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Influence of perioperative stress on central and peripheral oxytocin and arginine-vasopressin concentrations

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Abstract

Perioperative stress provides not only physical, but also psychic and emotional aspects, which may influence the hypothalamic neuropeptide system. Studies investigating the perioperative course of central neuropeptide activity are missing. Therefore, the present study aimed to determine perioperative fluctuations in central and concomitant peripheral concentrations of the hypothalamic neuropeptides oxytocin (OXT) and arginine-vasopressin (AVP), as well as their impact on perioperative anxiety and depression. Cerebrospinal fluid (CSF), blood and saliva were collected from 12 patients who underwent elective endovascular aortic repair with a routinely inserted spinal catheter. AVP and OXT concentrations were analysed at four timepoints: (i) the evening before the operation; (ii) the operation day immediately before anaesthesia induction; (iii) intraoperatively after the stent was placed; and (iv) on day 1 after the operation. Patients completed the Hospital Anxiety and Depression Scale (HADS) at timepoints 1 and 4. For CSF OXT, the present study showed a significant intraoperative decline, accompanied by a decrease in saliva. OXT blood concentrations before anaesthesia induction were higher than at the evening before the operation. OXT concentrations in CSF and saliva correlated well at timepoints 2-4. AVP concentrations in CSF, blood and saliva did not show any significant changes perioperatively. However, postoperative AVP blood concentrations showed a significant negative correlation with anxiety and depression scores according to the HADS. This pilot study demonstrates perioperative fluctuations in central OXT concentrations, which are better reflected by saliva than by blood. Further studies are required to determine whether OXT and AVP can predict postoperative post-traumatic stress disorder.

KEYWORDS

anaesthesia, anxiety, arginine-vasopressin, depression, oxytocin, perioperative stress

1 | INTRODUCTION

Once released into the blood, the posterior pituitary hormones oxytocin (OXT) and arginine-vasopressin (AVP) exert their well-described actions on the reproductive system, kidneys and blood vessels, maintaining blood pressure and water homeostasis.[1-3] Neuropeptide secretion in the blood is mostly accompanied by release within the central nervous system.[4,5] In distinct brain regions, the neuropeptides OXT and

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AVP act as neurotransmitters and influence cognition and behaviour.[6] The central neuropeptide system is activated by "stressful, challenging and potential threatening situations"[3] that occur as psychic and physical stressors. Patients undergoing major surgical procedures are faced with these situations over the perioperative time course in different manners. In the preoperative phase, anxiety predominates. Intraoperatively, physical stressors dominate, while the patients should be shielded from pain and anxiety by adequate anaesthesia. Postoperatively, restoration of physical homeostasis and emotional stability is essential to minimise morbidity and mortality.[7,8] However, studies investigating fluctuations in the central neuropeptide system over the perioperative course are missing. One reason for the lack of perioperative studies is that the central concentrations of neuropeptides are difficult to determine. It is generally considered that central neuropeptide activity is best represented by cerebrospinal fluid (CSF) concentrations,[4,6] thus always requiring invasive sampling procedures. As early as the 1980s, some studies examined perioperative blood concentrations of OXT and AVP[9,10] without investigating the correlation to the central compartment. Because central neuropeptide release is not necessarily accompanied by release in the blood,[3] these studies do not provide a complete insight into perioperative influences on the OXT/AVP system. Consequently, the role of blood or saliva neuropeptide concentrations as surrogate parameters for central activity in a perioperative setting has not been determined to date.[3,11]

An imbalance of the OXT/AVP system in the perioperative setting might be associated with postoperative psycho-cognitive deterioration. In this context, post-traumatic stress disorder occurs in up to 20% of patients after major surgery[7,8] and severely affects the patient's quality of life.

The present study aimed to determine perioperative fluctuations in central OXT/AVP concentrations in patients undergoing endovascular aortic repair with an indwelling lumbar CSF catheter for spinal pressure monitoring. In addition, we investigated whether fluctuations in the central compartment are reflected by neuropeptide concentrations in the peripheral compartments blood and saliva. Finally, we determined the association between the OXT/AVP system and perioperative anxiety and depression by means of the self-assessment tool: Hospital Anxiety and Depression Scale (HADS).[12]

