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EFFECT OF AN I.V. BOLUS OF PHENYLEPHRINE OR EPHEDRINE ON SKIN BLOOD FLOW DURING SPINAL ANESTHESIA

THÈSE

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Effet d'un bolus intraveineux de phénylephrine ou d'éphedrine sur le flux sanguin cutané lors d'une anesthésie rachidienne

Introduction : La phénylephrine et l'éphedrine sont des substances vaso-actives utilisées de routine pour corriger des épisodes d'hypotension artérielle induits par l'anesthésie intrarachidienne. L'influence de ces deux vasopresseurs sur le flux sanguin cutané (FSC) dans ce contexte n'a jusqu'à maintenant pas été décrite. Cette étude évalue l'effet d'une injection intraveineuse de 75 µg de phénylephrine ou de 7.5 mg d'éphedrine sur le FSC mesuré par Laser Doppler, dans les zones concernées par le bloc sympathique induit par l'anesthésie intrarachidienne (membres inférieurs) et dans les zones non concernées (membres supérieurs).

Méthode : Après acceptation par le Comité d'Ethique, et obtention de leur accord écrit, 20 patients devant subir une intervention chirurgicale élective en décubitus dorsal sous anesthésie intrarachidienne ont été inclus dans cette étude randomisée en double insu. Le FSC a été mesuré en continu par deux sondes fixées l'une à la cuisse (zone avec bloc sympathique) et l'autre sur l'avant-bras (zone sans bloc sympathique). Les valeurs de FSC ont été enregistrées après l'anesthésie rachidienne (valeur contrôle), puis après l'injection i.v. de phénylephrine (10 patients) ou d'éphedrine (10 patients) pour corriger une hypotension définie comme une chute de 20 mmHg de la pression artérielle systolique. Les variations de FSC exprimées en pourcentage de la valeur contrôle moyenne (+/- écart type) ont été analysées par le test t de Student.

Résultats : Les données démographiques des patients et le niveau sensitif induit par l'anesthésie rachidienne sont similaires dans les deux groupes. Aux doses utilisées, seule l'éphedrine restaure la pression artérielle aux valeurs précédant l'anesthésie rachidienne. La phénylephrine augmente le FSC de l'avant-bras de 44% (+/- 79%) et de la cuisse de 34% (+/-24%), alors que l'éphedrine diminue le débit sanguin cutané de l'avant-bras de 16% (+/- 15%) et de la cuisse de 22% (+/-11%).

Conclusion : L'injection intraveineuse de phénylephrine et d'éphedrine ont des effets opposés sur le flux sanguin cutané, et cette réponse n'est pas modifiée par le bloc sympathique. Cette différence peut s'expliquer par la distribution des sous-types de récepteurs adrénergiques alpha et leur prédominance relative dans les veines et les artères de différents diamètres perfusant le tissu sous-cutané et la peau. L'éphedrine, en raison de sa meilleure efficacité pour traiter les épisodes d'hypotension artérielle après anesthésie intrarachidienne devrait être préférer à la phénylephrine, leurs effets opposés sur le flux sanguin cutané n'étant pas pertinents en pratique clinique.

SUMMARY

Background: Phenylephrine or ephedrine is routinely used to correct hypotensive episodes following spinal anaesthesia (SA). The influence of these two vasopressors on skin blood flow (SBF) has not yet been described. We have therefore evaluated the effects of an i.v. bolus of 75 μg phenylephrine or 7.5 mg of ephedrine on SBF measured by laser Doppler flowmetry during sympathetic blockade induced by SA.

Methods: With Ethical Committee approval and written consent, 20 patients scheduled for elective procedures in supine position under SA were enrolled in this double-blind randomized study. SBF was measured continuously by two probes fixed at the thigh (area with sympathic blockade) and forearm level (area without sympathic blockade) respectively. SBF values were recorded after SA (control values) and then after a bolus administration of phenylephrine (n=10) or ephedrine (n=10) when systolic blood pressure decreased by 20 mmHg. Changes were expressed as percentage of control SBF values and analysed by Student's paired t-test.

