

The comparison of post-dural puncture headache treatment with acetaminophen-caffeine capsule and intravenous mannitol infusion: A randomized single-blind clinical trial

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Ali Shahriari¹, Masoumeh Nataj-Majd², Maryam Khooshideh³, Sepideh Salehi-Vaziri³

¹ Department of Anesthesiology, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

² Department of Anesthesiology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

³ Research Development Center, Department of Obstetrics and Gynecology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

Keywords

Acetaminophen; Caffeine; Mannitol; Spinal Anesthesia; Post-Dural Puncture Headache

Abstract

Background: Post-dural puncture headache (PDPH) is a common problem after spinal anesthesia. Depending on the severity of PDPH, there are both invasive and non-invasive treatments. Caffeine has been used for the treatment of PDPH since 1949, but the administration of mannitol is a novel management to tackle PDPH. This study was conducted to compare the effectiveness of acetaminophen-caffeine and mannitol in the treatment of PDPH.

Methods: We enrolled 80 patients with PDPH in the present clinical trial and observed them during 72 hours after cesarean section. Participants were randomly and equally allocated to two groups for treatment with intravenous (IV) mannitol or oral

acetaminophen-caffeine. The effects of treatment were evaluated using the visual analogue scale (VAS) questionnaire at hours of 1, 2, 3, 4, 6, 12, 18, 24, and 48. SPSS software was used.

Results: Forty patients in each group completed the study. There was a significant reduction in the pain scores of the both groups after treatment, but the interaction between time and group demonstrated that mannitol administration was superior to acetaminophen-caffeine in pain reduction of the patients undergoing spinal anesthesia ($P = 0.028$). Patients' satisfaction in the mannitol group was significantly higher than the caffeine group ($P = 0.001$).

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Conclusion: This study suggests that IV mannitol infusion affects faster and earlier for the treatment of PDPH than acetaminophen-caffeine capsule. Mannitol could be probably more effective for treatment of PDPH.

Introduction

Post-dural puncture headache (PDPH) is the most common complication resulting from spinal anesthetics.^{1,2} There are four criteria for PDPH according to the second edition of Headache Classification Subcommittee of the International Headache Society (IHS): a headache which worsens after dural puncture within 15 minutes during sitting or standing and relieves within 15 minutes after lying down; associated symptoms are accompanied by at least one of the following: neck stiffness, nausea, photophobia, tinnitus, and hypoacusis.³ Puncture of the dura can lead to excessive cerebrospinal fluid (CSF) leakage, reduction in CSF volume, and intracranial hypotension. The diminution in CSF pressure leads to traction on parietal dura and intracerebral structures; this traction causes PDPH.^{4,5}

Another pathophysiology for PDPH is based on the Monro-Kellie doctrine.⁶ The low-flow state induced by hypotension after spinal anesthesia causes a compensatory dilation of cerebral vessels, as the sum of the volume of the brain, CSF, and intracranial circulation is constant. Therefore, decrease of CSF volume leads to an increase in the blood volume and brain vasodilation that is attributed as the cause of the PDPH, similar to what occurs in hyperperfusion syndrome.⁶ Medical treatment of PDPH includes non-narcotic analgesics, sumatriptan, adrenocorticotrophic hormone (ACTH), and intravenous (IV) hydrocortisone.⁷⁻⁹

Epidural blood patch is the golden standard for the treatment of severe PDPH,^{10,11} and other invasive treatments are epidural injection of saline or dextran and sphenopalatine ganglion (SPG) block.^{12,13} Caffeine has been used for the treatment of PDPH since 1949;¹⁴ therefore, several studies have used caffeine with different doses and obtained various success rates.¹⁵⁻¹⁸ Caffeine can block adenosine receptors and induce cerebral vasoconstriction that leads to a reduction in cerebral blood flow (CBF) and brain blood volume. It also can stimulate sodium-potassium pumps and increase CSF production. These mechanisms probably result in relief of PDPH.^{19,20} Administration of mannitol is a novel practice to manage PDPH. A few studies investigated the

efficacy of mannitol infusion for the management of PDPH.^{22,23} Rizvi et al. used mannitol infusion to treat PDPH and obtained positive achievements.²¹ Mannitol increases the blood osmolality and decreases the brain liquid volume, so the brain bulk and intracranial pressure (ICP) will decrease.²² In this way, Kassim and Esmat conducted a clinical trial for the treatment of PDPH and administered 100 mg IV hydrocortisone every 8 hours for 48 hours, in comparison to 100 ml mannitol 20% IV infusion over 30 minutes followed by 100 ml every 12 hours. They declared that the IV infusion of mannitol is more effective in reducing the severity of PDPH within 48 hours.²³

No studies reported using mannitol for management of PDPH except for the study of Rizvi et al.²² and Kassim and Esmat;²³ thus, a unique protocol for treatment of PDPH was not determined, and the rate of patients that can benefit from this method was not anticipated. Therefore, the present study was planned to compare the efficacy of IV mannitol with a traditional method, oral acetaminophen-caffeine, for treatment of PDPH.

