Norepinephrine versus vasopressin infusion for prevention of spinal-induced hypotension: a placebo-controlled study

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Introduction

Spinal anaesthesia is the technique of choice for elective surgery as it is an easily achievable, fast and reliable technique. Block of pre-ganglionic sympathetic fibres located in the subarachnoid space during subarachnoid anaesthesia causes decreases in systemic vascular resistance secondary to arteriolar and venous dilation, with subsequent blood pooling in the body areas under the spinal block inducing systemic hypotension.

The common mechanism of bradycardia under subarachnoid block in addition to sympathetic blockade and decreased venous return is postulated as parasympathetic over-dominance leading to a decrease in right arterial pressure and pressure in the great veins as they enter the right atrium. Nevertheless, over time, probably favoured by the reverse Trendelenburg position, this parasympathetic inhibition leads to severe bradycardia. Moreover, spinal anaesthesia-induced hypotension (SAIH) increases the risk of nausea and vomiting, altered mental status, and aspiration.

A range of strategies including physical interventions, intravenous fluids and vasopressor drugs have been used to minimise or prevent SAIH. Intravenous fluid administration as an intervention to combat SAIH is still a matter of discrepancy regarding type of fluid: either crystalloid or colloid and timing of start of fluid therapy whether pre-load or co-load. In the case of using crystalloids, co-load is more effective than pre-load for SAIH prevention. Meta-analysis showed that colloid administration significantly reduces the incidence of SAIH compared with crystalloid use, including use in obstetric patients.

Vaspressors are routinely used to counteract hypotension after neuraxial anaesthesia. The understanding of the mechanism of hypotension and the choice of vasopressor has evolved over the years, but there is no definitive evidence showing absolute clinical benefit of one vasopressor over the other.

Hypothesis

Prophylactic vasopressor infusions started synchronously with spinal block could ameliorate and/or minimise spinal anaesthesia-induced hypotension. The infusion concentrations used and rate of administration are appropriate to achieve this target.

Objectives

Evaluation of heart rate (HR) and systolic arterial pressure (SAP) changes induced by nor-epinephrine (NE) or vasopressin (VP) infusions initiated synchronously with spinal local anaesthetic injection were compared with control patients, who received placebo infusion.

Patients and methods

The current prospective study was conducted in the Anaesthesia Department, Cairo University Hospital from January 2014 to August 2016. The study protocol was approved by the Local Ethical Committee. All adult males assigned for lower abdominal and lower limb surgeries that could be performed under spinal anaesthesia and who signed written fully informed consent were included in the study.
Patients maintained on cardiovascular medications including calcium-channel blockers, angiotensin convertase inhibitors, β- or α-blocking agents, or α2-adreno-receptor agonists, and patients with arterial disease, morbid obesity, diabetes mellitus or other metabolic diseases, and hypertension were excluded.

All patients underwent full clinical examination and laboratory investigations for assurance of inclusion criteria, ASA grading and determination of baseline HR and blood pressure measures: systolic, diastolic and mean arterial pressure (SAP, DAP and MAP).

Patients were randomly allocated, using sealed envelopes prepared by a blinded assistant and chosen by the patient himself, into three equal groups (Control, NE and VP) according to infusion used. All patients were premedicated by intravenous (IV) injection of metoclopramide 10 mg, ranitidine 50 mg and midazolam 0.01 mg/kg. All patients received lactated Ringer’s (LR) solution 20 ml/kg during the 20 min prior to induction of spinal anaesthesia as pre-load fluid therapy (FT). For all patients, irrespective of change in blood pressure, hourly maintenance FT was given in the range of 100–140 ml in addition to replacement of blood loss by 3 ml crystalloid for each ml blood loss and for loss in urine by 1 ml for each ml urine output. If SAP was decreased by > 20% of the baseline SAP, patients received an additional bolus of lactated Ringer’s solution in a dose of 10 ml/kg over a period of 10 min at a rate of 1 ml/kg/min.

Lumbar puncture was performed while the patient was in a sitting position, at the level of the L4–L5 interspace with a 90 mm, 27 or 25 G Sprottew spinal needle. Hyperbaric bupivacaine 10 mg was spinally injected and the level of sensory block was then assessed.

