Egyptian Journal of Anaesthesia (2014) **30**, 181–186

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Caffeine, Is it effective for prevention of postdural puncture headache in young adult patients?

Ashraf Ragab [a,*], **Khalid Noman Facharzt** [b]

[a] *Assistant Professor of Anesthesia, Faculty of Medicine, Cairo University, Egypt*
[b] *Consultant Orthopedic Surgeon, New Jeddah Clinic Hospital, Saudi Arabia*

Received 28 September 2013; revised 15 November 2013; accepted 25 November 2013
Available online 24 December 2013

KEYWORDS

Spinal anesthesia;
Caffeine;
Postdural puncture headache;
Knee arthroplasty

Abstract *Background and objectives:* Postdural puncture headache is a relatively common complication in spinal anesthesia, so several kinds of regimens have been suggested for treatment of this problem. The aim of this study was to evaluate the efficacy and safety of prophylactic administration of intravenous caffeine sodium benzoate for prevention of postdural puncture headache (PDPH) in young adult patients received spinal anesthesia.

Methods: One hundred ASA I and II patients undergoing elective knee surgeries either arthroscopy or anterior cruciate ligament reconstruction (ACL reconstruction) were included in this study. Patients were randomized by double-blind, placebo-controlled design to receive intravenously (IV) either 10 mL normal saline as control group (group S) or 10 ml with 500 mg caffeine sodium benzoate (CSB) as caffeine group (group C) during the first 60 min after spinal anesthesia administration. The patient's electrocardiogram, noninvasive blood pressure, and pulse oximetry were monitored and recorded. The patients' headaches were evaluated by using the visual analog

* Corresponding author. Address: 2 Fatma Roshdy St, Al Haram, Giza, Egypt. Tel.: +966 507200280.
E-mail address: aragabm3@hotmail.com (A. Ragab).
Peer review under responsibility of Egyptian Society of Anesthesiologists.

Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.egja.2013.11.005

scale (VAS), and the severity of the headache was classified as follows: no headache = 0, mild headache ⩽3, moderate headache from 4 to 6 and severe headache ⩾7. Analgesic requirements were recorded.

Results: Visual analog scale scores were significantly lower in group C than in group S. The incidence of moderate and severe headache was significantly higher in group S (11 patients) when compared with group C (2 patients). Analgesic demand was significantly lower in group C than in group S.

Conclusion: It seems that the incidence of postdural puncture headache decreases in those patients who received caffeine sodium benzoate. The article can potentially help clinicians to use caffeine as an effective drug for prevention of PDPH.

1. Introduction

The incidence of postdural puncture headache (PDPH) is estimated to be between 0% and 5% following spinal anesthesia and up to 81% following accidental dural puncture during epidural catheter insertion specifically in the pregnant woman [1].

The incidence is partly dependent on the skill and experience of the person performing the lumbar puncture, but even in the best hands headache occurs despite apparently a traumatic punctures of the theca [2].

PDPH is described as severe, distributed over the frontal and occipital areas radiating to neck and shoulders. Neck stiffness may be present. Pain is exacerbated by head movement, and in upright posture, and relieved by lying down. An increase in severity of headache on standing is the hallmark of PDPH, in some patients PDPH can be debilitating and may increase the length of hospital stay [3].

The presence of certain predisposing risk factors increases the incidence of PDPH. The age group at highest risk is from 18 to 40 years, being 3–4 times that at the age of 65 years [4–6]. Also patient position during the procedure is one of the contributing factors [7,8]. There is no evidence that either bed rest or additional IV fluids reduce the likelihood of a headache developing following dural puncture.

Although Epidural Blood Patch (EBP) is one of the most effective treatment methods for PDPH [8,9], pharmacologic management is less invasive method in comparison with EBP. Epidural injection of NaCL 0.9% or dextran is used as an alternative when the EBP is unsuccessful or contraindicated so pharmacological management to prevent PDPH is an attractive option used to relief patient symptoms and to decrease the length of hospital stay [8].

