Prevention of postoperative hypotension following spinal anesthesia for TURP: a double-blind randomized controlled trial comparing ephedrine with placebo

J. Verdeyen (*), J. P. Ory (**), W. Wyckmans (**), E. Vandermeersch (*), L. Jamaer (**) and A. Van Assche (**)

Abstract: Spinal hypotension (SH) is a common side effect of spinal anesthesia and may also occur after the surgical procedure. In this double-blinded, placebo-controlled, randomised clinical trial fifty patients undergoing transurethral prostatectomy under spinal anesthesia received 10 mg of ephedrine IV before being transferred from the operating table into their bed after the procedure, whereas fifty controls received saline IV. The number of per- and postoperative hypotensive episodes and vasopressor use, time delay between the administration of the study medication and the first hypotensive episode, level of spinal blockade at the start of surgery, pre- and postoperative hemoglobin and sodium concentration, cardiovascular co-morbidity and chronic medication were registered. There was no statistically significant difference in the incidence of postoperative hypotension between the two groups, but Poisson regression of the expected number of postoperative hypotensive episodes per patient showed a protective effect of ephedrine (p < 0.05). The occurrence of peroperative hypotension was a risk factor for developing postoperative hypotension (p < 0.05). There was no statistically significant relation between age, level of spinal blockade, cardiovascular co-morbidity or biochemical parameters and the risk of developing per- or postoperative hypotension, except for a correlation between preoperative alpha-receptor blocking drugs and peroperative hypotension (p < 0.05).

Postoperative hypotension (recorded incidence 31%) was almost as common as peroperative hypotension (recorded incidence 37%) and occurred as late as 190 minutes after the end of surgery. Ephedrine IV at the end of surgery reduced the number of postoperative hypotensive episodes per patient but did not reduce the overall incidence of postoperative SH.

Key words: Ephedrine; hypotension; spinal anesthesia; postoperative; transurethral resection of the prostate.

Introduction

Spinal hypotension (SH) is a common side effect of spinal anesthesia. Clinical experience and literature show that SH not only occurs after the initiation of anesthesia and during the procedure, but also during transport of the patient from the operating room to the PACU and during the early postoperative period (2).

Several means to prevent SH have been investigated, but no study has focused on the immediate postoperative period. We investigated if the prophylactic administration of 10 mg ephedrine IV just before the transfer of the patient from the operating table into his bed could decrease the number of postoperative hypotensive episodes. We also investigated if there was a relation between the occurrence of peroperative hypotension and postoperative hypotension and if patients who had experienced peroperative hypotension benefitted more from prophylactic ephedrine administration than the patients who had not experienced peroperative hypotension.

Many studies have tried to identify risk factors for the development of SH, but so far none has made the distinction between per- and postoperative hypotension. We looked for a correlation between per- and postoperative hypotension and age, cardiovascular comorbidity, cardiovascular drug use, level of spinal blockade and difference in hemoglobin concentration and natremia before and after the procedure.
METHODS

Following Ethics Committee approval 100 patients undergoing TURP under spinal anesthesia were included in a double-blind RCT. Except for patient’s refusal there were no exclusion criteria. Written informed consent was obtained from every patient. The spinal anesthesia and volume loading were standardised. According to the institution’s policy, all patients were preloaded with 500 ml of Ringer’s solution before the induction of anesthesia. Spinal anesthesia was performed in the seated position. A 27 gauge pencil point Pencan spinal needle was advanced through the L3-L4 intervertebral space until free flowing CSF was obtained. We injected two point eight ml of a hyperbaric 0.5% bupivacain solution intrathecally. Oxygen saturation and ECG were recorded continuously, blood pressure was measured non-invasively every five minutes or on clinical indication. Monitoring started before the induction of anesthesia. The level of spinal blockade was determined before the start of surgery by cold discrimination. All patients were breathing oxygen enriched air (3l of O2 per minute via nasal canula). Peroperative fluid administration and vasopressor use were guided by the attending anesthetist. After the procedure, just before being transferred back into bed, the patients in the placebo (S) group (n : 50) received 2 ml of a 0.9% NaCl solution IV, the patients in the intervention (E) group (n : 50) received 2 ml of a 0.5% ephedrine solution IV. Following the institution’s policy, postoperative hypotension was managed by administration of IV ephedrine unless the attending anesthetist decided differently. On arrival in the PACU haemoglobin concentration and natremia were determined. Postoperatively patients were monitored for at least two hours in the PACU and were then discharged after approval of the attending anesthetist and the treating surgeon.

Age, cardiovascular history and cardiovascular medication use, level of spinal blockade at start of surgery, number of peroperative hypotensive episodes (a hypotensive episode was defined as a decrease of the systolic blood pressure of 20% or more from the baseline value), peroperative vasopressor use, time of administration of study medication, number of postoperative hypotensive periods, delay between administration of study medication and occurrence of first postoperative hypotensive episode, postoperative vasopressor use, pre- and postoperative hemoglobin concentration and natremia were recorded.

