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Research Article

Comparative study between hydrocortisone and mannitol in treatment of postdural puncture headache: A randomized double-blind study

Dina Y. Kassim [a], **Ibrahim M. Esmat** [b,*]

[a] *Anesthesia and Intensive Care Medicine, Beni Sweif University Hospitals, El Rehab City, Group 71, Building 15, New Cairo 11841, Egypt*
[b] *Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo 11361, Egypt*

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KEYWORDS

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Abstract *Background:* Postdural puncture headache (PDPH) is a common complication after lumbar puncture. Anesthesiologists are the most likely to be consulted for the treatment. PDPH may be debilitating for a patient and can interfere with daily activities and quality of life.
Methods: Fifty patients of both sexes, aged 18–50 years and ASA I and II undergoing elective lower abdominal and pelvic surgery under spinal anesthesia were included in this randomized double-blind study. Patients were randomly divided into 2 groups 25 each: hydrocortisone group received intravenous hydrocortisone 100 mg every 8 h for 48 h and mannitol group received intravenous infusion of mannitol 20% 100 ml over 30 min followed by 100 ml every 12hours. Mean (±SD) of headache intensity at 0, 6, 12, 24 and 48 h after beginning of treatment was assessed using visual analogue scale.
Results: There was no significant difference regarding headache intensity between two groups before beginning of treatment. The VAS was significantly reduced in hydrocortisone group than in mannitol group at 6, 12, 24 h with *P*-value 0.030, 0.007, 0.004 respectively. At 48 h, both groups had nearly the same VAS of headache intensity, with *P*-value 0.305.
Conclusion: Both intravenous hydrocortisone and mannitol intravenous infusion were efficient in reducing postdural puncture headache within 48 h. Hydrocortisone showed earlier and significant relief of headache.

1. Introduction

According to the International Classification of Headache Disorders (ICHD-II), postdural puncture headache (PDPH) is iatrogenically conditioned orthostatic headache that follows lumbar puncture, worsens within 15 min of sitting or standing

* Correspondence to: Ibrahim M. Esmat, MD, Lecturer of Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo 11361, Egypt. Tel.: +20 0227748551, +20 01001241928.
E-mail addresses: dinayk31@yahoo.com (D.Y. Kassim), himadouh@hotmail.com (I.M. Esmat).
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and is relieved within 15 min of lying down, caused by low pressure in the spinal fluid space [1]. Ninety percent of PDPHs occur within three days of the procedure and 66% start in the first 48 h [2]. Postdural puncture headache (PDPH) is usually described as a severe, dull, non-throbbing pain, usually fronto-occipital. It may be accompanied by nausea, vomiting, visual disturbances and/or auditory disturbances. Headache begins 1 or 2 days after spinal anesthesia and usually relieves spontaneously within a week, but the patient suffers miserably during this period [3].

The pathophysiology PDPH is due to CSF leakage from the subarachnoid space through the dural puncture, resulting in a decrease of CSF volume and pressure [4]. According to Monro–Kellie–Burrows doctrine (the sum of the volumes of CSF, the blood and the brain tissue in the skull remain constant), loss of CSF may result in compensatory intracranial vasodilatation. Relative CSF hypovolemia results in painful, possibly adenosine-receptor-mediated, vasodilatation [5]. Headache continues until dural hole repairs and it is relieved when CSF volume and pressure return to normal [6].

As a result of buoyancy in the CSF, the weight of the structures in the central nervous system is reduced to around 50 mg [7]. An average human has approximately 150 ml of CSF within the subarachnoid space. About 500 ml of CSF is produced per day, and at any time the volume of CSF ranges from 125 to 150 ml, half of which is intracranial. The lumbar CSF pressure is 5–15 cm water but increases to 40 cm water in the upright position. In patients with PDPH, the loss of CSF (which may be as much as 12 ml/min) is greater than the rate of replacement (approximately 0.35 ml/min) [8].