Caffeine was first reported as a treatment for PDPH in 1949. Caffeine is a central nervous system stimulant and is thought to treat PDPH by inducing cerebral vasoconstriction. Doses from 75 to 500 mg have been investigated and caffeine has been administered orally, intramuscularly and intravenously [11].

Well-designed, adequately powered, randomized controlled trials showing the efficacy of caffeine in PDPH are lacking. Available studies are small and have methodological shortcomings.

This double blinded randomized controlled study was designed to evaluate the efficacy and safety of caffeine for prevention of PDPH in young adult patients received spinal anesthesia.

2. Patient and method

After approval of the ethical committee in New Jeddah Clinic hospital (Saudi Arabia), a written informed consent was obtained from 100 patients ASA physical status I–II, aged 20–30 years, who were scheduled for elective knee surgeries either arthroscopy or anterior cruciate ligament reconstruction (ACL reconstruction), were enrolled in this study.

Patients were excluded from the study if they had allergy to caffeine, a current psychiatric or neurological disorder or pre-existing hypertension, or intolerance to caffeine, or had consumed caffeinated beverages within the previous 4 h.

The patients received instructions on how to use a visual analog scale for the assessment of the degree of headache that consist of an unmarked 10 cm line, with 0 representing no headache and 10 cm representing the worst headache imaginable [12].

In pre-anesthesia room, standard noninvasive blood pressure (BP) and pulse rate were recorded and a peripheral 18-gauge i.v. cannula was inserted. All patients received 20 mL/kg of lactated Ringer's solution as a prehydration measure over 30 min. In the operative theater baseline values of heart rate (HR), mean arterial pressure (MAP), and hemoglobin oxygen saturation (SpO2) were recorded by Datex-Ohmeda; Aisys (GE healthcare) before anesthesia and every five min. during the procedure. For all cases in the study, the spinal anesthesia was performed with the patient in the sitting position at L3-4 or L4-5. Hyperbaric bupivacaine 0.5% 2–3 mL was administered after confirmation of cerebrospinal fluid through a 25-gauge Quincke spinal needle. Patients were placed immediately in supine position. After fixation of the upper sensory level which assessed at 5-min intervals, a tourniquet was applied to the thigh to give bloodless field. All operations were done by the same surgeon.

Patients were randomly allocated into two groups using a computer generated randomization chart to receive intravenously either caffeine sodium benzoate (CSB) 0.5 g, as a caffeine group (group C, $n = 50$) or normal saline as a controlled group (group S, $n = 50$). The study drug (caffeine) was diluted to a volume of 10 mL in one syringe and the other syringe contains 10 ml normal saline both of them presented as coded syringes by an anesthesiologist who was not involved in the management of the patients. For the two groups the injection was given slowly intravenously within the first 60 min after lumber puncture and then 12-hourly for 48 h.

The hemodynamic parameters and any side effects such as nausea, vomiting, rigor, discomfort or inadequate analgesia

were recorded and treated during the study. If any significant hypotension or bradycardia happened, it must be treated by i.v. administration of ephedrine in 5 mg increments and atropine 0.3 mg respectively. At the end of procedure, patients were shifted to recovery room with monitoring of hemodynamics and sensory level.

Postoperatively, blood pressure and heart rate were recorded every 8 h in the following 48 h by a clinician blinded to the study.

Severity of headache was scored and assessed by 10-point (VAS) with 0 = no headache and 10 = worst headache imaginable [12], and according to the degree of pain given by the patient, classification of headache severity was done as follows: no headache = 0, mild headache $\leqslant 3$, moderate headache 4–6 and severe headache $\geqslant 7$.

VAS was recorded every 6 h in the next 48 h by the same clinician blinded to the study and for the next 3 days after hospital discharge by telephone interview to complete 5 days after the procedure.

When headaches failed to resolve within 1 h by bed rest and fluids, it was managed by incremental doses of intramuscular morphine at a dose of 5 mg (rescue analgesia), and the total amount of analgesic requirements was calculated.