The efficacy of the intervention on the incidence of postoperative hypotension was analysed using the chi-square test, the efficacy on reducing the number of hypotensive episodes per patient by Poisson regression. Risk factors were analysed using logistic regression.

RESULTS

Data collection was complete except for the level of spinal blockade in 6 patients and the preoperative natremia in 1 patient. The S group and the E group were comparable for age, cardiovascular comorbidity, cardiovascular drug use, level of spinal blockade, preoperative and postoperative haemoglobin concentration, preoperative and postoperative natremia, preoperative versus postoperative hemoglobin concentration difference and preoperative versus postoperative natremia difference (Table I and II).

The number of patients experiencing peroperative hypotension was 21 in the S group versus 16 in the E group. Postoperatively there were 18 patients in the S group having at least one hypotensive episode versus 13 in the E group.

This difference was not statistically significant (RR of postoperative hypotensive episode after ephedrine 10 mg IV versus placebo : 0.75, (95% CI : 0.41 ;1.36), p = 0.34). Also subanalysis of the group of patients who had suffered at least one

Table I

Comparison of baseline variables between S group and E group. There were no statistically significant differences

<table>
<thead>
<tr>
<th></th>
<th>S group (mean +/- SD)</th>
<th>E group (mean +/- SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 +/- 9.3</td>
<td>66 +/- 9.4</td>
</tr>
<tr>
<td>Height of spinal blockade (segments)</td>
<td>710 +/- 2</td>
<td>710 +/- 2</td>
</tr>
<tr>
<td>Preop hemoglobin concentration (g/dl)</td>
<td>14.8 +/- 1.4</td>
<td>14.7 +/- 1.6</td>
</tr>
<tr>
<td>Preop hemoglobin concentration (g/dl)</td>
<td>12.2 +/- 2.1</td>
<td>13 +/- 1.6</td>
</tr>
<tr>
<td>Hemoglobin difference (g/dl)</td>
<td>-2 +/- 1.9</td>
<td>-1.6 +/- 1.1</td>
</tr>
<tr>
<td>Preop natremia (mmol/l)</td>
<td>140 +/- 3.6</td>
<td>141 +/- 2.2</td>
</tr>
<tr>
<td>Postop natremia (mmol/l)</td>
<td>137 +/- 6.2</td>
<td>139 +/- 3.8</td>
</tr>
<tr>
<td>Natremia difference (mmol/l)</td>
<td>-3 +/- 6.8</td>
<td>-2 +/- 3.9</td>
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peroperative hypotensive episode was unable to show a statistically relevant benefit of the study medication in preventing postoperative hypotension (Table III).

Occurrence of a peroperative hypotensive episode was a risk factor for developing postoperative hypotension (RR of postoperative hypotension after peroperative hypotension : 1.82, (95% CI : 1.02 ; 3.23), p = 0.042).

The use of per- and postoperative ephedrine use is shown in table IV. There were no statistically significant differences.

The number of peroperative hypotensive episodes per patient varied between 0 and 5 in the S group and between 0 and 4 in the E group. The number of postoperative hypotensive episodes per patient varied between 0 and 10 in the S group and between 0 and 12 in the E group. Using logarithmically transformed data (Poisson regression), there was a statistically significant difference in the number of postoperative hypotensive episodes to be expected per patient : 1.2 for the patients in the S group versus 0.37 for the patients in the E group (RR 0.31, (95% CI : 0.13 ;0.66), p = 0.004).

When applying the same statistics to the sub-group of patients who had experienced at least one peroperative hypotensive episode, this difference became even more important (RR 0.27, (95% CI : 0.06 ;0.84), p = 0.004) (Table V).

The first recorded postoperative hypotensive episode occurred as early as 1 minute after the administration of the study medication. One patient developed his first hypotensive episode 192 minutes after the administration of the study medication!

During the first 15 minutes following study-medication administration 8 patients developed hypotension, equally divided between the S group (n = 4) and the E group (n = 4).

The age of the patients varied between 46 and 87 years (mean 70 ± 9.5 years). There was no significant correlation between age and the incidence of peroperative or postoperative hypotension.

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**Table II**

Comparison of cardiovascular comorbidity and drug use between S group and E group.

<table>
<thead>
<tr>
<th></th>
<th>S group (% of total)</th>
<th>E group (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular (CV) morbidity</td>
<td>28 (56)</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>16 (32)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>3 (6)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>CA-antagonist</td>
<td>7 (14)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>9 (18)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (8)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Cumulative CV drug use</td>
<td>27 (54)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Taking more then one class</td>
<td>10 (20% of total, 37% of CV drug users)</td>
<td>10 (20% of total, 38% of CV drug users)</td>
</tr>
</tbody>
</table>

**Table III**

Number of patients experiencing at least one per- or postoperative hypotensive episode.