The resultant low intracranial pressure and relative deficit in CSF result in traction on pain-sensitive cranial structures (e.g. blood vessels, meninges, and cranial nerves). The pain associated with PDPH is most prominent in upright position. This position exacerbates the traction on intracranial structures and increases transdural lumbar CSF pressure, promoting further loss of CSF [8]. This pain is mediated by substance *P* and the upregulation of neurokinin-1 receptors [9].

Treatment of PDPH is divided into 4 stages: conservative management, aggressive medical management, conventional invasive therapy, and aggressive invasive treatment. On average, move from conservative to aggressive medical therapy occurred after several days, and from aggressive medical management to invasive treatment at about 4 days after onset of PDPH. Choice of treatment was according to the severity of symptoms [10].

Conservative management is appropriate because of the benign prognosis of PDPH. Bed rest in horizontal position, adequate hydration [11,12] and symptomatic treatment as analgesics (acetaminophen, non-steroidal anti-inflammatory drugs) are usually used. Antiemetics are used to obtain comfort till seal of the dura [13].

The Institute of Medicine determined that an adequate intake (AI) of fluid per day for men is roughly about 13 cups (3 l) of total beverage a day. The AI for woman is about 9 cups (2.2 l) of total beverage a day [14].

According to European Food Safety Authority (EFSA) on dietary reference values for water, the water adequate intake (AI) for adult men is 2500 ml/day and AI for women is 2000 ml/day to allow our body to perform optimally [15].

Aggressive medical management includes medications such as methylxanthines (caffeine and aminophylline) [16–18] and Triptans [19]. Adrenocorticotropic hormone (ACTH), pregabalin, gabapentin, and methergine with metoclopramide are successfully used [20–24].

Conventional invasive treatment, epidural blood patch (EBP) is used when conservative measures fail [25,26]. Other invasive treatment options include the use of epidural saline or dextran [27].

Sphenopalatine ganglion block is used for PDPH, without significant side effects or complications. The block is less invasive and works faster than EBP [28].

Aggressive invasive treatment, is an alternative to EBP when it fails to control PDPH. The diagnosis should be reevaluated. If confirmed, percutaneous computed tomography(CT)-guided injection of fibrin glue aimed to seal the dural tear [29]. Surgical treatment is the last resort to stop a CSF leak and cure PDPH [30].

The preventive effect of corticosteroids against PDPH can be due to their anti-inflammatory effect on the inflammatory process initiated at puncture site. Steroids suppress arachidonic acid production through lipocortin-induced phospholipase inhibition, which inhibits production of prostaglandins (PGE 2 and PGI 2), and leukotrienes (LTB 4). Also, corticosteroids block production of pro-inflammatory cytokines such as interleukin-1, interleukin-2, and tumor necrosing factor-alpha. The analgesic effect of steroids in PDPH, may relate to their anti-inflammatory effects at dural puncture site. During healing of dural puncture, inflammatory mediators are secreted from immune cells, spread in CSF, stimulate pain receptors, and cause headache. Steroids suppress production of these allogenic mediators and relieve headache [31,32].

Mannitol is an osmotherapy exerting its cerebral effects via two mechanisms, an immediate effect because of plasma expansion and slightly delayed effect through its osmotic action. The early plasma expansion decreases blood viscosity and so improves regional microvascular cerebral blood flow and oxygenation. Also it increases intravascular volume and therefore cardiac output. Both effects result in an increase in regional cerebral blood flow and compensatory cerebral vasoconstriction in brain areas where autoregulation is intact, reducing intracranial tension. The delayed effect is creating an osmotic gradient between plasma and brain cells, drawing water from the cerebral extracellular space into the vasculature, thereby reducing brain weight [33]. The peak effect of mannitol on intracranial pressure was achieved within 30–45 min and last around 6 h [34].

In this study, our primary measure was to compare between hydrocortisone and mannitol in treatment of PDPH within 48 h. And our secondary measure of the study was to find out a non-invasive effective rapid treatment of PDPH.

