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Original Article

Intranasal Vasopressin Relieves Orthopedic Pain After Surgery

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ABSTRACT

Background: Orthopedic pain after surgery is very common and difficult to manage. Although intranasal arginine vasopressin (AVP) relieves headache (tension-type headache and migraine mostly), the effect of intranasal AVP on the orthopedic pain after surgery is unknown.
Aims: This study investigated the effect of intranasal AVP on orthopedic pain after surgery in a randomized controlled trial with a double-blind design.
Participants: The study included 653 orthopedic patients and 661 health volunteers.
Methods: Orthopedic pain was analyzed by the visual analogue scales (VAS) and AVP concentration was determined by radioimmunoassay.
Results: (1) intranasal AVP decreased the VAS level in orthopedic patients 2-4 weeks after surgery in a dose-dependent manner; (2) the cerebrospinal fluid (CSF) AVP concentration in orthopedic patients after surgery was higher than that in the health volunteers (38.57 ± 6.11 pg/mL vs 11.74 ± 2.85 pg/mL, $p < .01$), but had no change in plasma ($p > .05$); (3) CSF AVP concentration increased significantly in orthopedic patients during 24 hours after the intranasal AVP ($p < .05$ or .01), which related with VAS level negatively (all $p < .01$); (4) during 24 hours, intranasal AVP did not influence not only plasma AVP concentration, but also blood pressure, heart rate, respiratory rate and body temperature in orthopedic patients.
Couclusions: The findings contribute valuable information that intranasal AVP can treat orthopedic pain after surgery, and AVP could be an option for pain relief by intranasal administration.

Introduction

Arginine vasopressin (AVP), a nonapeptide posterior hormone of the pituitary, has been proven as an important factor influencing analgesia. Aziz et al. (1968) might be the first group to observe AVP preventing lumbar puncture-induced headache. Intraventricular injection of AVP increases and intraventricular injection of anti-AVP serum decreases the pain threshold, but neither intrathecal nor intravenous injection of AVP (or anti-AVP serum) has an influence (Yang et al., 2009a; Yang, Song, Liu, & Lin, 2006e). The findings indicate that AVP in the brain, rather than in the spinal cord and blood circulation, plays a role in pain modulation.

Exogenous AVP reaches the brain with difficulty because of the blood-brain barrier (BBB) (Antunes & Zimmerman, 1978). In developing AVP as a drug for pain relief, it is important to find a way to deliver AVP from systemic administration to the brain rapidly. Interest has been expressed in the use of the nasal route for direct peptide delivery to the brain, exploiting the olfactory pathway (Dhuria et al., 2010; Merkus et al., 2003; Veronesi et al., 2011). Our previous study found that intranasal AVP relieves clinical headache, primarily tension-type headache and migraine (Yang et al., 2012).

Orthopedic pain after surgery is very common. Although intranasal AVP relieves the headache, the effect of intranasal AVP on orthopedic pain after surgery is unknown. The present study tried to investigate the effect of intranasal AVP on the orthopedic pain after surgery.

Materials and Methods

Materials

AVP (No. H31022938 approved by Chinese Food and Drugs Administration) was brought from Shanghai First Biochemical Pharmaceutical Co. Ltd., Shanghai, China. Physiologic saline (No.

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H33020623) was brought from Wenzhou Ouhai Meticulous Chemical Co. Ltd., Wenzhou, Zhejiang, China.

Anti-AVP serum was made by the rabbit immured in Xinxiang Institute for New Medicine; serum was diluted at >1:40,000 for radioimmunoassay. The antiserum cross-reaction was >99.9% with AVP and <0.1% cross reaction with other peptides, including lysine vasopressin, vasotocin, and oxytocin.

^{125}Iodine was brought from GE Healthcare (Amersham Pharmacia Ltd., Buckinghamshire, England). The other chemicals were brought from Sigma-Aldrich Co. (Darmstadt, Germany).

Patients with Orthopedic Pain

A total of 653 patients, including 326 men and 327 women, 18-67 years old (average 36.3 ± 10.2 years), were asked to participate in the study between January 2012 and July 2015. The patients were selected from 2 weeks to 4 weeks (average 20.6 ± 3.1 days) after orthopedic surgery.

These patients were divided into four groups: control group (167 cases, only physiologic saline), 100 ng AVP group (162 cases, 100 ng AVP/physiologic saline), 200 ng AVP group (165 cases, 200 ng AVP/physiologic saline), and 400 ng AVP group (159 cases, 400 ng AVP/physiologic saline) (Table 1).

Health Volunteers

A total of 661 health volunteers, including 337 men and 324 women, 18-65 years old (average 36.7 ± 9.2 years) were asked to participate in the study between January 2012 and July 2015. They did not report any pain during the experiment.