<table>
<thead>
<tr>
<th></th>
<th>S group (%)</th>
<th>E group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroperative hypotensive episode</td>
<td>21 (42)</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Postoperative hypotensive episode</td>
<td>18 (36)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Postoperative hypotensive episode (subpopulation experiencing at least one peroperative hypotensive episode)</td>
<td>10 (48)</td>
<td>6 (38)</td>
</tr>
</tbody>
</table>

**Table IV**

Comparison of per- and postoperative ephedrine use between S group and E group.

<table>
<thead>
<tr>
<th></th>
<th>S group</th>
<th>E group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroperative ephedrine (range, mean, +/- SD in mg)</td>
<td>0-50, 15 +/- 3.5</td>
<td>0-30, 10 +/- 3.5</td>
</tr>
<tr>
<td>Postoperative ephedrine (range, mean, +/- SD in mg)</td>
<td>0-30, 15 +/- 7.7</td>
<td>0-30, 10 +/- 8.6</td>
</tr>
</tbody>
</table>
Concerning peroperative hypotension, we observed an increasing incidence with age until the age of 70 years, after which there was a levelling of the incidence. This factor almost reached statistical significance (p = 0.053). Concerning postoperative hypotension we observed an increase in incidence from 46 years to 68 years and then a gradual decline in the patients over 68 years.

Fifty-six patients (56%) suffered from cardiovascular comorbidity (AHT, ischemic heart disease, heart failure, rhythm disorders) and 53 patients (53%) were treated with cardiovascular active medication. In general, there was no significant correlation between cardiovascular comorbidity or cardiovascular drug use and the occurrence of peroperative or postoperative hypotension. The only statistically significant relationship was between the use of alpha-receptor blocking drugs and the occurrence of peroperative hypotension (RR of peroperative hypotension when taking alpha-receptor blocking drugs : 5.903 (95% CI : 1.125 ; 30.975), p = 0.035).

The level of spinal blockade at the start of surgery varied between T3 and T12 (mean T9 ± 2 segments). There was no statistical correlation between the level of spinal blockade and the incidence of per- or postoperative hypotension.

The preoperative hemoglobin concentration varied between 9.4 g/dl and 17.3 g/dl (mean 14.7 ± 1.5 g/dl). The postoperative hemoglobin concentration varied between 5.7 g/dl and 15.8 g/dl (mean 12.7 ± 1.9 g/dl), resulting in a preoperative versus postoperative hemoglobin concentration difference ranging from plus 0.3 g/dl to minus 8.3 g/dl. The preoperative natremia ranged from 135 mmol/l to 158 mmol/l (mean 140 ± 3 mmol/l). The postoperative natremia ranged from 121 mmol/l to 144 mmol/l (mean 138 ± 5.3 mmol/l), resulting in a preoperative versus postoperative natremia difference ranging from minus 2 mmol/l to plus 30 mmol/l. There was no statistical correlation between any of these biochemical parameters and the occurrence of peroperative or postoperative hypotension.

**DISCUSSION**

There are abundant publications on the prevention of SH. Not surprisingly since the incidence of SH is very high with reported incidences ranging from 15 to more than 50% (5, 10, 15) of patients.

Both the preventive preloading by crystalloids or colloids and the preventive administration of vasopressors such as ephedrine, phenylephrine and ergotamine have been studied in detail. Studies concerning the effect of preloading give conflicting results. Generally colloids seem to be more effective than crystalloids (3, 15), although some studies fail to detect any differences (7). Also hypertonic saline has proved to be potentially beneficial (20). The timing of preloading equally seems to be of importance (13). Arnott et al. found in a large RCT that the beneficial effect of preloading with colloids only lasts during the first 15 minutes after volume administration (1). Peroperative fluid administration was not standardised in our study because of difficulties with reproducibility and the need for invasive monitoring techniques to do so.

Different agents and different means of administration (intramuscular, oral, intravenous) have been studied and most interventions are effective to a certain point (4, 6, 8, 14, 16). It is important to determine the advantages such an intervention can provide since side-effects of vasopressors are rare, but can be serious, as reported by Wahl et al. (19). This is why some authors have recommended the use of atropine in the prevention of SH (considering the fact that the absence of reflex-tachycardia is an important factor in the pathogenesis of SIH). Although this was effective in at least one study (11), the doses used (10 microgr/kg) were prone to eliciting cardio-vascular side-effects as well. In our trial we didn’t see any adverse reactions on the administration of 10 mg ephedrine IV.