3. Statistical analysis

MedCalc version 12.0.3 was used for the calculation of the sample size, in a previous study, about 70% of patients demonstrated satisfactory relief of PDPH within 60 min of used 500 mg intravenous caffeine sodium benzoate, so a sample size of 100 (50 patients per group) provided 80% power at 0.05 level of significance to detect a 40% difference in the proportion of patients who attain satisfactory relief of headache between single dose IV caffeine and placebo.

Statistical analysis was done on a personal computer using the Statistical Package of Social Sciences (SPSS©, SPSS Inc., Chicago, IL) version 17.0.

Shapiro–Wilk test was first conducted to test the hypothesis that numerical data are normally distributed.

Normally distributed numerical data were presented as mean (standard deviation) comparison between the two groups was performed using unpaired Student's *t* test. Categorical variable was compared using Chi-squared or Fisher's exact tests as appropriate. A *P* value less than 0.05 was considered statistically significant

4. Results

One hundred patients were studied and divided into two groups; 50 received caffeine and 50 received saline (placebo), and there was no statistically significant difference between the two groups as regards age, height, weight, sex and duration of surgery (Table 1).

Intraoperatively, there were no significant changes in MAP and HR between the studied groups.

Postoperatively, MAP and HR were significantly lower in group C compared to group S during the whole postoperative recording period (Table 2) ($P < 0.05$).

There was a statistical significant difference between the two groups of the study as regards the VAS scores

Table 2 Postoperative mean arterial pressure (MAP) and heart rate (HR) in the two groups of the study.

	Group S $N = 50$	Group C $N = 50$	
MAP			
Baseline	96.1 ± 4.15	84.5 ± 3.6	< 0.05
After 8	93.1 ± 3.2	83.8 ± 3.7	< 0.05
After 16	88.4 ± 6.4	81.8 ± 5.2	< 0.05
After 24	97.5 ± 5.5	87.1 ± 2.3	< 0.05
After 32	95.6 ± 2.5	85.9 ± 2.4	< 0.05
After 40	90.5 ± 2.8	88.3 ± 2.8	< 0.05
After 48	92.12 ± 3.5	86.3 ± 2.6	< 0.05
HR			
Baseline	85.3 ± 3.7	69.1 ± 4.3	< 0.05
After 8	84.8 ± 3.8	68.8 ± 5.4	< 0.05
After 16	90.7 ± 4.5	82.8 ± 5.1	< 0.05
After 24	92.7 ± 4.5	82.7 ± 4.5	< 0.05
After 32	95.7 ± 4.5	80.7 ± 4.5	< 0.05
After 40	89.7 ± 4.4	80.7 ± 4.5	< 0.05
After 48	93.7 ± 4.5	84.7 ± 4.5	< 0.05

Data are expressed as mean ± SD.

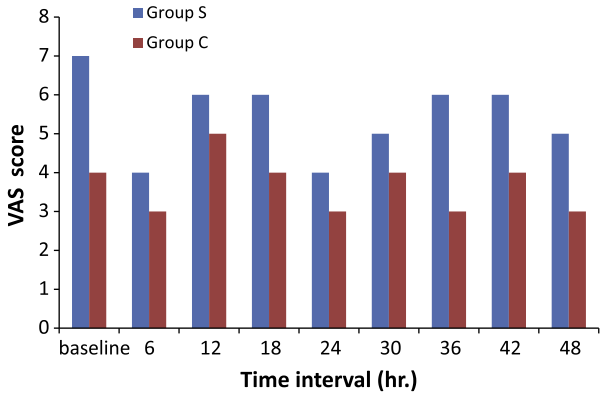

Figure 1 Comparison between the two studied groups as regards VAS.

Table 1 Demographic and operative data.

	Group S $N = 50$	Group C $N = 50$	*P*-value
Age (years)	23.55 ± 3.29	22.91 ± 6.02	> 0.05
Height (cm)	172.4 ± 2.46	174.1 ± 1.10	> 0.05
Weight (kg)	72.6 ± 4.46	71.8 ± 1.99	> 0.05
Sex prevalence (F/M)	23/27	24/26	
Duration of surgery (min)	60 ± 4	65 ± 1	> 0.05

Data are expressed as mean ± SD.

Table 3 Postopertative analgesic consumption in first 48 h.