Table 1
Basic Data for Each Group

Group	Vasopressin			Control
	400 ng	200 ng	100 ng	
Number (case, %)	159 (100.0)	165 (100.0)	162 (100.0)	167 (100.0)
Sex (number, %)				
Male	81 (50.9)	84 (50.9)	78 (48.1)	83 (49.7)
Female	78 (49.1)	81 (49.1)	84 (51.9)	84 (50.3)
Age (y)	37.6 ± 6.3	35.7 ± 7.1	36.7 ± 6.8	36.3 ± 6.1
Body mass index (kg/m^2)	23.01 ± 3.09	23.03 ± 3.21	23.10 ± 3.78	23.07 ± 3.56
Systolic pressure (mm Hg)	130.1 ± 20.0	127.5 ± 17.5	129.5 ± 19.4	128.9 ± 18.3
Diastolic pressure (mm Hg)	78.2 ± 11.2	77.0 ± 9.7	78.3 ± 10.7	77.4 ± 10.1
Heart rate (min^{-1})	83.4 ± 8.3	81.7 ± 7.26	82.7 ± 7.1	82.3 ± 7.6
Respiratory rate (min^{-1})	17.9 ± 2.6	18.7 ± 2.4	18.2 ± 2.2	18.5 ± 2.3
Religious belief (case, %)				
Yes	40 (25.1)	45 (27.3)	43 (26.5)	50(29.9)
No	119 (74.9)	120 (72.7)	119 (73.5)	117(70.1)
Degree of education (case, %)				
Primary school	13 (8.2)	16 (9.7)	19 (11.7)	17 (10.2)
Junior middle school	73 (45.9)	72 (43.6)	76 (46.9)	77 (46.1)
High school or technical second school	47 (29.6)	48 (29.1)	43 (26.6)	45 (26.9)
College, university, or above	26 (16.4)	29 (17.6)	24 (14.8)	28 (16.8)
Occupation (case, %)				
Employed	24 (15.1)	26 (15.8)	25 (15.4)	27 (16.2)
Unemployed	135 (84.9)	139 (84.2)	137 (84.6)	140 (83.8)
Marriage (case, %)				
Unmarried	32 (20.1)	36 (21.8)	30 (18.5)	34 (20.3)
Married	119 (74.9)	120 (72.7)	122 (75.3)	125 (74.9)
Divorced or widowed	8 (5.0)	9 (5.5)	10 (6.2)	8 (4.8)
Pain sensitivity questionnaire	1.61 ± 1.83	1.54 ± 1.67	1.52 ± 1.61	1.56 ± 1.72
Chronic pain (case, %)				
Yes	24 (15.1)	23 (13.9)	22 (13.6)	23 (13.8)
No	135 (84.9)	142 (86.1)	140 (86.4)	144 (86.2)
State anxiety	43.72 ± 5.66	43.91 ± 6.01	43.86 ± 5.75	43.85 ± 5.87
Trait anxiety	44.04 ± 4.85	43.92 ± 4.55	44.01 ± 4.86	43.96 ± 4.62
Waiting for operation (day)	4.57 ± 2.32	4.26 ± 2.40	4.43 ± 2.24	4.32 ± 2.11
Operation times (case, %)				
First time	102 (64.2)	110 (66.7)	105 (64.8)	106 (63.5)
Second time	46 (28.9)	45 (27.3)	48 (29.6)	49 (29.3)
Third time or more	11 (6.9)	10 (6.0)	9 (5.6)	12 (7.2)
Operative site (case, %)				
Neck, chest, lumbar, sacral vertebra	33 (20.8)	37 (22.4)	36 (22.2)	35 (21.0)
Limbs, trunk	75 (47.2)	79 (47.9)	77 (47.5)	80 (47.9)
Joint	42 (26.4)	40 (24.2)	43 (26.6)	44 (26.3)
Multiple sites	9 (5.6)	9 (5.5)	6 (3.7)	8 (4.8)
Surgical grading (case, %)				
Class A	4 (2.5)	5 (3.0)	3 (1.9)	4 (2.4)
Class B	69 (43.4)	73 (44.2)	70 (43.2)	71 (42.5)
Class C	49 (30.8)	49 (29.8)	48 (29.6)	52 (31.1)
Class D	37 (23.3)	38 (23.0)	41 (25.3)	40 (24.0)
Duration operation (min)	139.4 ± 67.3	137.8 ± 72.1	140.2 ± 71.5	138.7 ± 68.9
Primary caregiver (case, %)				
Spouse	79 (49.7)	85 (51.5)	81 (50.0)	85 (50.9)
Parents	41 (25.8)	40 (24.2)	42 (25.9)	43 (25.7)
Children	25 (15.7)	24 (14.5)	23 (14.2)	22 (13.2)
Other person related by blood	9 (5.7)	9 (5.4)	10 (6.2)	11 (6.6)
Employment relationship	5 (3.1)	4 (2.4)	6 (3.7)	6 (3.6)