2. Methods

This study was designed to be a randomized double-blind parallel study in which patients, investigators and anesthesiologists were blinded to the given treatment. This study was conducted between October 2014 and November 2015. A total number of 167 patients scheduled for elective lower abdominal and pelvic surgery e.g. repair of inguinal hernia, incisional hernia, varicocele and hydrocele done under spinal anesthesia were arranged to be enrolled in the study. A total of 57 patients developed PDPH and were assessed for eligibility

and finally 50 patients completed the study. After approval of the ethical committee in Heliopolis hospital (Cairo, Egypt), a written consent was obtained from the fifty patients aged 18–50 years of both sexes, ASA physical status I–II of 70–90 kg body weight and height 160–180 cm.

Patients with impaired kidney or liver functions, history of cardiac or central nervous system disease (a history of convulsions, cerebro-vascular accident, preeclampsia, eclampsia or high intracranial pressure), history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs or opioids within 24 h before surgery or allergy to the used medications, coagulation defect, patient refusal or duration of surgery more than 120 min were excluded from the study.

Preoperatively, peripheral 18-gauge intravenous cannula was inserted, and standard non-invasive blood pressure and pulse rate were recorded. All patients received 20 ml/kg of lactated Ringer's solution as a pre-hydration measure over 30 min. Monitoring of the patients, hemoglobin oxygen saturation (SpO2), mean arterial blood pressure (MAP), and 5-leads ECG were recorded by Dräger Vista 120 prior to anesthesia and every 5 min intraoperatively. Granisetron (1 mg IV) was given as a prophylactic antiemetic.

For all patients in the study, the spinal anesthesia was performed at L3-4 or L4-5 with the patient in the sitting position, midline approach with 25-gauge needle (UNIEVER K-3 LANCET, made in JAPAN) and hyperbaric bupivacaine was administered after confirmation of cerebrospinal fluid (MYLAN, anhydrous hydrochloride, hyperbaric solution sterile, 20 mg/4 ml). Patients were placed immediately in supine position. After fixation of the upper sensory level, operation was proceeded.

Significant intraoperative hemodynamic changes as hypotension or bradycardia (More than 20% of the recorded baseline values) will be treated by intravenous administration of ephedrine in 5 mg increments and atropine 0.4 mg respectively. At the end of procedure, patients were transferred to post anesthetic care unit (PACU) with monitoring of hemodynamics and sensory level.

Patients with postoperative PDPH were randomly allocated in two groups 25 each. Randomization was done using computer-generated number table of random numbers in a 1:1 ratio and conducted using sequentially numbered, opaque and sealed envelope (SNOSE). Hydrocortisone group, received hydrocortisone 100 mg, dissolved in 2 ml normal saline, intravenously/8 h for 48 h (hydrocortisone as sodium succinate, vial, equivalent to hydrocortisone 100 mg, Egyptian INT, Pharmaceutical Industries CO. ARE,EIPI.CO.EGYPT) and mannitol group, received mannitol 20% 100 ml intravenously which was given over 30 min and followed by 100 ml on a 12hour basis for 48 h (Manufactured by Allmed Middle East, Egypt). Urinary catheter was inserted for patients in mannitol group under complete aseptic conditions by the anesthesia resident before the start of mannitol infusion and removed after its discontinuation, accompanied by the intravenous fluid infusion over 48 h of 500 ml of normal saline or Ringer's solution every 8 h and the input/output fluid chart for evaluation of fluid balance. Treatment in both groups started once patient complained of headache. The study drugs were prepared by the anesthesia resident and follow -up of patients was conducted by the same anesthesia resident not involved in any other part of the study.

Postoperatively, severity of headache was assessed and scored by 10-point visual analogue scale (VAS). The patients were instructed on how to use VAS for the assessment of the degree of headache (with 0 representing no headache and 10 cm representing the worst imaginable headache). According to the degree of headache or pain given by the patient, classification of headache severity was done as follows: no headache = 0, mild headache <3, moderate headache 4–6 and severe headache >7. VAS was recorded after 6 h, 12 h, 24 h, and 48 h after the start of the treatment in both groups by the anesthesia resident not involved in any other part of the study.