Variable	Group S $N = 50$	Group C $N = 50$	P-value
Cumulative postoperative morphine consumption in first 48 h (mg)	20 (10–15)	5 (5–7)*	<0.001
Time to first analgesic (h)	1 (1–2)	6 (5–8)*	<0.001

Data are given as means ± SD.
* P value Significant

Table 4 Total number of headaches of given severity recorded by 100 patients given caffeine or placebo.

	Group S $N = 50$	Group C $N = 50$	P-value
NO headache	31	46	<0.001
Mild headache	8	2	<0.001
Moderate headache	4	2	<0.05
Severe headache	7	0	<0.001

Data are expressed as mean ± SD.

($P < 0.05$) as VAS score was higher in group S than in group C (Fig. 1). There was a high statistical significant difference between the two groups as regards total morphine consumption ($P < 0.001$) (Table 3). There was also, a high significant difference between the groups as regards the time of first rescue analgesic dose ($P < 0.001$) (Table 3), group S patients needed the first analgesic dose within 1 h postoperatively while group C patients needed the first analgesic dose after 12 h. As shown in (Fig. 1) VAS at rest was significantly high in group S from the 1st hour postoperatively in comparison to groups C ($P < 0.001$) and that was managed as scheduled in the study protocol by giving 5 mg morphine intra-muscularly (IM) with subsequent decrease in VAS scores. Six hours postoperatively, the VAS scores started to increase again and became significantly higher in S group ($P < 0.001$), so a second dose of rescue analgesia (in the form of 5 mg morphine intramuscularly) was given with subsequent decrease in VAS scores. Nine patients needed a 3rd dose of rescue analgesia between the 12th and 48th hour postoperatively.

In group C, the VAS started to increase after the 12th hour postoperatively before which the VAS remained <50 mm. Only 2 patients needed a rescue analgesic dose of morphine between the 12th and 48th hour postoperatively.

In group C, 4 patients (8%) developed headache (2 (4%) of them had mild headache and the other 2(4%) had moderate headache) in 48 h after operation. In control group (group S), 19 (38%) patients were reported with the headache (8 (16%) of them had mild headache, 4 (8%) of them had moderate headache and the remaining 7 (14%) complained of severe headache) which is statistically significant ($P < 0.001$). Table 4 shows the headache incidence in the two studied groups.

No significant side effects of the studied drugs occurred during the first 48 h postoperatively only two patients in group C complained from mild and transient flushing and it was resolved spontaneously without treatment.

5. Discussion

PDPH is described as severe, searing and spreading like hot metal, distributed over the frontal and occipital areas radiating to neck and shoulders. Ninety percent of headaches occur within the first 3 days of the procedure, and 66% start within the first 48 h. rarely, the headache develops between 5 and 14 days after the procedure. Headache may present immediately after dural puncture [13].

The current clinical study was designed to evaluate the efficacy and safety of prophylactic administration of intravenous caffeine for prevention of PDPH in young adult patients (the most risky age group to develop headache) received spinal anesthesia.

The main finding in this study was that the reduction in the incidence of occurrence of PDPH is more in caffeine group than in the control group. VAS is higher in control group than in caffeine group. Also the doses of analgesics in control group were greater than the doses given in caffeine group.

The pathogenesis of PDPH remains unclear but is thought to be caused by CSF leakage into the epidural space via a tear in the dura. CSF loss leads to a reduction in intracranial pressure and downward traction on pain-sensitive intracranial structures, including veins, meninges and cranial nerves, resulting in a headache that is classically worse in the upright position. The fall in intracranial pressure may also cause compensatory cerebro-vascular vasodilation and this may contribute to the development of the headache [3].

Prevention and treatment for headache following dural puncture allow early ambulation, enabling effective physiotherapy and early discharge from the hospital.

The most clinically evaluated treatment option for PDPH is use of an epidural blood patch (EBP). However, this invasive procedure carries a risk of infection, seizures, back pain, and exacerbation of the headache [14,15].