Saline solutions (plain in Group C and containing vasopressors in Groups NE and VP) were on standby and infusion was initiated synchronously with spinal anaesthetic injection. In the NE group, nor-epinephrine (Levophed, Hospira Inc., Brussels, Belgium) infusion was prepared by a blinded assistant as 0.1 mg/ml in physiological (0.9%) saline and given at rate of 3 ml/h. In the VP group, vasopressin infusion was prepared by diluting 20 U of VP in 60 ml of physiological saline, so each 3 ml contained 1 U of VP and continuous infusion was started at the rate of 1 U/h (3 ml/h). Vasopressor infusion rates were adjusted to achieve SAP of ≤ 10% of baseline SAP levels therapy and infusion was then stopped.

**Evaluated parameters**

1. Arterial blood pressure measures (SAP, DAP and MAP) and HR measures were monitored non-invasively at 1, 4, 7 and 10 min and then every 5 min for 30 min after spinal injection.

2. The extent of change of SAP in comparison with baseline SAP was noted:
   - Reduction of SAP by ≤ 10% of baseline SAP was considered as no hypotension and received only maintenance fluid therapy.
   - Reduction of SAP by > 10% was treated using supplementary fluid loading and adjustment of infusion rate.
   - Reduction of SAP by > 20% and/or cases that developed hypotension resistant to fluid therapy and infusion rate adjustment received ephedrine in a dose of 10 mg intravenous bolus.
   - Increased SAP to any extent was managed through infusion rate adjustment.

3. The extent of change of HR in comparison with baseline HR:
   - Increased HR to any extent was managed through infusion rate adjustment.
   - Decreased HR down to < 60 beats/min was treated by an intravenous atropine bolus of 0.01 mg/kg.

4. Frequency of nausea and vomiting and need for anti-emetic therapy was also recorded.
Norepinephrine versus vasopressin infusion for prevention of spinal-induced hypotension: a placebo controlled study

Table 1: Enrolment data of studied patients categorised according to modality used for management of SAIH

| Group data                  | Control          | NE              | p-value | VP             | p-value |
|-----------------------------|------------------|-----------------|---------|----------------|---------|
| Age (year)                  | 33.3 ± 6.7       | 34.5 ± 8.9      | p₁ = 0.611 | 33 ± 8.6       | p₁ = 0.9 |
| Weight (kg)                 | 81.6 ± 8.3       | 81 ± 9.8        | p₁ = 0.899 | 79.3 ± 10.8    | p₁ = 0.292 |
| Height (cm)                 | 169.9 ± 3.8      | 170 ± 3.5       | p₁ = 0.803 | 169.8 ± 3.5    | p₁ = 0.789 |
| BMI (kg/m²)                 | 28.3 ± 2.7       | 28 ± 3.5        | p₁ = 0.892 | 27.5 ± 3.8     | p₁ = 0.336 |
| ASA grade                   |                  |                 |         |                |         |
| ASA I                       | 69 (86.3%)       | 66 (82.5%)      | p₁ = 0.514 | 67 (83.8%)     | p₁ = 0.658 |
| ASA II                      | 11 (13.7%)       | 14 (17.5%)      |         | 13 (16.2%)     |         |
| Indications for surgery     |                  |                 |         |                |         |
| Inguinal hernia             | 20 (25%)         | 22 (27.5%)      | p₁ = 0.399 | 21 (26.2%)     | p₁ = 0.703 |
| Bladder stone               | 14 (17.4%)       | 16 (20%)        |         | 11 (13.7%)     |         |
| Bilateral varicocele        | 16 (20%)         | 18 (22.5%)      |         | 13 (16.3%)     |         |
| Minor orthopaedic surgery   | 9 (11.3%)        | 8 (10%)         |         | 12 (15%)       |         |
| Scrotal swelling            | 12 (15%)         | 9 (11.3%)       |         | 13 (16.3%)     |         |
| Varicose vein               | 9 (11.3%)        | 7 (8.7%)        |         | 10 (12.5%)     |         |

Notes: Data are presented as mean ± SD and numbers; percentages are in parentheses; NE: nor-epinephrine; VP: vasopressin; p₁: significance of difference versus control measure; p₂: significance of difference versus NE measures; p > 0.05 indicates non-significant difference.