Assessment of postoperative hemodynamic variables such as heart rate (HR) and mean arterial pressure (MAP) and the monitoring of arterial SpO_2 at 6, 12, 24, 36 and 48 h after the start of the treatment in both groups were fulfilled.

2.1. Analysis of data

PASS 11 was used for sample size calculation, where a sample size of 22 patients per group would achieve 80% power to detect a difference of 50% in proportion of post-treatment headache relief. The reference group proportion was 0.5. The calculations assume that two-sided Z test was used. 25 patients per group were intended to be included to replace any dropouts.

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA 2013.

Descriptive statistics were done: for quantitative data it was minimum and maximum of the range as well as mean ± SD (standard deviation) and for quantitative parametric data, median, while it was done for qualitative data as number and percentage.

Inferential analysis was done using 95% confidence interval as well as independent t-test in cases of two independent groups with parametric data. In qualitative data, inferential analysis for independent variables was done using Chi square test for difference between proportions and Fisher's Exact test for variables with small expected numbers. The level of significance at P value <0.05 was significant, otherwise non-significant.

3. Results

This study was conducted between October 2014 and November 2015. A total number of 167 patients scheduled for elective lower abdominal and pelvic surgery e.g. repair of inguinal hernia, incisional hernia, varicocele and hydrocele done under spinal anesthesia were arranged to be enrolled in the study (Fig. 1). A total of 57 patients developed PDPH and were assessed for eligibility (Fig. 1). Five patients were not included in this study on account of patient's refusal (3 patients) and history of chronic analgesic consumption (2 patients). Out of which 52 patients received study medications after randomization and 50 patients completed the study (25 patients for each group) and their data were included in the final analysis (Fig. 1). Two patients were considered as drop-outs after initial

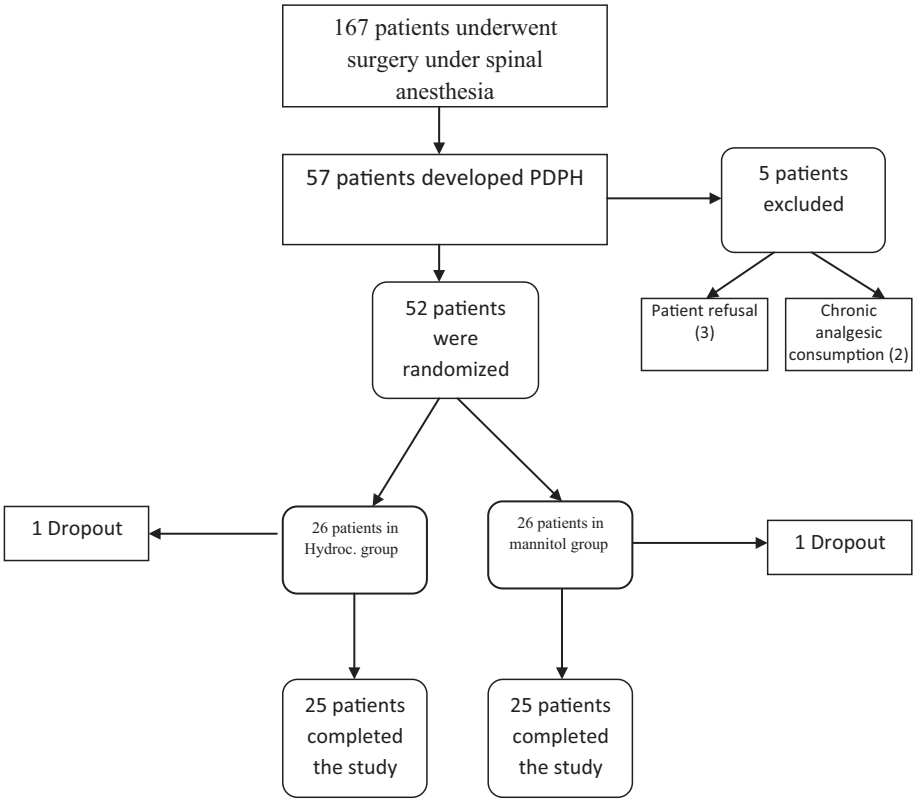

Figure 1 Flowchart of patients (study design).