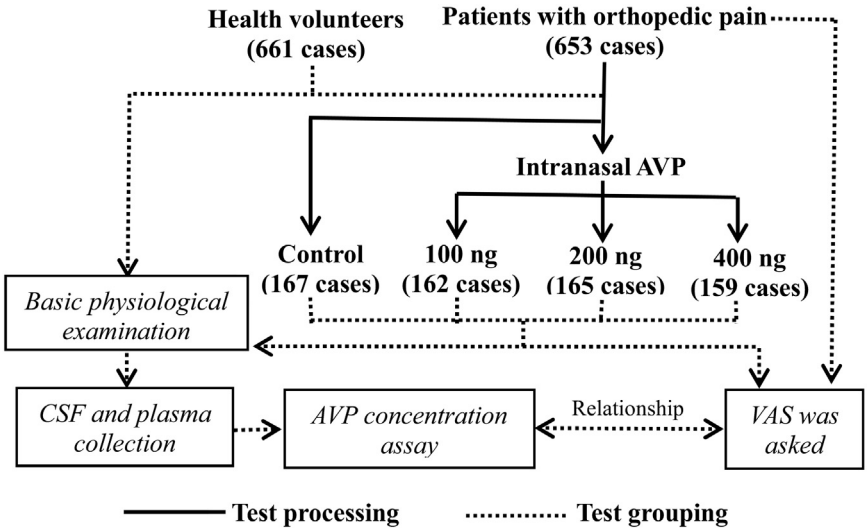

Figure 1. The consort diagram. AVP = arginine vasopressin; CSF = cerebrospinal fluid; VAS = visual analog scale.

Orthopedic pain was caused by the surgery before from 2 weeks to 4 weeks. The number of patients with orthopedic pain was similar to that of the health volunteers (653 cases vs. 661 cases). Before the intranasal AVP treatment, AVP levels in cerebrospinal fluid (CSF) and plasma in the patients with orthopedic pain were compared with those in the health volunteers.

Inclusion Criteria

To be included in the study, (a) participants had to agree to sign the informed consent form; (b) eligibility was checked before the experiments to exclude participants with pregnancy, tumor, and cardiovascular, gastrointestinal, respiratory, brain, endocrine, psychiatric, or other diseases; (c) participants were asked not to smoke any cigarettes or drink any alcohol or caffeine-containing beverages and to refrain from using analgesic medication during the experiment; (d) participants were asked not to eat anything during the day of the blood and CSF sample collection; and (e) participants had to be older than 18 years old. All experimental sessions were carried out between 08:00 a.m. and 10:00 a.m.

The project was approved by the Ethics Committees of the Central Hospital of Xinxiang Medical University and accorded to the Declaration of Helsinki.

Procedure

The study (Fig. 1) was a randomized controlled trial with a double-blind design. The orthopedic operations included