Table 2: Intra-operative data of studied patients categorised according to modality used for management of SAIH

| Group data                  | Control group | NE group       | p-value | VP group | p-value |
|-----------------------------|---------------|----------------|---------|----------|---------|
| Level of anesthesia         | T8            | 5 (6.25%)      | p₁ = 0.508 | 6 (7.5%) | p₁ = 0.719 |
| T9                          | 10 (12.5%)    | 11 (13.75%)    |         | 10 (12.5%) | p₁ = 0.722 |
| T10                         | 37 (46.25%)   | 39 (48.75%)    |         | 40 (50%) |         |
| T11                         | 23 (28.75%)   | 20 (25%)       |         | 18 (22.5%) |         |
| T12                         | 3 (3.75%)     | 2 (2.5%)       |         | 3 (3.75%) |         |
| L1                          | 2 (2.5%)      | 1 (1.25%)      |         | 3 (3.75%) |         |
| Surgical approach           | Open          | 62 (77.5%)     | p₁ = 0.768 | 61 (76%) | p₁ = 0.775 |
| Endoscopic                  | 18 (22.5%)    | 20 (25%)       |         | 19 (23.7%) | p₁ = 0.804 |
| Amount of IO blood loss (ml)| 220±105.4     | 203.5±118.2    | p₁ = 0.352 | 212±103  | p₁ = 0.768 |

Notes: Data are presented as mean ± SD and numbers; percentages are in parentheses; NE: nor-epinephrine; VP: vasopressin; p₁: significance of difference versus control measure; p₂: significance of difference versus NE measures; p > 0.05 indicates non-significant difference.

Study outcome

(1) Primary outcome: the study primary outcome targets prevention and/or amelioration of the spinal anaesthesia-induced hypotension.

(2) Secondary outcome: this included proper adjustment of rate and duration of infusion to obtain minimal intraoperative (IO) HR and SAP fluctuation, and minimising other manifestations of SAIH such as nausea and vomiting during surgery.

Statistical analysis

Considering the incidence of hypotension in spinal blocks to be 70% with placebo infusion and 40% with vasopressor infusion, this gave the possibility of a decrease in hypotension frequency of 30% with the use of vasopressor infusion. The sample size was calculated using the standard equation proposed by Kadam amd Bhalerao, with α error at 0.05, Zα of 70%, Z₁-β of 40% and to avoid types I and II errors a sample size of 78 patients per group is required to obtain a study power of 80%. Sample size and power were re-calculated and assured using the Power and Sample Size Calculation Software program provided by the Department of Biostatistics, Vanderbilt University (Nashville, TN, USA). Obtained data were presented as mean ± SD, ranges, numbers and ratios. Results were analysed using a paired t-test for inter-group changes, one-way ANOVA with post hoc Tukey HSD test for inter-group changes and a chi-square test for numbers and percentages. Statistical analysis was conducted using the SPSS Version 15® (SPSS Inc., Chicago, IL, USA) for Windows statistical package. A p-value of < 0.05 was considered statistically significant.
### Results

There was a non-significant difference between the studied groups as regards enrolment data as shown in Table 1. All patients had successful spinal block in the range of T8–L1; 177 patients had a block level of T10–T11, 49 patients had a block level of T8–T9 and 14 patients had a block level of T12–L1. A total of 183 (76.2%) underwent open surgery, while 57 patients (23.8%) underwent endoscopic surgery. Mean intraoperative blood loss was 150 ± 103 ml; range: 35–450 ml. There was a non-significant difference between studied groups as regards operative data, as shown in Table 2.

In the control group, SAP was decreased to >20% of baseline SAP in eight patients (10%), while in 22 patients (27.5%) SAP was decreased by <10% and in 50 patients (62.5%) SAP decrease was in the range of 10–20% of baseline SAP. In the NE and VP groups, no patient had decreased SAP by >10% of baseline SAP, while 15 patients had increased SAP by >10% and 145 patients showed no SAP change with a significant difference between the two groups (p = 0.0003). Details of the extent of SAP change in relation to baseline SAP of studied patients throughout the 30 min after spinal block are shown in Table 3.

Throughout the 30 min after spinal block, all HR and SAP measures of control patients were significantly (p = 0.001) lower compared with their baseline measures and with corresponding measures of patients in the NE and VP groups, with a non-significant difference between the two groups, as shown in Table 4.