Results: Patient characteristics and dermatomal sensory levels were similar in both groups. Phenylephrine increases mean SBF at the forearm level by 44% (79%) [mean (SD)] and at the thigh by 34% (24%). Ephedrine decreases SBF at the forearm level by 16% (15%) and at the thigh by 22% (11%). Ephedrine bolus restores arterial blood pressure to pre-anaesthesia values, whereas phenylephrine does not.

Conclusion: Administration of phenylephrine and ephedrine has opposite effects on skin blood flow and sympathetic blockade does not modify this response. These findings could be explained by the distribution of the alpha-adrenoreceptor subtypes and their relative predominance among veins and arteries of different size perfusing the subcutaneous tissue and the skin. Ephedrine, due to its better efficacy to correct hypotensive episodes following SA, should be preferred to phenylephrine, their opposite effects on SBF being not relevant for clinical practice.

Keywords: Anaesthetic techniques, regional, spinal
Blood flow, skin
Sympathetic nervous system, ephedrine
Sympathetic nervous system, phenylephrine
Measurement techniques, laser Doppler flowmetry

Introduction :

Hypotension during spinal anaesthesia (SA) (1) is a common complication which may have detrimental effects, particularly during caesarean delivery (2) or in the geriatric population (3). The administration of vasopressors associated with intravenous cristalloids preload to counteract vasoplegia induced by spinal anaesthesia is widely accepted, but the choice of the best vasopressor remains a controversial topic among anesthesiologists (4,5). Recent studies have indeed challenged the efficacy of prophylactic intravenous ephedrine given either in small bolus doses or by infusion during spinal anaesthesia for elective cesarean section (6). Several trials suggest also that phenylephrine may have similar efficacy to ephedrine for preventing and treating hypotension during spinal anaesthesia (6,7). Moreover, it has been shown that the addition of phenylephrine to prophylactic ephedrine infusion halved the incidence of hypotension during SA for scheduled cesarean delivery (7).

Ephedrine, a mixed alpha and beta-adrenergic agonist (8) has a good track record in non-obstetric practice to treat bradycardia and hypotension, but in prophylactic use it could trigger episodes of marked hypertension and tachycardia (4,9).

Phenylephrine, a pure alpha1-adrenergic agonist (10), is effective also for treating hypotension induced by blockade of the sympathetic nervous system. It produces marked arterial vasoconstriction and subsequent bradycardia (8).

While changes on skin blood flow (SBF) induced by sympathetic blockade have already been studied (11), the effects of these two vasopressors have not yet been described in the setting of spinal anaesthesia. This study was conducted to verify wether the vasoconstrictor effect of ephedrine and phenylephrine on SBF is of same magnitude.

Patients and Methods :

After obtaining approval by the institutional Clinical Research Ethics Committee and written informed consent, twenty ASA status I-II adult patients scheduled for elective surgery under spinal anaesthesia (SA) were enrolled in this prospective, randomized, double-blind study. Patients with neurologic disease, autonomic dysfunction, hypertension or under treatment with β-blocking or vasoconstricting agents were excluded. Pregnant patients were not included.

After an oral premedication with 7.5 mg midazolam one hour before surgery, standard monitoring devices were applied (Datex AS 3; Datex-Ohmeda ; Instrumentarium Corporation, Helsinki, Finlande), and an 18G venous canula was inserted in a large vein on the dorsum of the hand. An intravenous preload of 500 ml Lactated Ringer's solution was then started and a SA was performed at the L3-L4 or