Materials and Methods

Present single-blind randomized clinical trial study was conducted in Arash Women's Hospital, Tehran, Iran, between February 2019 to October 2020, after receiving approval from the Ethics Committee of Tehran University of Medical Sciences with ID: IR.TUMS.MEDICINE.REC.1397.28 and registering in Iranian Registry of Clinical Trials (IRCT) with ID: IRCT20121006011020N12.

Study population: Parturient women who underwent elective cesarean section under spinal anesthesia were assessed for PDPH. One expert anesthesiologist, using 25 gauge Quincke needle with injection of hyperbaric bupivacaine 0.5% solution (volume 2 ml), performed spinal block. The puncture was performed at L₄-L₅ intervertebral space, in sitting position. Eighty patients with PDPH were enrolled in the study after signing the informed consent form.

The headache was considered as a PDPH which is worsened by sitting or standing and improved by lying back. The inclusion criteria were patients within 18-35 years old, American Society of Anesthesiologists (ASA) physical status I and II, and absence of underlying diseases such as chronic headache, hypertension (HTN), tachycardia, diabetes, coagulopathy, preeclampsia, and epilepsy. The exclusion criteria were increased

ICP, hemodynamically unstable or markedly hypovolemia, infection, sensitivity to caffeine, and the use of caffeine-containing medications, tobacco, and opioid drugs. The block randomization method was applied for random allocation. Our sample size was 80 people, with 40 people in each group. The epidemiologist using Stata software (version 13, Stata Corporation, College Station, TX, USA) designed block randomization method. Then the participants were randomly and equally allocated to one of the oral acetaminophen-caffeine or IV mannitol groups. The random allocation list was solely available to the epidemiologist. Eighty cards containing sequences of treatments were written and placed inside sealed envelopes. A 10-digit random code, as the patient's identification number, was provided for each packet. When the physician announced the eligibility of a patient, the methodologist provided the physician with the envelope. Besides, the person evaluating the outcomes was a third person who was unaware of the random allocation process and type of treatment. A statistician who was not aware of all the processes performed the data analysis.

Intervention: All participants completed a questionnaire including demographics, pain characteristics, the satisfaction of treatment, and the presence of side effects. A visual analogue scale (VAS) recorded the severity of the headache. For the treatment of PDPH, 40 patients were allocated in the mannitol group and received 100 ml IV 20% mannitol serum (manufactured by Shahid Ghazi, Tabriz Pharmaceutical Co., Iran) over 30 minutes (single dose), and 40 patients were allocated in the caffeine group, who received a capsule containing 500 mg acetaminophen and 65 mg caffeine (Dr. Abidi Pharmaceutical Company, Iran) every 6 to 48 hours. In the mannitol group, if a moderate and severe pain persisted for 12 hours later, a sodium diclofenac suppository 100 mg was administered and recorded. We advised patients in both groups to take a sodium diclofenac suppository 100 mg and report it, if an intolerable pain persisted 12 hours after the treatment.

Outcomes measurement: A nurse who was unaware of the group location of the patients asked the patients for the headache intensity. The severity of pain of the patients was recorded with VAS (a 10-point scale was used with a score of 0 representing no pain and a score of 10 representing intolerable pain) before the treatment. In addition, pain scores were interviewed by the telephone on

the 1, 2, 3, 4, 6, 12, 18, 24, and 48 hours after the treatment. Adverse effects were assessed through 48 hours after intervention. Patients' satisfaction was assessed by a four-level score: excellent, good, moderate, and low.

We used the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). To describe the qualitative variables, we used frequency and percent and quantitative variables were presented as mean \pm standard deviation (SD). Student's t-test was used for comparing quantitative variables. The chi-square test or Kruskal-Wallis test was used to compare the categorical variables. Repeated measures analysis of variance (ANOVA) was used to compare the mean of pain at different times between the two groups. A statistically significant level was considered as ≥ 0.05 .

Results

A total number of 1815 parturient women underwent elective cesarean section under spinal anesthesia.