### Table 3: Extent of SAP change in relation to baseline SAP of studied patients throughout the 30 min after spinal block

| Group  | Extent of change | 1 min | 4 min | 7 min | 10 min | 15 min | 20 min | 25 min | 30 min |
|--------|------------------|-------|-------|-------|--------|--------|--------|--------|--------|
| Control| Increase of < 10 | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      |
|        | Decrease of (%)  | < 10  | 80 (100%) | 49 (61.3%) | 22 (27.5%) | 36 (45%) | 48 (60%) | 58 (72.5%) | 64 (80%) | 68 (85%) |
|        |                  | 10–20 | 0     | 28 (35%) | 50 (62.5%) | 36 (45%) | 26 (32.5%) | 19 (23.8%) | 14 (17.5%) | 12 (15%) |
|        |                  | > 20  | 0     | 3 (3.8%) | 8 (10%)  | 8 (10%)  | 6 (7.5%)  | 3 (3.8%)  | 0      | 0      |
| NE     | Increase of < 10 | 9 (11.3%) | 19 (23.8%) | 18 (22.5%) | 24 (30%)  | 23 (28.8%) | 19 (23.8%) | 9 (11.3%) | 11 (13.8%) |
|        | Decrease of (%)  | < 10  | 66 (82.5%) | 55 (68.8%) | 50 (62.5%) | 34 (42.5%) | 28 (35%)  | 27 (33.8%) | 22 (27.5%) | 12 (15%) |
|        |                  | 10–20 | 0     | 0     | 0     | 0     | 0     | 0     | 0     |
|        |                  | > 20  | 0     | 0     | 0     | 0     | 0     | 0     | 0     |
| VP     | Increase of < 10 | 0     | 0     | 0     | 0      | 0      | 10 (12.5%) | 13 (16.3%) | 7 (8.8%) | 4 (5%) |
|        | Decrease of (%)  | < 10  | 80 (100%) | 49 (61.3%) | 22 (27.5%) | 36 (45%) | 48 (60%) | 58 (72.5%) | 64 (80%) | 68 (85%) |
|        |                  | 10–20 | 0     | 28 (35%) | 50 (62.5%) | 36 (45%) | 26 (32.5%) | 19 (23.8%) | 14 (17.5%) | 12 (15%) |
|        |                  | > 20  | 0     | 3 (3.8%) | 8 (10%)  | 8 (10%)  | 6 (7.5%)  | 3 (3.8%)  | 0      | 0      |

Note: Data are presented as numbers, percentages are in parentheses; NE: nor-epinephrine; VP: vasopressin.

### Table 4: Mean (±SD) of HR and SAP measurements recorded in studied patients throughout the 30 min after spinal block

| Parameter         | Group  | Baseline | 1 min | 4 min | 7 min | 10 min | 15 min | 20 min | 25 min | 30 min |
|-------------------|--------|----------|-------|-------|-------|--------|--------|--------|--------|--------|
| HR (beats/ min)   | Control| 82.1 ± 4.1 | 76.4 ± 3.3 | 74.2 ± 6.9 | 70.1 ± 7.6 | 68.3 ± 6.2 | 67.2 ± 6.4 | 71.5 ± 9.2 | 73.6 ± 6.6 | 75.2 ± 8.1 |
|                   | NE     | 81.7 ± 4 | 78.8 ± 5.6 | 79.4 ± 5.6 | 79.1 ± 7.6 | 79.4 ± 7.1 | 79.3 ± 6.8 | 79.2 ± 5.6 | 79.4 ± 7.1 | 79.4 ± 7.7 |
|                   | VP     | 81.9 ± 3.4 | 78.7 ± 3.9 | 78 ± 7.5 | 78.6 ± 5.7 | 79 ± 8.3 | 79.4 ± 6.3 | 79.4 ± 6.3 | 79.3 ± 5.5 | 79.8 ± 5.8 |
| SAP (mmHg)        | Control| 120.2 ± 3.8 | 113.9 ± 5.1 | 108.5 ± 5.7 | 102.6 ± 7.7 | 105.8 ± 8.1 | 106.5 ± 6.5 | 109 ± 5.5 | 111.4 ± 4.4 | 113.9 ± 5.2 |
|                   | NE     | 120.4 ± 6.3 | 117.7 ± 7.7 | 118.7 ± 6.7 | 119 ± 5.7 | 120.2 ± 6 | 120.4 ± 6 | 120.1 ± 5.8 | 120 ± 6.1 | 120.3 ± 6.3 |
|                   | VP     | 119.7 ± 6.9 | 115.5 ± 7 | 114.9 ± 6.8 | 116.7 ± 6.4 | 117.5 ± 6.5 | 118.6 ± 6.6 | 118.7 ± 6.3 | 118.9 ± 6.4 | 119.1 ± 6.6 |

Notes: NE: nor-epinephrine; VP: vasopressin; p1: significance of difference versus baseline; p2: significance of difference versus control measure; p3: significance of difference versus NE measures; p < 0.05 indicates significant difference; p > 0.05 indicates non-significant difference.
During the 30 min after spinal injection seven patients (8.8%) in the control group had nausea and three (3.8%) of them had one bout of vomiting. Only one patient (1.3%) required injection of anti-emetic therapy, while the others responded to fluid therapy. No patient in the NE and VP groups had nausea or required anti-emetic therapy.