Table 1 The demographic data.

Variable	Measure	Hydrocortisone ($N = 25$)	Mannitol ($N = 25$)	P
Age (years)	Mean ± SD	36.4 ± 9.1	35.1 ± 7.7	^0.553
	Range	20.0–50.0	22.0–50.0	
Sex (n, %)	Male	15 (60.0%)	14 (56.7%)	#0.793
	Female	10 (40.0%)	11 (43.3%)	
Weight (kg)	Mean ± SD	76.4 ± 4.2	77.0 ± 4.2	^0.549
	Range	69.2–84.2	66.9–87.3	
Height (cm)	Mean ± SD	169.5 ± 5.8	170.5 ± 5.1	^0.512
	Range	160.0–180.0	162.0–180.0	
Length of surgery (minutes)	Mean ± SD	108.0 ± 8.6	105.7 ± 10.1	^0.340
ASA (n, %)	I	13 (53.3%)	14 (56.7%)	#0.795
	II	12 (46.7%)	11 (43.3%)	

$P > 0.05$ was considered statistically non-significant.
^ Independent t-test.
# Chi square test.

randomization and were therefore not subjected to further statistical analysis (two patients needed re-exploration on account of the postoperative bleeding).

Results of the current study did not show any significant difference in the demographic data of the groups of patients regarding age, sex (male to female ratio), body weight, height, ASA physical status and the length of surgery in minutes as shown in Table 1.

The VAS for headache intensity for both groups showed non-significant difference at the start of the study (0 h). But headache intensity per VAS was reduced in both groups but reduction was more significant in hydrocortisone group at 6, 12, 24 h after the start of the treatment. At 48 h of the study, the VAS intensity for headache showed non-significant difference between the two groups (Table 2).

The comparison of mean headache intensities between both groups is plotted in Fig. 2. It showed reduction of headache intensity for both groups during 48 h after treatment. Patients of hydrocortisone group under hydrocortisone treatment showed earlier at 6, 12, 24 h after the start of the treatment and more reduction of headache rather than mannitol group under mannitol treatment throughout the time of the study.

Table 3 and Fig. 3 compared the percentage of headache relief in both study groups at each time of follow-up of the patients.

Table 2 Visual analogue scale (VAS).

Time points	Hydrocortisone (N = 25)	Mannitol (N = 25)	^P
Hour 0	9.0 (8–9)	9.0 (8–10)	0.714
Hour 6	3.0 (0–3)	3.0 (1.5–4)	**0.030***
Hour 12	0.0 (0.0–1.0)	2.0 (0.0–3.0)	**0.007***
Hour 24	0.0 (0.0–0.5)	0.0 (0.0–2.0)	**0.004***
Hour 48	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.305

The VAS for headache intensity was expressed as median and interquartile range (IQR).
^ Mann–Whitney test.
* Significant.

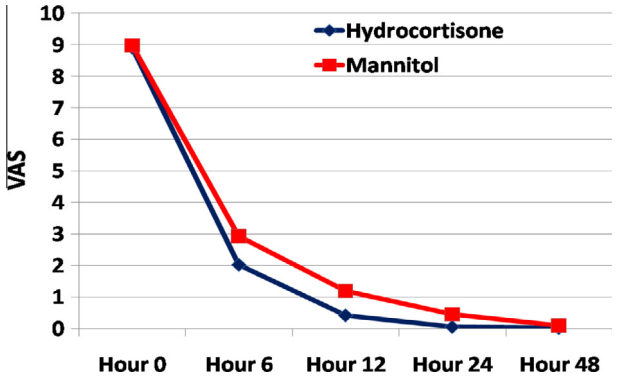

Figure 2 Comparison of headache relief per VAS between the two study groups.