Table 2
Effect of Intranasal Vasopressin on Orthopedic Pain

Group	Number	VAS	Case (No., %)							
			Before	10 min	1 h	2 h	4 h	8 h	16 h	24 h
Vasopressin 400 ng	159	0, 1, 2	0 (0)	2 (1.3)	58 (36.5)	82 (51.6)	74 (46.6)	43 (27.0)	23 (14.5)	12 (7.6)
		3, 4, 5	15 (9.4)	38 (23.9)	63 (39.6)	51 (32.1)	57 (35.8)	67 (42.1)	59 (37.1)	44 (27.7)
		6, 7, 8	65 (40.9)	56 (35.2)	37 (23.3)	26 (16.3)	21 (13.2)	30 (18.9)	39 (24.5)	43 (27.0)
		9, 10	79 (49.7)	63 (39.6)	1 (0.6)	0 (0)	7 (4.4)	19 (12.0)	38 (23.9)	60 (37.7)
	p				<.01; <.01*	<.01; <.01*; <.05†	<.01; <.01*; <.01†	<.01; <.01*; <.01†	<0.01; *<0.05; +<0.05	<0.05; *<0.05
Vasopressin 200 ng	165	0, 1, 2	0 (0)	1 (0.6)	49 (29.7)	64 (38.8)	47 (28.5)	31 (18.8)	11 (6.7)	5 (3.0)
		3, 4, 5	17 (10.3)	40 (24.2)	57 (34.6)	56 (33.9)	53 (32.1)	43 (26.1)	36 (21.8)	27 (16.4)
		6, 7, 8	67 (40.6)	55 (33.4)	54 (32.7)	43 (26.1)	47 (28.5)	59 (35.8)	63 (38.2)	64 (38.8)
		9, 10	81 (49.1)	69 (41.8)	5 (3.0)	2 (1.2)	18 (10.9)	32 (19.3)	55 (33.3)	69 (41.8)
	p				<.01; <.05*	<.01; <.01*	<.01; <.05*	<.01; <.05*	<0.01; *<0.05	
Vasopressin 100 ng	162	0, 1, 2	0 (0)	0 (0)	32 (19.8)	43 (26.5)	28 (17.3)	17 (10.5)	3 (1.9)	0 (0)
		3, 4, 5	15 (9.2)	34 (21.0)	53 (32.7)	61 (37.7)	50 (30.9)	36 (22.2)	29 (17.9)	18 (11.1)
		6, 7, 8	68 (42.0)	58 (35.8)	65 (40.1)	51 (31.5)	61 (37.7)	68 (42.0)	72 (44.4)	73 (45.1)
		9, 10	79 (48.8)	70 (43.2)	12 (7.4)	7 (4.3)	23 (14.1)	41 (25.3)	58 (35.8)	71 (43.8)
	p				<.05	<.01	<.01	<.01		
Control	167	0, 1, 2	0 (0)	0 (0)	10 (6.0)	5 (3.0)	1 (0.6)	0 (0)	0 (0)	0 (0)
		3, 4, 5	16 (9.6)	35 (21.0)	23 (13.8)	18 (10.8)	17 (10.2)	16 (9.6)	15 (9.0)	14 (8.4)
		6, 7, 8	69 (41.3)	61 (36.5)	66 (39.5)	73 (43.7)	76 (45.5)	77 (46.1)	77 (46.1)	74 (44.3)
		9, 10	82 (49.1)	71 (42.5)	68 (40.7)	71 (42.5)	73 (43.7)	74 (44.3)	75 (44.9)	79 (47.3)

VAS = visual analog scale.
$p < .05$ or $p < .01$ is used for the comparison of the VAS change from the vasopressin 400, 200, or 100 ng group and the control group.
* $p < .05$ or $p < .01$ is used for the comparison of the VAS change from the vasopressin 400 or 200 ng group and the vasopressin 100 ng group.
† $p < .05$ or $p < .01$ is used for the comparison of the VAS change from the vasopressin 400 ng group and the vasopressin 200 ng group.