2 | MATERIALS AND METHODS

In total, 12 patients (eight males, four postmenopausal females, aged 52-84 years, median 73 years) who were scheduled for elective endovascular aortic repair were included in the present study. Anamnestically, patients did not suffer from psychiatric diseases. Written informed consent was obtained from each patient. The study was approved by the ethics committee of the Technical University of Munich (reference number 423/14). Patient characteristics and intraoperative parameters are shown in Table 1. Patients underwent general anaesthesia and received no anxiolytic premedication. Propofol (100-250 mg), sufentanil (15-30 µg) and rocuronium (30-50 mg) were used for anaesthesia induction. Anaesthesia was maintained using the volatile anaesthetic sevoflurane. Sufentanil (5-10 µg) and rocuronium (10 mg) boli were repeatedly administered intraoperatively to maintain analgesia and muscle relaxation. Intraoperative target values were a mean arterial pressure of 60-80 mm Hg and a urine output volume of at least 0.5 mL kg^{-1} h^{-1}. To achieve these targets, crystalloids (ringer-acetate) and noradrenaline were administered i.v. Neither dopamine, nor dobutamine was used throughout the perioperative course. Vital parameters (electrocardiogram, peripheral oxygen saturation, heart rate and invasive blood pressure) were recorded continuously during the operation. Sufficient depth of anaesthesia was ensured by using entropy monitoring (GE Healthcare, Chicago, IL, USA) with the recommended state entropy target value of 40-60.[13]

Patients received a lumbar CSF drain for lumbar pressure monitoring, which was routinely inserted according to our local protocol on the evening before the operation at about 8.00 PM Two hours later, patients completed the HADS. Afterwards, blood and CSF samples were taken in pre-chilled ethylenediaminetetraacetic acid tubes from the pre-existing venous access and the lumbar drain. Saliva was collected by aid of a saliva collection system (Salivette®; Sarstedt AG & Co., Nümbrecht, Germany) with a solid base for saliva absorption and a conical tube for centrifugation and recovery of the collected saliva. Further samples of the three compartments blood, CSF and saliva were collected simultaneously on the operation day at 8.00 AM directly before anaesthesia induction, intraoperatively after stent positioning in a steady-state with stable blood circulation and heart rhythm and on the first postoperative day at the ward approximately 24 hours after the end of the operation. At that timepoint, the HADS was determined again. Samples were centrifuged for 10 minutes at 1300 *g* at 4°C immediately after collection and stored at −80°C until analysis.

All samples were extracted and assayed identically in the same batch at the same time as described elsewhere.[14,15] Briefly, samples (0.5 mL) were extracted using LiChroprep® Si60 (Merck, Kenilworth, NJ, USA) heat-activated for 3 hours. Next, 20 mg of LiChroprep® Si60 in 1 mL of distilled water was added to the sample, mixed for 30 minutes, washed twice with distilled water and 0.01 mol L^{-1} HCl and eluded with 60% acetone. The lyophilised extracts and the evaporated saliva samples were analysed for both oxytocin and vasopressin in a highly sensitive and specific radioimmunoassay (RIAgnosis, Regensburg, Germany). Assay sensitivities were in the range 0.1-0.5 pg, cross-reactivities with related peptides were <0.7%, and intra- and inter-assay variabilities were <10%.

Statistical analysis was performed using R, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). For detecting differences in the time course of OXT and AVP concentrations in the different compartments, the Friedman test was applied because values were lacking a normal distribution. Post-hoc analysis at specific time points was performed by the Wilcoxon signed-rank test using the Bonferroni correction for multiple comparisons. Additionally, the factors sex and time and their interaction were investigated with linear mixed-effect model analysis. Correlations of OXT and AVP levels in blood, CSF and saliva were calculated

TABLE 1 Patient characteristics and intraoperative parameters

Age	Sex	Surgery duration (min)	Blood loss (mL)	Transfusion (number of PRBC)	Minimum Hb (g dL^{-1})	Fluid intake (mL)	Urine output (mL)	Mean norepinephrine (μg kg^{-1} min^{-1})	Mean MAP (mm Hg)
52	Female	345	800	2	9.6	2200	990	0.20	81
79	Female	309	500	1	8.1	4600	980	0.08	89
71	Female	232	300		10.4	2900	250	0.10	80
69	Female	235	<100		10.0	3000	1600	0.03	85
71	Male	116	<100		11.4	5200	1040	0.10	78
82	Male	407	<100		7.4	3900	2000	0.12	79
66	Male	224	*	2	8.0	4300	1300	0.08	81
74	Male	314	400		10.3	2100	1170	0.12	83
82	Male	149	200		10.4	3500	220	0.12	86
84	Male	417	1500	2	8.3	4600	1420	0.07	61
76	Male	141	<100		10.7	3000	200	0.22	73
68	Male	169	400		10.0	2100	380	0.08	76