L4-L5 interspace with the patient in the lateral jack-knife position using a 9-cm 25 gauge Whitacre spinal needle. Once free flow of cerebrospinal fluid had been recognized, hyperbaric 0.5 % bupivacaine (12.5-15 mg) was injected intrathecally over 20 seconds. The patient was then placed in the supine position and arterial pressure measured by an automatic non-invasive monitor at intervals of one minute. Dermatomal sensory block was assessed with ether, ten, thirty and sixty minutes after completion of the spinal injection. If systolic blood pressure decreased by 20 mmHg from baseline, an i.v. bolus dose of ephedrine 7.5 mg or phenylephrine 75 µg was injected by the anaesthetist who was unaware of the vasopressor administered. This procedure was repeated if necessary. SBF was assessed by a non-invasive dual-channel laser Doppler (Periflux PF-4001, Perimed, Stockholm, Sweden) flowmetry technique (12, 13). To eliminate blood flow changes induced by skin temperature variations (14), local warming was performed using special thermostatic probe holders (Peritemp 4005, Perimed, Stockholm, Sweden) which were attached to the skin via a double-adhesive tape rings. One laser probe was positioned on the volar surface of one forearm and the second one in an area under SA blockade on the mid-internal upper part of the thigh. The continuous laser Doppler flowmeter signal expressing blood flow in arbitrary perfusion units (PU) was transferred on line to a computer and analyzed with the Perisoft software (Perimed, Stockholm, Sweden). Because of the instantaneous variability of the laser Doppler signal, mean SBF averaged during one minute was measured before SA (baseline value), twenty minutes after completion of SA then immediately before random vasopressor bolus injection and finally few minutes (at peak effect) after the first injection of the vasopressor. Cutaneous vascular conductance (CVC) was calculated as mean SBF divided by mean arterial pressure (MAP) obtained from the electrical integration of the pressure signal.

Datas are expressed as mean (SD) unless stated otherwise. Demographic, haemodynamic and SBF characteristics of both groups were compared by using Fisher's exact test and unpaired Student's t-test when appropriated. An analysis of variance for repeated measures in the same subjects followed by Bonferroni correction was used to detect differences within the two groups (15).

Results :

Patients characteristics and dermatomal sensory levels after SA were similar in both groups (Table 1). Likewise, hemodynamic variables, mean SBF measured before and twenty minutes after spinal anaesthesia in non glabrous skin areas of the forearm and the thigh, along with calculated cutaneous vascular conductance (CVC) and perfusion variation (ΔP) are presented in table 2.

Twenty minutes after SA, mean arterial pressure decreases significantly in both groups, whereas mean SBF and skin conductance increase in the forearm and in the upper thigh (table 2).

After an i.v. bolus of phenylephrine 75 µg or ephedrine 7.5 mg, administered to treat an hypotensive episode, mean arterial pressure increases significantly (figure 1). Whereas ephedrine restore MAP to baseline value, phenylephrine does not (figure 1). At any time during the study (before SA, twenty

minutes after SA, before and after the administration of vasopressors), there were no differences in MAP between the two groups (Tables 2 and 3).

SBF and conductance are increased by phenylephrine and decreased by ephedrine (table 3). These responses –albeit non significant- were similar and of same magnitude whether measured in skin areas under sympathetic blockade or not (table 3). Individual and mean variation of SBF triggered by both vasopressors are presented in figure 2 and table 3. When expressed in percentage, phenylephrine increase SBF in the upper and lower limbs by 44% (79%) and 34% (24%) respectively. After ephedrine injection, the decrease of SBF in the upper and lower limbs was 16% (15%) and 22% (11%) respectively (table 3). When compared, SBF differences between ephedrine and phenylephrine injections are significant ($p < 0.05$).

Discussion:

Our results show that an i.v. bolus of 75 µg of phenylephrine increase the SBF while 7.5 mg of ephedrine decreases the SBF. At these doses, ephedrine is more efficient than phenylephrine to treat -at least transiently- the drop of blood pressure induced by the sympathetic blockade. The effects of both vasopressors on SBF and skin vascular conductance are similar in both upper and lower limbs (Table 3).

