .001) in the neostigmine/atropine group compared to the saline treatment group. Furthermore, none of the patients in the neostigmine/atropine group required an epidural blood patch, whereas 7 patients (15.9%) in the placebo group did.

Regarding the incidence of nausea and vomiting in our study, there was an insignificant difference between the two groups (P = 0.018), with 40% of Group 2 patients experiencing nausea and

vomiting compared to 12% among Group 1 patients. An old study, **Eason et al. (1989)** demonstrated that side effects, including nausea and vomiting, are associated with aminophylline, contrary to our study findings. Consistently, the study by **Abdelaal et al. (2018)** reported insignificant differences in nausea or vomiting, reinforcing our study's outcomes.

Conclusion

Our study suggests that neostigmine plus atropine may offer superior pain relief for patients undergoing cesarean sections with spinal anesthesia compared to aminophylline. However, the higher incidence of nausea and vomiting associated with neostigmine plus atropine should be carefully weighed against its pain-relieving benefits when making treatment decisions in clinical practice.

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