Ephedrine is a direct and indirect sympathicomimetic. This means that its action is partially dependent on the condition of the patient. When

**Table V**

<table>
<thead>
<tr>
<th></th>
<th>S group</th>
<th>E group</th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire population</td>
<td>1.2</td>
<td>0.37</td>
<td>0.31 (0.13;0.66)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Subgroup</td>
<td>2.1</td>
<td>0.60</td>
<td>0.27 (0.06;0.84)</td>
<td>0.0042</td>
</tr>
</tbody>
</table>
administered intravenously it will have a limited
time of action which is difficult to predict.

Transferring the patient from the operating
table into his bed and to the PACU is an event prone
to SH because of the positional changes of the
patient during the process. In the study of BANDI et
al. ten percent of patients developed SH during this
procedure (2). In our study 8% of patients devel-
oped SH during the first 15 minutes following study
medication administration. There was no difference
between the S group and the E group. When we
extended the observation to the entire postoperative
period in the PACU, we also didn’t find any benefit
of the prophylactic administration of 10 mg
ephrine IV on the incidence of SH. Even the
group of patients who had had a peroperative
hypotensive episode (and who were at greater risk
of developing postoperative hypotension, cfr.supra)
didn’t seem to benefit from prophylactic ephrine
administration. But when we performed a Poisson
regression on the number of postoperative hypoten-
sive episodes per patient, we did find a statistically
significant difference since we forecasted an aver-
age of 1.2 postoperative hypotensive episodes for
the patients in the S group versus 0.37 hypotensive
episodes for the patients in the E group (table V).
This resulted in a relative risk after prophylactic ephrine
administration of 0.31 (95% CI : 0.13 ; 0.66), with a p-value of 0.0042. As mentioned
above, this risk reduction became even more impor-
tant when applied to the subgroup of patients who
had experienced at least one peroperative hypoten-
sive episode.

Postoperative hypotension was in our study
with an overall incidence of 31% almost as frequent
as peroperative hypotension (incidence 37%).
Noteworthy is the fact that one patient experienced
a first hypotensive episode 192 minutes after the
administration of the study medication. This finding
calls for an adequately long observation of patients
after such procedures.

Many studies have looked for risk factors for
SH, but none has made the distinction between per-
and postoperative hypotension. During this
trial we tried to identify risk factors for per- as well
as postoperative SH. In the benchmark article of
CARPENTER et al. (5), several risk factors were iden-
tified, the most important ones being age above
40 years, level of spinal blockade higher than T5, a
baseline systolic blood pressure lower then
120 mmHg, a combined general and spinal anesthe-
sia and level of spinal puncture at L2-L3 or higher.
Other studies of the same period (17, 18) came to
the same conclusion regarding age and level of
spinal blockade, but didn’t confirm the other risk
factors. A more recent, extensive study by
HARTMANN et al. (9) only confirmed the level of
spinal blockade as a risk factor and added 4 more
risk factors, i.e. obesity, chronic alcohol consump-
tion, history of arterial hypertension and emergency
surgery.

Our study didn’t show a statistically significant
relationship between per- or postoperative SH and
age, level of spinal blockade, cardiovascular comor-
bidity or the use of cardiovascular medication. The
only statistically significant relationship was
between the preoperative use of alfa-receptor block-
ing drugs and the occurrence of peroperative
hypotension (OR : 5.9, p : 0.0358) and between the
occurrence of intraoperative hypotension and post-
operative hypotension (RR : 1.8, p = 0.042).

Also the differences between pre and postop-
erative hemoglobin concentration and sodium con-
centration, values which are indicators of the blood
loss and irrigation fluid absorption (and in that way
of the duration and the extensiveness of the surgery)
were statistically not correlated with the risk of per-
or postoperative SH.

CONCLUSION

The prophylactic administration of 10 mg
ephrine IV before transferring the patient back
into bed after a TURP procedure was not an effec-
tive way of reducing the incidence of postoperative
hypotension in our trial although Poisson regression
showed a reduction of the number of hypotensive
episodes per patient. We could not establish any
relation between age, cardiovascular comorbidity,
use of cardiovascular drugs, changes in pre- versus
postoperative hemoglobin and sodium concentra-
tion, level of spinal blockade and the occurrence of
per- or postoperative hypotensive episodes. Patients
taking alfa-receptor blocking drugs had an
increased risk of developing peroperative hypoten-
sion and patients who had experienced intraopera-
tive hypotension were at increased risk of develop-
ing postoperative hypotension.

This trial confirms that both peroperative and
postoperative hypotension are frequent after spinal
anesthesia for TURP procedures. Even three hours
postoperatively some patients experienced hypoten-
sive episodes requiring vasopressor administration.
This finding calls for rigorous per- and postopera-
tive monitoring and an adequately long stay in the
PACU.
References