Despite the important interindividual variability, the decrease of SBF after ephedrine has been shown in all but one patient, only in the superior limb (figure 2), and an increase in SBF in all patients of the phenylephrine group. Our results therefore strongly suggest that phenylephrine induces an increase in SBF, and ephedrine induces a decrease of SBF.

Before commenting our findings, the mechanisms of control of skin perfusion should be briefly discussed. Cutaneous circulation, which represents at rest a marginal part of the cardiac output (5-6%), is complex and includes thermoregulatory and non-thermoregulatory reflex inputs to the central nervous system (CNS)(16). In humans, reflex control of the skin blood flow is mediated through two sympathetic efferent pathways: an adrenergic vasoconstrictor system with norepinephrine as transmitter, which acts on postsynaptic alpha-1 and alpha-2 adrenergic receptors (17,18). The second pathway is a non-adrenergic active vasodilator system by cholinergic nerve co-transmission through release of an unknown transmitter (17). Other substances released by the vascular endothelium modulate also arterial blood flow. Endothelin, a vasoconstrictor peptide, interferes with alpha-adrenergic receptor (19), while prostacyclin and nitric oxide relax vascular smooth muscle (20, 21).

The mechanisms of decrease in SBF induced by ephedrine can be explained by previous in-vitro studies. According to Nielsen and Borbujo, postjunctional alpha-2 adrenoreceptors are present in human subcutaneous resistance arteries, and are predominent over the alpha-1 adrenoreceptor

subtype (22,23). Preparations of human subcutaneous arteries indeed are more sensitive to clonidine, a predominantly alpha-2 adrenoreceptor agonist than to norepinephrine, a mixed alpha-1 and alpha-2 adrenoreceptor agonist, and to phenylephrine, an alpha-1 adrenoreceptor agonist (23). In vivo confirmation is provided by Dinenno and colleagues, which concludes that vasoconstricting post-junctional alpha-2 adrenoreceptors contribute more to basal vascular tone than alpha-1 adrenoreceptors in the forearms of young healthy men (24). Ephedrine therefore, by its non-selective alpha-adrenoreceptor agonist property and its inhibition of norepinephrine re-uptake, is a potent subcutaneous arterial vasoconstrictor. A mixture of alpha-1 and alpha-2 adrenoreceptors have also been found in vein (25). Since ephedrine can increase the venous tone, it could indirectly contribute to the decrease in arterial skin blood flow. For these reasons and according to our results, the SBF decreases after the administration of ephedrine also in skin areas under sympathetic blockade.

The increase in SBF induced by phenylephrine has been also shown in an animal model by Banic et al, who investigated the effect of local and systemic injection of phenylephrine on muscular and skin blood flow in free musculocutaneous flaps (26, 27). In these investigations they also assess the flow variations in control territories, under the effects of an epidural anaesthesia or not. In both studies systemic administration of phenylephrine increase mean skin blood flow by 9% and 16% respectively. Other informations concerning the influence of muscle blood flow variations induced by vasopressors on skin blood flow are still lacking.

We may consider two mechanisms, alone or in combination, that could explain these findings. Phenylephrine, a pure alpha1-adrenergic agonist, is known to constrict mainly arterioles with a diameter larger than 110 µm (28). Because of its more prominent alpha-2 adrenoreceptors population, smaller skin arterioles do not respond to systemic infusion of phenylephrine (23). It should be mentioned however that SBF measured by laser-doppler flowmetry is not influenced by underlying skeletal muscle blood flow when vasodilation is triggered by mild muscular hyperhemia (29). We can therefore postulate that phenylephrine administration, by its vasoconstrictive effect, reduces muscle blood flow, creating thereby an "overflow" to the skin whose arterioles are less constricted. Such an overflow could not be observed with ephedrine, which induces a stronger subcutaneous vasoconstriction. This hypothesis is only partly sustained by our datas since we did not measure muscular blood flow.