Ninety-one patients who developed PDPH were enrolled in this study. Eleven patients were not included due to patient's refusal. Eighty patients received medications and all of them completed the study (40 patients for each group). Participants were randomly and equally divided into two groups, IV mannitol serum or oral acetaminophen-caffeine groups (Figure 1).

Demographic data are illustrated in table 1. Based on the results, there was no statistically significant difference in age, body mass index (BMI), and parity between the two groups (Table 1).

Table 1. The baseline characteristics of participants who received either caffeine or mannitol

Variables	Groups	Value	P*
Age (year)	Caffeine	31.10 \pm 4.53	0.25
	Mannitol	29.80 \pm 5.49	
Weight (kg)	Caffeine	78.22 \pm 15.03	0.82
	Mannitol	78.92 \pm 11.72	
Height (cm)	Caffeine	158.35 \pm 4.76	0.69
	Mannitol	158.85 \pm 6.23	
BMI (m/kg ²)	Caffeine	31.22 \pm 6.48	0.99
	Mannitol	31.28 \pm 4.39	
Gravidity	Caffeine	2 (0.77)	0.45
	Mannitol	2 (0.98)	
Parity	Caffeine	1 (0.65)	0.28
	Mannitol	1 (0.95)	

Data are reported as mean \pm standard deviation (SD) or number and percentage

*P-value was obtained from independent samples t-test; P < 0.05 was considered statistically significant

BMI: Body mass index

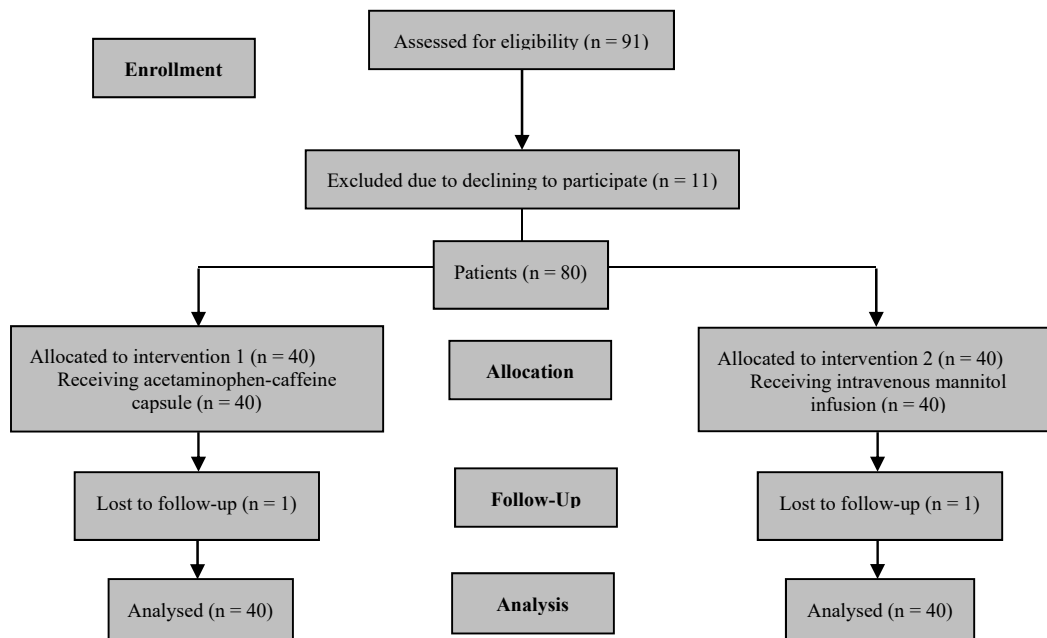


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram for study

Moreover, the parturient women in the two groups did not differ significantly in pain location, pain onset, nausea and vomiting, vertigo, and blurred vision (Table 2).

The most common symptom along with headache was nausea and vomiting (Table 2). Sixty patients (75%) had a history of the previous cesarean section under spinal anesthesia, of which 26 (32.5%) had PDPH in the previous cesarean section [12 (30%) in caffeine group vs. 14 (35%) in mannitol group; $P = 0.63$].

There was no significant difference for the VAS scores between both groups before treatment. The VAS scores were significantly reduced in both groups, but they were significantly lower in the

mannitol group (Table 3, Figure 2). The analysis of variance for repeated measurements indicated that the interaction between time and group demonstrated that mannitol administration was superior to acetaminophen-caffeine in pain reduction of the patients undergoing spinal anesthesia through 48 hours after initiation of treatment (Table 3).

P-values were adjusted for baseline demographic characteristics of participants. No patients in both groups declared the need for analgesic drug. Some side effects such as palpitation, insomnia, and anxiety were significantly higher in the caffeine group than the mannitol group (Table 4).