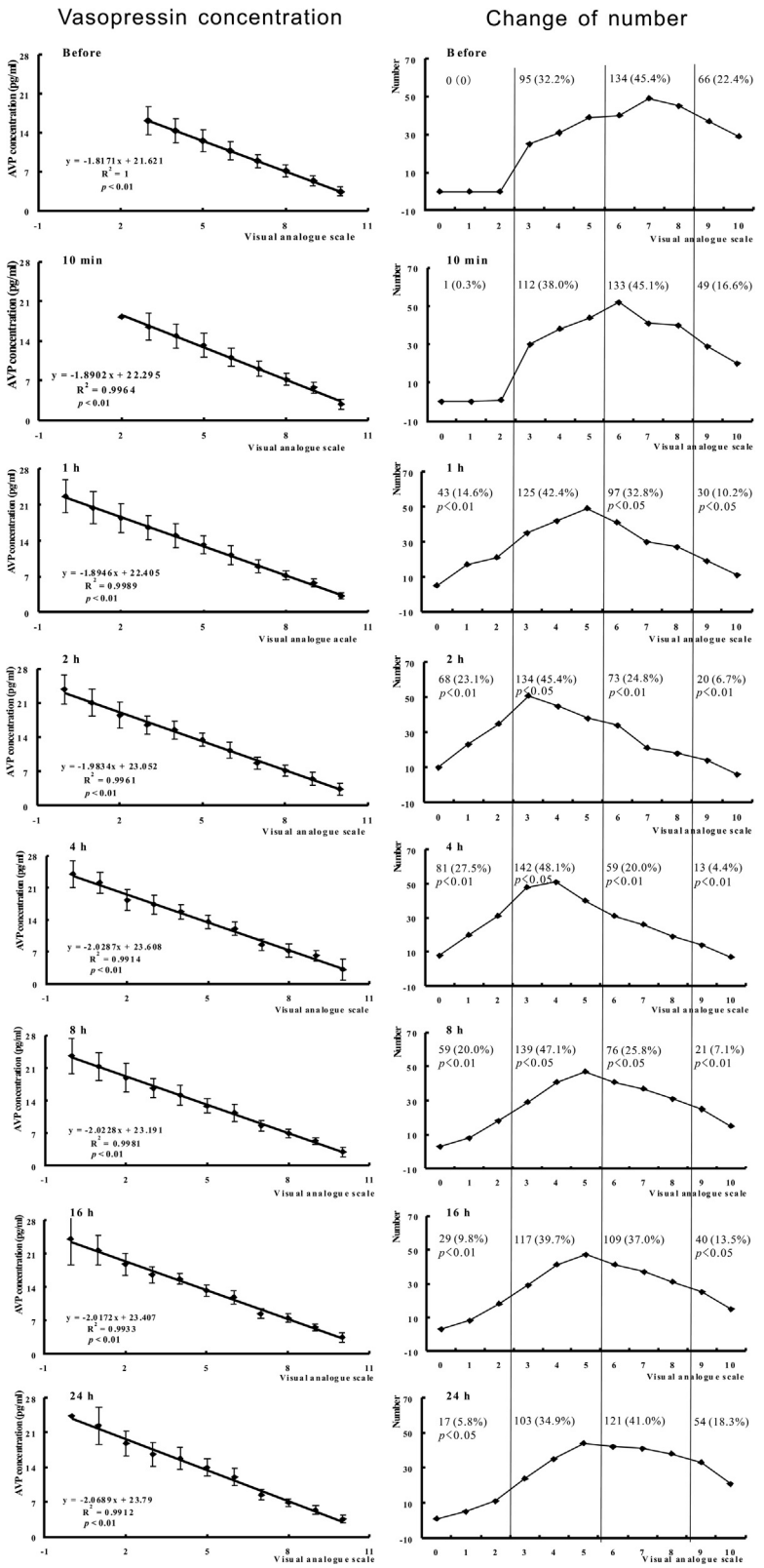

Figure 2. The relationship between the visual analogue scale (VAS) and arginine vasopressin (AVP) concentration in cerebrospinal fluid (CSF) in different time during intranasal AVP treatment.

debridement of skin, muscle, bone, or fracture (21.5%); repair of femoral shaft fracture (17.2%); repair of fracture of the distal part of radius (15.1%); repair of fracture of the radius (bone) or ulna (14.3%); repair of ankle fracture (fibula) (7.8%); repair of ankle fracture (bimalleolar type) (4.9%); low back intervertebral disc surgery (3.1%); and other surgeries (16.1%). The experiments began from 2 weeks to 4 weeks after the orthopedic operation. In this time, many interference factors, such as surgeries and medicines, could be eliminated. The participants completed a set of questionnaires and were given a basic examination. The experimental period was 24 hours.

After measuring the pain ratings, the patients with orthopedic pain were administered three puffs of AVP per nostril (100 ng AVP, 200 ng AVP, or 400 ng AVP) or physiologic saline (0 ng AVP). AVP or physiologic saline was given one time to each case in the study because it was easy to understand the effect of intranasal AVP on orthopedic pain after surgery.

The only samples collected from the health volunteers were blood and CSF.

Visual Analog Scale

The participants with pain were asked to mark the pain rating on a 100 mm, nonhatched visual analog scale (VAS) marked at one end as “no pain” (score of 0) and at the other as “worst pain imaginable” (score of 10).

Basic Examination

The participants’ blood pressure, heart rate, respiratory rate and body temperature were assessed.

Sample Collection

The blood was collected by venipuncture and put into an EDTA-Na_2–treated vacutainer, then immediately stored at 4°C.

The CSF was collected by lumbar puncture and put into the silicone oil–treated tube, then immediately stored at 4°C.

After the centrifugation at 10,000 g for 20 minutes at 4°C, the supernatant of the sample was withdrawn and stored at −80°C for assay (Yang et al., 2012).

AVP Assay

We used the chloramines T method to label ^{125}iodine and AVP, and ^{125}iodinated peptide was purified by Sephadex G-50. The normal range of AVP radioimmunoassay was 1-64 pg/mL, and sensitivity was 1.0 pg/tube. The intra- and interassay coefficients of variation were 4.5% and 6.4%, respectively.

Statistical Analysis

Data were expressed as mean ± standard error of the mean. We used the SPSS Version 18.0 statistical software (SPSS Inc., Chicago, IL, USA) for statistical analysis. Means of continuous variables were compared by t tests with Bonferroni correction and categorical variables by χ^2 tests. A value of $p < .05$ was considered statistically significant.

Results

Effect of Intranasal AVP on Orthopedic Pain

Intranasal AVP relieved the orthopedic pain in a dose-dependent manner. It took from 1 to 16 hours (average 4.53 ± 2.11 hours) for intranasal AVP to relieve the orthopedic pain during 24 hours’ follow-up ($p < .05$ or .01) (Table 2 and Fig. 2).