Table 4 shows the fluid chart for patients of mannitol group on mannitol treatment which was done for 48 h across the time of the study. It evaluated the difference between fluid input both oral and intravenous and fluid output through urine output. After first 24 h, the mean ± SD fluid balance was 1120.0 ± 220.3 ml, and after the second twenty-four hours, the mean ± SD fluid balance was 1071.7 ± 220.3 ml. It denoted no signs of dehydration with the dose of mannitol included in this study.

No significant changes were noted in the heart rate (P = 0.289), the mean arterial blood pressure (P = 0.371) and the SpO_2 (P = 0.340) between the studied groups throughout the study period.

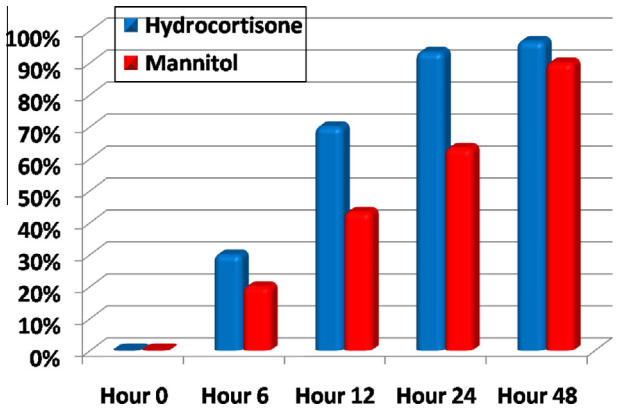

Figure 3 Comparison between reduction of headache intensity in the two groups.

Table 4 Input and output fluids (ml) for mannitol group.

Variable	Mean ± SD	Range
Day-1 IV fluid	1500.0 ± 0.0	1500.0–1500.0
Day-2 IV fluid	1500.0 ± 0.0	1500.0–1500.0
Day-1 oral fluid	1140.0 ± 161.0	900.0–1500.0
Day-2 oral fluid	1078.3 ± 114.2	900.0–1300.0
Day-1 urine	1520.0 ± 144.8	1200.0–1800.0
Day-2 urine	1506.7 ± 191.1	1000.0–1800.0
Day-1 balance	1120.0 ± 220.3	700.0–1600.0
Day-2 balance	1071.7 ± 220.3	800.0–1500.0

No significant side effects of the studied drugs occurred during the first 48 h after the start of the treatment except for two patients in hydrocortisone group complained of mild flushing and it was resolved spontaneously without treatment.

4. Discussion

This study compared IV hydrocortisone versus mannitol intravenous infusion in treatment of PDPH. It showed that 93.3% of patients under treatment of hydrocortisone recovered from headache treatment after 3 doses of hydrocortisone within 24 h, while 90% of patients on mannitol treatment showed recovery from headache at 48 h. It denoted early treatment of PDPH by hydrocortisone rather than mannitol. In addition,

Table 3 Comparison between study groups regarding percentage of headache relief throughout the study.

Time points	Measure	Hydrocortisone (N = 25)	Mannitol (N = 25)	^P	Difference (Efficacy)
At 6 h	n, %	9 (30.0%)	6 (20.0%)	^0.371	10.0%
	95% CI	13.6–46.4%	5.7–34.3%		0.0–20.7%
At 12 h	n, %	21 (70.0%)	13 (43.3%)	^**0.037***	26.7%
	95% CI	53.6–86.4%	25.6–61.0%		10.9–42.5%
At 24 h	n, %	28 (93.3%)	19 (63.3%)	^**0.005***	30.0%
	95% CI	84.4–100.0%	46.1–80.6%		13.6–46.4%
At 48 h	n, %	29 (96.7%)	27 (90.0%)	#0.612	6.7%
	95% CI	90.3–100.0%	79.3–100.0%		0.0–15.7%

CI: Confidence interval. n = number of patients relieved from headache.
Chi square test.
^ Fisher exact test.
* Significant.

Mannitol is an osmotherapy and urinary catheter is needed for follow-up fluid chart which is annoying to patients and increased risk for urinary tract infections.