Table 2. Comparison of pain characteristics before treatment between two groups

Variable		Caffeine	Mannitol	Total	P
Pain location	Frontal	23 (57.5)	23 (57.5)	46	0.090*
	Occipital	3 (7.5)	9 (22.5)	12	
	Other	14 (35.0)	8 (20.0)	22	
Onset of pain	Operative day	9 (22.5)	12 (30.0)	21	0.051**
	24 hours	18 (45.0)	13 (32.5)	31	
	48 hours	12 (30.0)	9 (22.5)	21	
	72 hours	1 (2.5)	6 (15.0)	7	
Nausea and vomiting	Yes	9 (22.5)	12 (30.0)	21	0.610*
	No	31 (77.5)	28 (70.0)	59	
Blurred vision	Yes	5 (12.5)	5 (12.5)	10	> 0.999*
	No	35 (87.5)	35 (87.5)	70	
Vertigo	Yes	11 (27.5)	14 (35.0)	25	0.630*
	No	29 (72.5)	26 (65.0)	55	

Data are reported as number and percentage

*Calculated by chi-square test; **Calculated by Kruskal-Wallis test

Table 3. Comparison of pain score between two groups through 48 hours after treatment

VAS	Mannitol	Caffeine	P*	P**
Baseline	6.72 ± 1.50	6.17 ± 1.64	< 0.001	0.028
1 hour	3.70 ± 1.97	5.00 ± 2.05		
2 hours	3.35 ± 2.91	4.71 ± 2.10		
3 hours	1.65 ± 2.40	4.38 ± 1.58		
4 hours	1.00 ± 1.61	4.03 ± 1.44		
6 hours	0.60 ± 1.32	2.96 ± 1.34		
12 hours	0.26 ± 0.82	2.50 ± 1.50		
18 hours	0.13 ± 0.50	1.70 ± 1.38		
24 hours	0.06 ± 0.36	0.73 ± 1.04		
48 hours	0.06 ± 0.36	0.26 ± 0.72		
P***	0.018	0.014		

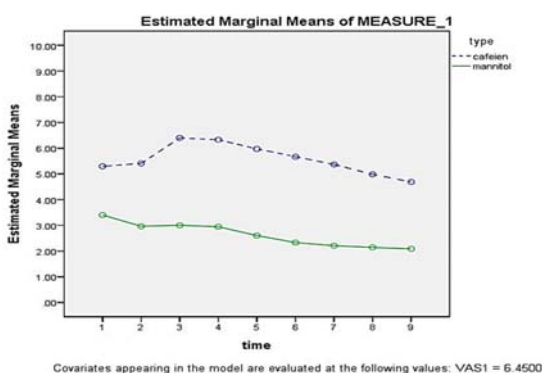
Data are reported as mean ± standard deviation (SD)

*Between groups P-value obtained from repeated measures analysis of variance (ANOVA);

Time × group P-value obtained from repeated measures ANOVA; *Time effect P-value obtained from repeated measures ANOVA; P < 0.05 was considered statistically significant;

P-values were adjusted for baseline demographic characteristics of participants

VAS: Visual analogue scale

**Figure 2.** Comparison of headache relief per visual analogue scale (VAS) between the two study groups

Blurred vision, vertigo, and urinary retention were higher in the mannitol group, but no significant differences were detected between the groups (Table 4). Patients' satisfaction in the mannitol group was significantly higher than the caffeine group (Table 4). A low satisfaction rate was seen among patients who had a severe headache before treatment (VAS score ≥ 8) with both methods.

Discussion

The present study compared mannitol IV infusion versus oral acetaminophen-caffeine in the treatment of PDPH.

Table 4. Comparison of adverse effects through 48 hours after treatment and patient satisfaction between two groups

Post-interaction variable		Caffeine	Mannitol	Total	P
Palpitation	Yes	19 (47.5)	1 (2.5)	20	< 0.001*
	No	21 (52.5)	39 (97.5)	60	
Insomnia	Yes	21 (52.5)	2 (5.0)	23	< 0.001*
	No	19 (47.5)	38 (95.0)	57	
Anxiety	Yes	10 (25.0)	1 (2.5)	11	< 0.001*
	No	30 (75.0)	39 (97.5)	69	
Nausea and vomiting after therapy	Yes	1 (2.5)	3 (7.5)	4	0.310*
	No	39 (97.5)	37 (92.5)	76	
Diarrhea	Yes	1 (2.5)	0 (0)	1	0.310*
	No	39 (97.5)	40 (100)	79	
Blurred vision after therapy	Yes	1 (2.5)	3 (7.5)	4	0.310*
	No	39 (97.5)	37 (92.5)	76	
Vertigo after therapy	Yes	1 (2.5)	3 (7.5)	4	0.310*
	No	39 (97.5)	37 (92.5)	76	
Urine retention	Yes	0 (0)	1 (2.5)	1	0.680*
	No	40 (100)	39 (97.5)	79	
Satisfaction	Low	15 (37.5)	10 (25.0)	25	0.001**
	Medium	17 (42.5)	5 (25.5)	22	
	Good	8 (20.0)	23 (57.5)	31	
	Excellent	0 (0)	2 (5.0)	2	