Other agents that have been evaluated for the treatment of PDPH include epidural administration of saline, caffeine, theophylline, sumatriptan, adrenocorticotropic hormone, dextran patch, morphine sulfate, and bed rest. Caffeine therapy is a noninvasive, safe alternative treatment for PDPH; however, caffeine has been poorly studied for this indication [15].

The proposed mechanism of action of caffeine involves a decrease in cerebral blood flow, a reduction in cerebrospinal pressure, and cerebral vasoconstriction [16,17].

In the current study, the caffeine was used as pharmacologic prophylaxes for prevention of PDPH but all the previous studies were used it or other drugs as a treatment after headache occurred.

Methylxanthine derivatives, such as caffeine and aminophylline, are a mainstay of treatment for PDPH although their efficacy is not proven [18]. Under the theory, methylxanthine derivatives relieve the headache by blocking adenosine receptors, which in turn leads to vasoconstriction of cerebral blood vessels [19]. Methylxanthines may also stimulate sodium–potassium pumps to increase CSF production, which can lead to headache relief [19].

Well-designed, adequately powered, randomized controlled trials showing the efficacy of caffeine in PDPH are lacking. Available studies are small and have methodological shortcomings. For example, in the study by Sechzer et al. [20], 41 patients were given 500 mg of caffeine sodium benzoate or saline intravenously [20]. The headache was relieved in 75% of patients after the first dose of caffeine compared with 14% in the saline group. Further improvement was seen with a second dose, which was given 24 h after the first dose. In this study, relief from caffeine may have been temporary. Twenty-four hours after treatment, there were no significant differences between the caffeine treated and saline treated groups [20]. Treatment with intravenous caffeine was not associated with a reduction in the number of patients who required epidural blood patches (EBP). The results of this study were different from the current study, because Sechzer et al., used only two doses of caffeine instead of four doses in our study and also they gave caffeine after headache occurred. This explanation was supported by Sechzer conclusion which was an intravenous injection of 0.5 g CSB is effective for treatment of spinal headache also supplemental doses may be administered at 8 h intervals.

In a widely quoted, but uncontrolled nonrandomized study, Jarvis et al. [21] reported that PDPH was relieved in 80% of patients treated with intravenous CSB (500 mg) in 1 L of Ringer's lactate solution, followed by an additional liter of Ringer's lactate during the subsequent 2 h. Although the results of the study by Jarvis et al. [21] were promising and consistent with those reported by Sechzer [20], this nonrandomized study is confounded by the unknown effects of acute 2-L hydration on PDPH, inasmuch as no placebo control was used.

The dose of caffeine used in our study (500 mg) contains 250 mg of caffeine plus 250 mg of sodium benzoate to enhance solubility before parenteral use, but in the study by Sechzer [20] oral caffeine (300 mg of anhydrous powder) the dose was 120% greater than the dose used in our study, caffeine is almost completely absorbed after oral administration (with minimal first-pass effect) [22].

In another study William and his colleagues [23], demonstrated that a single oral dose of caffeine (300 mg) is safe and efficacious, and merits consideration in the early treatment for PDPH. In contrast to intravenous caffeine, the use of oral caffeine is more convenient and less expensive.

Although a majority of patients had relief of headaches without recurrence, some did recur after completion of treatment. The tendency for caffeine, as a single oral dose, to provide only temporary relief from PDPH precludes its recommendation as a definitive treatment for this syndrome. Whether long-term relief would occur with multiple doses of caffeine in combination with fluids, analgesics, or other vasoactive drugs remains to be determined. Their study done on forty postpartum patients with postdural puncture headache (PDPH) were randomly assigned to receive oral caffeine (300 mg) or a placebo. Intensity of headache, quantitated using a visual analogue pain scale (VAS), was assessed immediately before drug administration and 4 and 24 h later. Relief of PDPH measured as AVAS (initial VAS–VAS at 4 h) was significantly better in the caffeine than in the placebo group ($P = 0.014$). Six patients (30%) whose PDPH was relieved by caffeine at 4 h had recurrence of symptoms the following day.

The present findings are in agreement with those from studies using intravenous and oral caffeine but in the current study using of caffeine as a prophylactic measure and also every 12 h for the first 2 days postoperatively that gave better control of PDPH and better results.