There were no side effects and no correlations between the AVP alterations and the sex or age of the participants in this study (all $p > .05$).

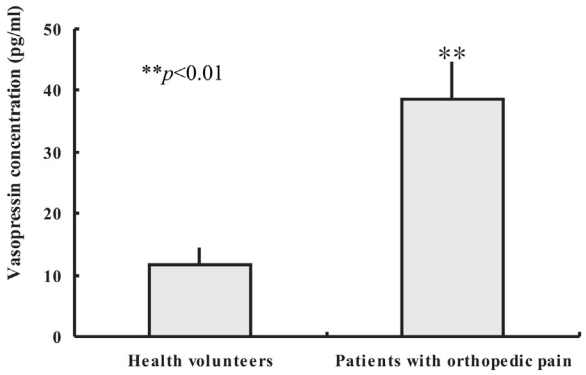

Figure 3. Arginine vasopressin (AVP) concentration in cerebrospinal fluid (CSF).

AVP Level in Patients with Orthopedic Pain

Compared with that in the health volunteers, CSF AVP concentration was increased significantly in the patients with orthopedic pain (38.57 ± 6.11 pg/mL vs. 11.74 ± 2.85 pg/mL, $p < .01$) (Fig. 3); plasma AVP concentration in the patients with orthopedic pain did not change (11.12 ± 3.32 pg/mL vs. 8.33 ± 2.46 pg/mL, $p > .05$) (Fig. 4).

Intranasal AVP Influenced AVP Level in Patients with Orthopedic Pain

A total of 295 patients with orthopedic pain agreed to the CSF and blood sample collection. Intranasal AVP not only made the patients with orthopedic pain feel better but also increased the CSF AVP level in patients with orthopedic pain during the 24 hours after intranasal AVP administration ($p < .05$ or .01) (Table 3).

The CSF AVP level was negatively related to the VAS level. There were many negative relationships between the VAS and CSF AVP concentration in from 0 (before the intranasal administration of AVP) to 24 hour after the intranasal administration of AVP (Table 4 and Fig. 2).

The plasma AVP concentration in patients with orthopedic pain was not influenced by intranasal AVP (all $p > .05$) (Table 3).

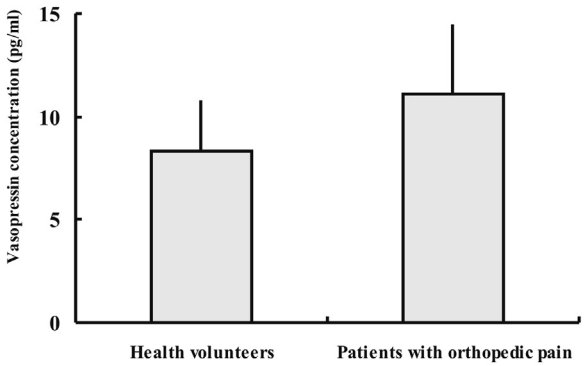

Figure 4. Arginine vasopressin (AVP) concentration in plasma.

Table 3
Visual Analog Scale (VAS) and Arginine Vasopressin (AVP) Concentration in the Cerebrospinal Fluid (CSF) and Plasma