Data are reported as number and percentage

*Independent samples t-test; **One-way analysis of variance (ANOVA)

The VAS score was reduced in both groups after 48 hours, but it was significantly lower in the mannitol group. In our study, 75% of patients had a history of the previous cesarean section under spinal anesthesia, which 32.5% had PDPH in previous cesarean section. History of previous PDPH is a risk factor for repeated PDPH when spinal anesthesia is re-administered to these patients.²⁴

Ragab and Facharzt¹⁵ believe that caffeine administration is a safe treatment that decreases the use of invasive methods such as epidural blood patch; Lin and Geiderman²⁵ also confirmed this finding. In addition, Camann et al. administered 300 mg of oral caffeine to parturient women with PDPH and concluded that oral caffeine could be administered for pain relief in PDPH.²⁴

Caffeine was 75% to 80% effective in the initial treatment of PDPH; however, all patients had a return of their headache and long-term relief would occur with multiple doses. Our results have supported these findings. In our study, 61% of patients in the caffeine group within 24 hours, and 75% at 48 hours after treatment showed recovery from headache. We used multiple doses of acetaminophen-caffeine in this study. Indeed, caffeine is a central nervous stimulant.²⁴ In this study, the side effects of caffeine such as palpitation, insomnia, and anxiety were seen more frequently than the mannitol group. We found in our study that infusion of 100 ml mannitol 20% significantly and rapidly decreased the intensity of pain score and led to significant patients' satisfaction.

This study showed that 75% of patients in the mannitol group within 24 hours, and 100% at 48 hours recovered from headache. Our results are consistent with the study of Kassim and Esmat.²³ They found that IV infusion of mannitol 20% 100 ml over 30 minutes followed by 100 ml every 12 hours reduced greatly the intensity of headache after spinal anesthesia. In their study, 90% of patients in the mannitol group showed recovery from headache at 48 hours.²³ Rizvi et al. used mannitol infusions to treat PDPH successfully for years.²²

Rizvi was the first investigator who proposed the administration of mannitol for PDPH.²¹ He recommended 20% mannitol (100 ml) IV infusion over 30 minutes, followed by 100 ml every 12 hours for management of PDPH, at most until 48 hours.²² In this study, we planned a single dose of infusion of mannitol for the patients, because the patients in our hospital were discharged the day after the surgery.

Mannitol is an osmotherapy exerting its cerebral effect by two mechanisms: an immediate effect because of plasma expansion, and a delayed effect through the osmotic effect. The early plasma expansion decreases blood viscosity, and so increases regional microvascular CBF.^{22,26,27} In addition, it increases intravascular volume, leading to an increased CBF. This phenomenon is a minor benefit of mannitol therapy.²⁷ The main effect of mannitol is creating an osmotic gradient, drawing water from the cerebral extracellular space into the intravascular space, thereby reducing brain weight.²⁸ With this mechanism, mannitol infusion also was successfully used by Amini-Saman et al. to treat a parturient with abducens nerve palsy after cesarean section under spinal anesthesia.²⁹

In our study, patients' satisfaction in the mannitol group was significantly higher than the caffeine group. The patients who suffered from a severe PDPH (VAS score ≥ 8) did not announce a good satisfaction after treatment of 100 ml infusion of mannitol or caffeine administration. Therefore, we repeated dose of infusion of mannitol for the treatment of severe PDPH, every 12 hours until 24 hours, or performed an epidural blood patch. Further researches in other settings are recommended to confirm our findings.

Conclusion

The present study suggests that acetaminophen-caffeine and mannitol are effective medicines for management of PDPH, but mannitol decreases the score of PDPH pain faster and leads to a higher degree of patients' satisfaction. Mannitol could be probably more effective for treatment of PDPH.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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The research was registered (ID: IR.TUMS.MEDICINE.REC.1397.28) in the Research Ethics Committee of Tehran University of Medical Sciences. Written informed consent was obtained from all participants involved in this study.

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