Discussion
The results obtained fulfilled the study hypothesis where throughout the 30 min after spinal block, all SAP and HR measures of patients who received plain saline infusion were significantly lower compared with their baseline measures and with corresponding measures of patients who received vasopressor infusions, with a non-significant difference between the NE and VP groups. No patient in the NE and VP groups had decreased SAP of > 10%, while in the control group eight patients had decreased SAP of > 20%. 50 patients had SAP decrease of 10–20% and 22 patients had SAP decrease of < 10%. Moreover, 145 of those patients who received vasopressor infusion showed no SAP change and 15 patients showed increased SAP of > 10%; 11 received NE and four received VP with a significantly higher frequency in the case of the NE than the VP group.

Unfortunately, few studies have evaluated the use of vasopressor infusion for the management of SAIH that has developed in patients undergoing non-obstetric surgery. However, the outcome of the current study supports that previously reported by Braun et al.17 who presented a case of severe primary pulmonary hypertension in a patient undergoing skin grafting for a leg ulcer under spinal anaesthesia (SA) with an IV infusion of vasopressin, and documented that VP infusion prevented systemic hypotension resulting from sympathetic blockade while avoiding increases in pulmonary vascular resistance, which may result from catecholamine usage. Also, Shamshey et al.18 reported that in patients undergoing lower limb and abdomen surgeries under neuraxial blockade, mean systolic and diastolic arterial pressure were significantly lower in patients in a control group at the initial 14 min than in patients who received VP infusion.

Despite the previously documented exaggerated response to spinal anaesthesia in females,19–22 the effectiveness of NE infusion for maintaining blood pressure with associated greater heart rate and cardiac output than with phenylephrine during SA for Caesarean section, as documented in the literature,23–25 could be considered as support for the results of the current study.

From an ethical point of view, all patients received pre-load crystalloid fluid therapy to minimise the decrease in blood pressure and to guard against post-lumbar-puncture headache, especially in the control group, which did not receive other medication. Such a rationale coincided with previous studies which documented that fluid loading before administration of spinal anaesthesia decreases the incidence of postoperative nausea and vomiting,26 minimises hypotension in the first 10 min after spinal anaesthesia27 and results in an increase in stroke volume and cardiac output.28 Moreover, all patients were premedicated with antiemetics to minimise the frequency and severity of spinal-anaesthesia-associated nausea and vomiting. This policy for the use of pre-medication with anti-emetics goes hand in hand with previous studies that used various antiemetics as prophylaxis prior to dural puncture.29,30

The current study relied on initiation of the vasopressor infusion synchronously with spinal injection of local anaesthetic as prophylaxis against SAIH. In support of the prophylactic use of the vasopressor infusion prior to spinal anaesthesia, Ferré et al.31 found prophylactic phenylephrine infusion to be an effective method of reducing SAIH in the elderly undergoing orthopaedic surgery as it delays the onset time of hypotension with reduction in number of hypotensive episodes per patient. Also, Singh et al.32 found ephedrine pre-treatment before subarachnoid block in elderly patients undergoing orthopaedic surgeries to be effective for the prevention of post-subarachnoid block hypotension, and Abbavish et al.33 compared the outcome of prophylactic phenylephrine and ephedrine in patients undergoing hip surgery and reported favourable control of blood pressure, irrespective of the difference between these drugs.

Conclusion
Vasopressor infusion given synchronously with spinal injection is an appropriate prophylactic policy against SAIH. VP infusion allowed control of blood pressure despite the significant decrease till 7 min after spinal injection. However, NE infusion was superior to VP infusion and provided better haemodynamic stability after spinal injection.

Conflict of interest – No conflict of interest was reported by the authors.

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Norepinephrine versus vasopressin infusion for prevention of spinal-induced hypotension: a placebo controlled study

100
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