Time	VAS		0	1	2	3	4	5	6	7	8	9	10	Total
Before	CSF	AVP (pg/mL)	—	—	—	16.17 ± 2.53/	14.35 ± 2.21	12.54 ± 1.97	10.72 ± 1.65	8.90 ± 1.20	7.08 ± 1.07	5.27 ± 0.89	3.45 ± 0.76	
	Plasma		—	—	—	30.63 ± 5.43	29.77 ± 4.87	28.68 ± 5.01	27.80 ± 4.32	28.75 ± 3.95	29.14 ± 4.27	27.68 ± 3.42	28.72 ± 4.61	
		n	0	0	0	25	31	39	40	49	45	37	29	295
10 min	CSF	AVP (pg/mL)	—	—	18.23	16.47 ± 2.39	14.86 ± 2.09	13.21 ± 2.11	11.07 ± 1.57	9.03 ± 1.35	7.17 ± 1.03	5.72 ± 0.91	2.83 ± 0.85	
	Plasma		—	—	31.23	29.84 ± 5.03	28.59 ± 4.66	29.85 ± 4.52	27.99 ± 3.78	30.07 ± 4.13	30.35 ± 6.02	28.67 ± 4.62	29.17 ± 5.71	
		n	0	0	1	30	38	44	52	41	40	29	20	295
1 h	CSF	AVP (pg/mL)	22.62 ± 3.22	20.39 ± 3.05	18.39 ± 2.79	16.52 ± 2.41	15.01 ± 2.35	13.12 ± 1.73	11.14 ± 1.79	8.96 ± 1.31	7.20 ± 0.95	5.69 ± 0.78	3.21 ± 0.62	
	Plasma		28.71 ± 6.12	29.15 ± 5.24	27.98 ± 5.31	28.05 ± 4.76	28.46 ± 5.08	29.35 ± 4.87	28.64 ± 4.26	30.20 ± 5.73	29.80 ± 5.55	28.43 ± 4.76	29.27 ± 4.78	
		n	5	17	21	35	42	48	40	30	27	19	11	295
2 h	CSF	AVP (pg/mL)	23.75 ± 3.01	21.06 ± 2.78	18.47 ± 2.65	16.47 ± 1.93	15.43 ± 1.84	13.41 ± 1.32	11.23 ± 1.65	8.75 ± 1.23	7.14 ± 1.12	5.45 ± 1.35	3.33 ± 1.21	
	Plasma		29.16 ± 5.23	28.92 ± 4.94	27.74 ± 5.15	28.34 ± 5.15	29.02 ± 5.33	28.76 ± 5.43	27.98 ± 5.76	29.02 ± 5.43	30.17 ± 6.03	28.21 ± 4.06	29.24 ± 5.63	
		n	10	23	35	51	45	38	34	21	18	14	6	295
4 h	CSF	AVP (pg/mL)	24.01 ± 2.87	22.12 ± 2.25	18.32 ± 2.32	17.31 ± 2.12	15.78 ± 1.57	13.56 ± 1.41	12.04 ± 1.48	8.53 ± 1.32	7.22 ± 1.43	6.13 ± 1.10	3.09 ± 2.21	
	Plasma		28.33 ± 5.46	28.37 ± 5.26	29.41 ± 5.35	28.41 ± 5.75	30.13 ± 6.32	29.21 ± 5.67	28.37 ± 5.42	28.06 ± 5.42	27.89 ± 5.36	28.22 ± 4.79	29.32 ± 5.03	
		n	15	27	39	57	48	37	27	19	13	11	2	295
8 h	CSF	AVP (pg/mL)	23.56 ± 3.87	21.35 ± 2.95	18.90 ± 3.02	16.63 ± 2.07	15.21 ± 2.13	12.89 ± 1.47	11.35 ± 1.78	8.67 ± 1.14	6.98 ± 0.89	5.32 ± 0.78	2.99 ± 1.01	
	Plasma		28.32 ± 5.44	27.78 ± 4.56	28.34 ± 5.07	28.88 ± 5.65	29.43 ± 5.92	30.23 ± 5.66	28.67 ± 5.53	30.05 ± 6.51	27.64 ± 5.31	28.33 ± 4.56	29.31 ± 5.25	
		n	8	20	31	48	51	40	31	26	19	14	7	295
16 h	CSF	AVP (pg/mL)	24.07 ± 5.52	21.67 ± 3.15	18.73 ± 2.34	16.55 ± 1.67	15.69 ± 1.11	13.21 ± 1.21	11.85 ± 1.36	8.36 ± 0.96	7.47 ± 0.86	5.51 ± 0.75	3.42 ± 1.04	
	Plasm		27.89 ± 6.02	28.10 ± 4.33	27.31 ± 5.73	28.26 ± 4.51	29.31 ± 6.12	27.75 ± 6.04	28.35 ± 5.32	29.16 ± 5.76	29.16 ± 5.23	27.33 ± 4.67	29.25 ± 5.03	
		n	3	8	18	29	41	47	41	37	31	25	15	295
24 h	CSF	AVP (pg/mL)	24.32	22.34 ± 3.81	18.78 ± 2.56	16.57 ± 2.34	15.77 ± 2.14	13.89 ± 1.69	12.01 ± 1.75	8.46 ± 1.13	6.87 ± 0.79	5.36 ± 0.88	3.53 ± 0.75	
	Plasma		28.93	29.85 ± 6.83	30.13 ± 5.23	28.75 ± 5.23	27.93 ± 5.03	30.12 ± 3.79	31.04 ± 4.17	28.67 ± 4.23	27.88 ± 3.77	28.63 ± 4.54	29.32 ± 5.43	
		n	1	5	11	24	35	44	42	41	38	33	21	295

Table 4
Relationships Between Visual Analog Scale (VAS) and Arginine Vasopressin (AVP) Concentration in Cerebrospinal Fluid (CSF)