No significant changes were noted in the heart rate, the mean arterial blood pressure and the SpO_2 between the studied groups throughout the study period. No significant side effects of the studied drugs occurred during the first 48 h after the start of the treatment except for two patients in hydrocortisone group complained of mild flushing and it was resolved spontaneously without treatment.

Concomitant with our study, Turiel et al., proposed use of Hydrocortisone in treatment of PDPH. In that study, patients with severe spinal headache after cesarean section, received hydrocortisone 100 mg IV every 8 h for 3 days. Headache disappeared completely 12 h after last dose [35].

These results are in agreement with the findings of Neves et al., who in their case series of three patients had reported one woman with cesarean delivery who relived completely from PDPH (after failure of conventional treatments of PDPH) and two cases of dural puncture who did not develop PDPH when IV hydrocortisone was administered prophylactically [31].

Our results were supported with the findings of Noyan Ashraf et al., who had demonstrated that IV hydrocortisone could significantly decrease the intensity of headache in women who underwent cesarean section under spinal anesthesia in the 48 h following surgical delivery [22].

Our results were consistent with the findings of Posso et al., who approved the efficacy of single dose of intravenous hydrocortisone 1000 mg and dipyrone 1000 mg orally every 6 h and venous hydration in treatment of PDPH in four female and two male patients experiencing headache after spinal anesthesia given for cesarean section, hemorrhoidectomy and knee arthroscopy [36].

Tavakol et al. used dexamethasone 0.2 mg/kg (16 mg maximum) intravenously with 1000 mL normal saline within 2 h. The findings showed that the mean pain score changed from 1.8 ± 6.5 to 1.2 ± 1.6 after treatment [37].

Hamzei et al., approved the efficacy of dexamethasone (8 mg) on PDPH and its incidence in cesarean section patients in the first 24 h and up to 1 week after surgery [38].

Doroudian et al., approved the use of intravenous (iv) dexamethasone (8 mg) prior to spinal anesthesia to limit the incidence of PDPH and improve quality of life during the postoperative period [39].

Jaun et al., showed effective prophylactic treatment of PDPH by using one prophylactic dose of iv methylprednisolone 500 mg within the first two hours after dural puncture in 10 patients out of 14 who underwent wide range of surgeries under epidural anesthesia [40].

Gherghina et al., evaluated the efficacy of intravenous methylprednisolone in reducing headache after spinal anesthesia in a study comparing the use of single dose of intravenous methylprednisolone, 500 mg versus conventional therapy [41].

Hakim, showed that the administration of Cosyntropin (ACTH) after accidental dural puncture was associated with significant reduction in the incidence of PDPH and the need for therapeutic epidural blood patch [42].

In contrary to Hakim (2010) *results*, Rucklidge et al., administered a long acting ACTH analogue (Tetracosactin zinc phosphate) or placebo to a series of 18 parturients with PDPH after deliberate or accidental dural puncture and failed to demonstrate a difference in the severity of PDPH [43].

No studies were done using mannitol for treatment of PDPH except for the study of Rizvi et al., which was in agreement with our results, who used mannitol 20% for treatment of PDPH in obstetric patients underwent cesarean section under spinal anesthesia. Their results showed that the use of mannitol 20% 100 ml infusion over ½ h followed by 100 ml every 12 h settled PDPH after first dose for 6–8 h and there was no need for mannitol infusion after 48 h [44].

5. Conclusion

Meticulous follow-up for patients with PDPH is an important responsibility of the anesthetic team. Hydrocortisone and Mannitol are effective noninvasive treatments for PDPH. But hydrocortisone got earlier relief of PDPH and needs neither urinary catheter insertion which was annoying to the patient, with increased risk of urinary tract infections (UTI), nor input/output fluid chart which was an extra follow-up item.

Strengths and limitations

Although hydrocortisone dose of the study was safe, adverse effects of steroids should not be ignored (e.g. increased risk of wound infection and delayed wound healing). Regarding use of hydrocortisone in diabetic patients, follow-up for blood sugar measurement should be done.

Clinical trial registration

ClinicalTrials.gov Identifier: NCT02760862.

Conflict of interest

None.

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