The direct effects of ephedrine or phenylephrine on venous tone could also contribute to modulate the SBF. Steen et al showed in isolated human groin vessels that phenylephrine was significantly more potent in arteries than in veins, whereas norepinephrine was more potent in veins than in arteries. These results suggest that there is a functional predominance of alpha 2-adrenoreceptors in the veins (30). These findings could explain why ephedrine, compared to phenylephrine, increases venous tone leading thereby to SBF reduction.

This study has several limitations. We used a single dosage of vasopressors. We choose boluses of 75 µg of phenylephrine and 7.5 mg of ephedrine because these are considered as standard doses commonly used in our institution. Whether lower or higher doses of phenylephrine and/or ephedrine would act similarly on SBF is unknown. The primary goal of vasopressors administration in our study was to counteract the hypotension induced by SA, not to establish a dose-response curve.

Since we did not have any previous data on the SBF variations induced by phenylephrine and ephedrine, we could not calculate an appropriate sample size for each patient group. According to the large inter-individual SBF differences (see Table 2 and 3) measured by the Laser Doppler technique during a surgical procedure, ten patients per group were probably not sufficient to reach statistical significance. Another limitation of this investigation is a lack of simultaneous measurement of muscular blood flow.

In conclusion, our study strongly suggests that an i.v. bolus of phenylephrine increase the SBF while ephedrine decreases SBF. These findings could be explained by the distribution of the alpha-adrenoreceptor subtypes, and their relative predominance, among veins and different size of arteries in the subcutaneous tissue and in the skin. Further studies are needed for a better understanding of the physiology of SBF regulation under anaesthesia, as well as of the perfusion of other organs (placenta, kidney), in order to determine the most suitable vasopressor for clinical practice.

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Table 1 : Patient characteristics and dermatomal sensory levels after spinal anaesthesia.

	Ephedrine n = 10	Phenylephrine n = 10	p
Sex : M/F	6/4	8/2	NS
Age (yr)	38 (14)	45 (15)	NS
Weight (kg)	67 (13)	75 (16)	NS
Height (cm)	170 (9)	175 (7)	NS
Dermatomal sensory level	T_7 (T_3-T_{10})	T_7 (T_2-T_{11})	NS

Datas are mean (SD), except dermatomal sensory level expressed as median and range.

Table 2 : Heart rate (HR), mean arterial pressure (MAP), mean skin blood flow (MSBF), conductance and variation of perfusion before and 20 minutes after spinal anaesthesia (SA) expressed in mean value (SD)

	HR (bpm)		MAP (mmHg)		MSBF (PU)		Conductance (PU mmHg-1)		Δ Perfusion (%)
	before SA	Twenty minutes after SA	before SA	Twenty minutes after SA	before SA	Twenty minutes after SA	before SA	Twenty minutes after SA	
Phenylephrine n=10	68(8)	73(9)	102(13)	87(10) *	UL 130(74)	UL 265(257)	UL 1.31(0.84)	UL 3.19(3.24)	UL +105 (150)
					LL 113 (61)	LL 186 (77)	LL 1.15(0.71)	LL 2.21(1.05)	LL +75 (55)
Ephedrine n=10	67(11)	64(11)	95(11)	84(12) *	UL 151(97)	UL 207(204)	UL 1.56(0.96)	UL 2.33(2.28)	UL +34 (74)
					LL 100(79)	LL 168(140)	LL 1.07(0.86)	LL 2.03(1.65)	LL +78 (56)