Time After Intranasal Administration	Relationship Between AVP and CSF AVP Concentration	n	r^2	p
0 (before)	$y = -1.8171x + 21.621$	8	1.0000	<.01
10 min	$y = -1.8902x + 22.295$	9	0.9964	<.01
1 h	$y = -1.8946x + 22.405$	11	0.9989	<.01
2 h	$y = -1.9834x + 23.052$	11	0.9961	<.01
4 h	$y = -2.0287x + 23.608$	11	0.9914	<.01
8 h	$y = -2.0228x + 23.191$	11	0.9981	<.01
16 h	$y = -2.0172x + 23.407$	11	0.9933	<.01
24 h	$y = -2.0689x + 23.790$	11	0.9912	<.01

Basic Examination in Patients With Orthopedic Pain During Intranasal AVP

Intranasal AVP did not influence blood pressure (including systolic pressure and diastolic pressure), heart rate, respiratory rate, or body temperature in patients with orthopedic pain.

Discussion

AVP is mainly synthesized and secreted in the hypothalamic paraventricular nucleus (PVN), and supraoptic nucleus (Antunes and Zimmerman, 1978). AVP in the brain, rather than in the spinal cord and blood circulation, plays a role in pain modulation (Yang et al., 2006d, 2006e, 2007b, 2008, 2009a). Intranasal delivery of AVP provides a potentially promising alternative to other administration routes because a direct pathway exists between the olfactory neuroepithelium and the brain (Veronesi et al., 2011). Although intranasal AVP did not pass directly from the nose to the brain (Merkus et al., 2003), the present study found that intranasal AVP relieved the orthopedic pain in a dose-dependent manner. The data suggested that intranasal AVP could treat clinical orthopedic pain.

Pain stimulation decreases AVP level in the PVN; increases AVP level in the periaqueductal gray (PAG), nucleus raphe magnus (NRM), and caudate nucleus (CdN); but does not influence AVP level in the hypothalamic arcuate nucleus, locus coeruleus, hippocampus, pituitary, spinal cord, and serum (Yang et al., 2006e, 2009a). Pain stimulation induces PAG, NRM, and CdN, releasing AVP (Yang et al., 2006d; Yang, Chen, Liu, Song, & Lin, 2006b). Pain stimulation enhances PVN synthesis and secretion of AVP (Yang et al., 2006d), which is transferred to PAG (Yang et al., 2007a), NRM (Yang et al., 2009c), and CdN (Yang et al., 2011) to influence pain modulation. The present study found that the CSF AVP level increased in the patients with orthopedic pain, which related to the VAS level negatively.

Injection of AVP into the PVN, PAG, NRM, and CdN increases, and anti-AVP serum (or vasopressin receptor antagonist) decreases the pain threshold (Yang et al., 2006b, 2006d, 2008, 2009a; Yang, Chen, Liu, Song, & Lin, 2006a, 2006c). It was anticipated that intranasal AVP may transfer to these brain structures to influence pain modulation, such as the process of orthopedic pain. However, this needs to be studied in the future.

AVP enhances the PAG synthesis and secretion of endogenous opiate peptides (Yang et al., 2006c, 2006f, 2007c), the NRM release of serotonin (Yang et al., 2009b), and CdN release of acetylcholine (Wang et al., 2010) to participate in pain modulation. Bypassing the BBB through the olfactory region, intranasal AVP may influence the endogenous opiate peptide, serotonin, and acetylcholine systems to influence pain modulation. However, this needs to be proven.

The present study found that CSF AVP level increased in patients with orthopedic pain after intranasal AVP. The data indicated that

intranasal AVP influenced the CSF AVP level in relation with the orthopedic pain relief.

The remarkable functions of AVP include body fluid homeostasis and cardiovascular control in the blood circulation and body temperature, learning, and memory in the central nervous system. Intranasal AVP did not influence the blood pressure (including systolic pressure and diastolic pressure), heart rate, respiratory rate, or body temperature. It is suggested that intranasal AVP (100-400 ng) might be well tolerated when used to treat orthopedic pain.

Conclusions

AVP level in CSF, not in plasma, in orthopedic patients was higher than that in healthy volunteers. AVP not only increased CSF level but also reduced VAS levels in orthopedic patients for 24 hours after intranasal administration, although it did not influence plasma AVP concentration, blood pressure, heart rate, respiratory rate, or body temperature.

Intranasal AVP, when delivered to the brain through the olfactory region, could be used to treat clinical orthopedic pain, and AVP might be a potential drug for clinical orthopedic pain relief by intranasal administration. However, intranasal AVP for pain treatment 2-4 weeks after orthopedic surgery is recommended because the experiments were performed 2-4 weeks after orthopedic surgery in this study, and the effects of AVP in the early postoperative period were not investigated. Also, the molecular neural mechanism for intranasal AVP in treating orthopedic pain was further studied.

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