In our study side effects were infrequent and mild and relived without treatment, and it was in the form of mild and transient flushing in two patients only in caffeine group.

In conclusion, this study demonstrates that use of caffeine (500 mg) IV is safe and efficacious, and merits consideration in the early prevention of PDPH.

Conflict of interest

None declared.

References

[1] Costigan SN, Sprigge JS. Dural puncture: the patients' perspective. A patient survey of cases at a DGH maternity unit 1983–1993. Acta Anaesthesiol Scand 1996;40:710–4.
[2] Hasan A, Pearce J, Miller E. Vasopressin in prevention of lumber puncture headache. Br Med J 1968;4:677–8.
[3] Alam MR, Raheen MR, Iqbal KM, Chowdhury MRA. Headache following spinal anaesthesia: a review on recent update. J Bangladesh Coll Phys Surg 2011;29(1).
[4] Velde MV, Schepers R, Berends N. Ten years of experience with dural punctures and PDPH in obstetric anaesthesia department. Int J Obstet Anaesth 2009;17:329–35.
[5] Zencira Beyazit. PDPH & pregabailin. J Pain Res 2010;3:11–4.
[6] Candido Kenneth D, Stevens Rom A. Post dural puncture headache: pathophysiology, prevention and treatment. Best Pract Res Clin Anaesth 2003;17:451–69.
[7] Jones RJ. The role of recumbency in the prevention and treatment of postspinal headache. Anesth Analg 1974;53:788–95.
[8] Flaatten H, Krakenes J, Vedeler C. Post-dural puncture related complications after diagnostic lumbar puncture, myelography and spinal anesthesia. Acta Neurol Scand 1998;98:445–51.
[9] Frank Robert L. Lumbar puncture and postdural puncture headaches: implications for the emergency physicians. J Emerg Med 2008;35:149–52.
[10] Schwarz U, Schwan C, Strumpf M, et al. Post dural puncture headache: diagnosis, prevention and therapy. Schmerz 1996;13:332–40.
[11] Halker RB et al. Caffeine for the prevention and treatment of postdural puncture headache: debunking the myth. Neurologist 2007;13:323–7.
[12] Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191–8.
[13] Weir EC. The sharp end of the dural puncture. Br Med J 2000;320:127–8.

[14] Sudlow C, Warlow C. Epidural blood patching for preventing and treating post-dural puncture headache. Cochrane Database Syst Rev 2001;(2).
[15] Abouleish E, Vega S, Blendinger I, Tio TO. Long term follow-up of epidural blood patch. Anesth Analg 1975;54:459–63.
[16] Morewood GH. A rational approach to the cause, prevention and treatment of postdural puncture headache. Can Med Assoc J 1993;149:1087–93.
[17] Choi A, Laurito CE, Cunningham FE. Pharmacologic management of postdural headache. Ann Pharmac Other 1996;30:831–9.
[18] Lin W, Geiderman J. Medical myth: fluids, bed rest, and caffeine are effective in preventing and treating patients with post-lumbar puncture headache. West J Med 2002;176:69–70.
[19] Straube A, Neudert C, Glas M, Brüning R, Padovan CS. The so-called spontaneous low CSF pressure pressure syndrome. Case results indicating a disturbance in CSF/blood volume regulation. Nervenarzt 2004;75:1194–9.
[20] Sechzer PH, Abe L. Post-spinal anesthesia headache and treatment with caffeine: evaluation with demand method. Part I. Curr Ther Res 1976;24:307–12.
[21] Jarvis AP, Greenawalt JW, Fagraeus L. Intravenous caffeine for post-dural puncture headache. Anesth Analg 1986;65:316.
[22] Bonati M, Latini R, Galleti F, Young JF, Tognoni G, Garattini S. Caffeine disposition after oral doses. Clin Pharmacol Ther 1982;32:98–106.
[23] Camann William R, Scott Murray R, Mushlin Phillip S, Lambert Donald H. Effects of oral caffeine on postdural puncture headache a double-blind, placebo-controlled trial. Anesth Analg 1990;70:181–4.