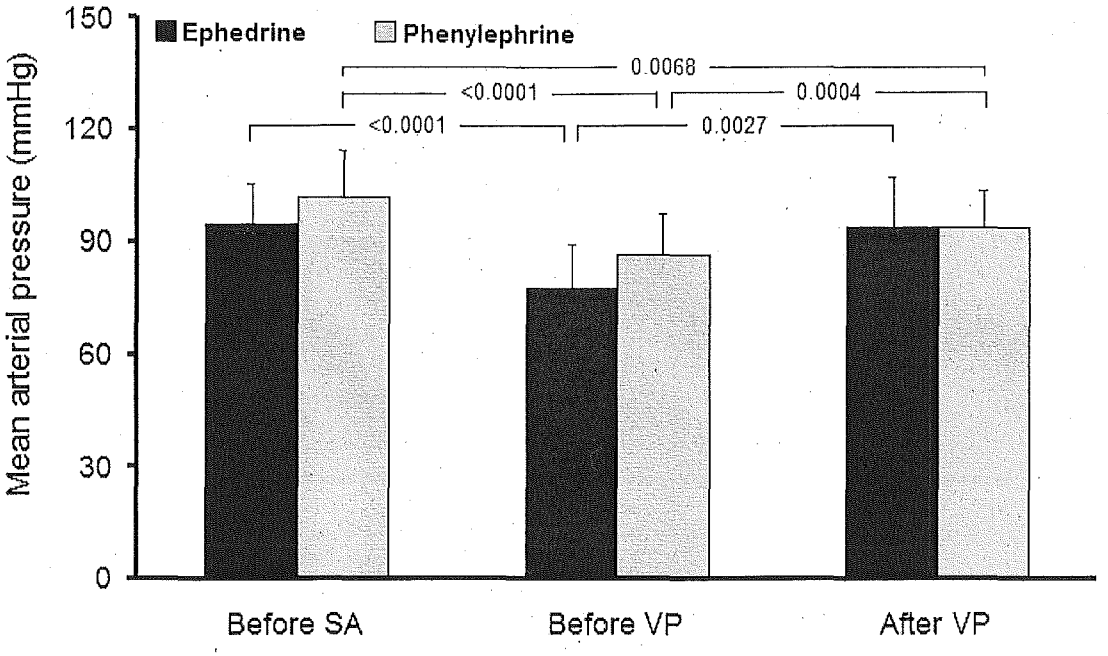
* $p < 0.05$ when compared to MAP before SA. UL= upper limb; LL= lower limb.

Table 3 : Heart rate (HR), mean arterial pressure (MAP), mean skin blood flow (MSBF), conductance and variation of perfusion prior and after administration of vasopressor (VP) expressed in mean value (SD)

	HR (bpm)		MAP (mmHg)		MSBF (PU)		Conductance (PU mmHg-1)		Δ Perfusion (%)
	before VP	after VP	before VP	after VP	before VP	after VP	before VP	after VP	
Phenylephrine n=10	73(9)	65(13)	86(11)	93(10) *	UL 292(280)	UL 358(286)	UL 3.61(3.79)	UL 3.96(3.20)	UL +44 (79)
					LL 180(73)	LL 246(133)	LL 2.16(1.00)	LL 2.74(1.71)	LL +34 (24)
Ephedrine n=10	60(8)	61(9)	78(12)	94(13) *	UL 248(232)	UL 207(209)	UL 3.08(2.73)	UL 2.14(2.16)	UL -16 (15) §
					LL 162(114)	LL 122(77)	LL 2.16(1.58)	LL 1.30(0.78)	LL -22 (11) #

* $p < 0.05$ when compared to MAP before VP. § $p < 0.05$ when compared to Δ Perfusion at the upper limb after Phenylephrine. # $p < 0.05$ when compared to Δ Perfusion at the lower limb after Phenylephrine. UL= upper limb; LL= lower limb.

Figure 1 : Mean arterial pressure (X (SD)) before SA, before vasopressor (VP) and after VP, with significant P values.



All aboved mentioned *p* values show significant differences after Bonferroni correction ($p < 0.0125$)

Figure 2 : Individual and mean value (X (SD)) of skin perfusion variation after bolus administration of ephedrine or phenylephrine.