Note: Patient age (years), sex and intraoperative parameters (duration of surgery, blood loss, number of packed red blood cells [PRBC], minimum intraoperative haemoglobin, intraoperative fluid intake and urine output, mean intraoperatively applied norepinephrine concentration and mean of intraoperative mean arterial pressure [MAP]).
*No blood loss documented in the anaesthesia record.

using Spearman's rank correlation coefficient at each of the four timepoints. A paired *t* test was used for comparing the items of the HADS, and Spearman's rank correlation coefficient was used to assess correlations of OXT and AVP concentrations and anxiety and depression scores of the HADS for all patients, as well as the male and female subgroups. $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Time course of OXT and AVP

Medians and ranges of central and peripheral OXT and AVP levels at the four timepoints are shown in Table 2. In brief, OXT blood levels were lowest at baseline, showed a significant rise preoperatively, fell intraoperatively to baseline levels and increased again on day 1 after the operation. OXT CSF and saliva levels showed concordant changes over the time, which included an intraoperative decline that was statistically significant compared to the preoperative levels.

Changes in AVP levels during the whole perioperative period showed no statistical significance. Individual perioperative neuropeptide concentrations are depicted as line graphs in Figure 1 and post-hoc *P* values are shown in Table 3. In one patient, the postoperative timepoint was missing as a result of early removal of the spinal catheter.

The influence factors sex and time and their interaction were investigated using a linear mixed-effect model. Neither influence of sex, nor interaction between sex and time could be detected for OXT and AVP concentrations in one of the three compartments blood, CSF and saliva.

3.2 | Correlations between blood, CSF and saliva levels

Correlations between OXT blood and saliva levels were not statistically significant at any of the four timepoints. OXT blood and CSF levels showed a moderate significant correlation only at the intraoperative timepoint 3 ($r = 0.71$, $P = 0.013$). Moderate to strong correlations could be shown in both sexes throughout for OXT CSF and saliva. Statistical significance was achieved in males and in all patients at timepoints 2-4 (timepoint 2: $r = 0.73$, $P = 0.009$; timepoint 3: $r = 0.73$, $P = 0.008$; timepoint 4: $r = 0.85$, $P = 0.001$ for all patients).

Almost no significant correlation between AVP blood, CSF and saliva levels could be detected. The only exception was timepoint 2, where a moderate correlation between AVP blood and saliva could be shown ($r = -0.65$, $P = 0.03$).

Scatter plots of OXT CSF and saliva levels at the four timepoints are depicted in Figure 2.

3.3 | Neuropeptide levels and HADS score

Pre- and postoperatively determined HADS scores did not differ significantly. Scores of the anxiety and depression subscales pre- and postoperative are shown in Table 4. Preoperatively, two patients showed a high anxiety score of 12, whereas the depression score was low (0-7, median 3.5) in all patients. Postoperatively, only one patient showed a high anxiety score of 13 (median of all patients 5, range 1-13) and the depression score also remained low (median 4, range 1-9). In none of the three compartments were OXT levels correlated significantly with the HADS scores at the pre- and postoperative timepoints, nor did AVP levels in blood, CSF and saliva correlate well with the preoperative HADS for all patients. Only

in males was there was a significant negative correlation between AVP blood and the anxiety score on the evening before the operation (r = −0.872, P = 0.005). Postoperatively, AVP levels in blood showed a moderate and significant negative correlation with the anxiety (r = −0.67, P = 0.024) and depression (r = −0.66, P = 0.03) subscales for all patients. By contrast to males, females showed a positive correlation between postoperative AVP blood concentrations and the anxiety score of the HADS. Correlation coefficients of OXT and AVP concentrations in the three compartments with the two HADS subscales are shown in Table 5.

TABLE 2 Median oxytocin (OXT) and arginine-vasopressin (AVP) concentrations in blood, cerebrospinal fluid (CSF) and saliva in pg mL^{-1} and interquartile range (Q25-Q75)

Timepoint		1	2	3	4	*P* value
OXT	Blood	1.52 (1.38-1.87)	1.95 (1.72-2.21)	1.53 (0.93-2.21)	1.96 (1.06-2.36)	.009*
	CSF	3.52 (2.77-3.94)	3.65 (3.17-4.62)	2.94 (2.14-3.43)	3.28 (2.77-3.47)	.003*
	Saliva	2.02 (1.73-2.09)	2.07 (2.00-2.96)	1.91 (1.77-2.12)	2.11 (1.88-2.28)	.027*
AVP	Blood	2.27 (1.82-2.49)	1.88 (1.73-3.04)	2.04 (1.82-2.57)	2.44 (2.21-3.66)	.301
	CSF	1.82 (1.42-2.38)	2.11 (1.46-2.29)	1.83 (1.29-2.83)	3.09 (2.49-4.84)	.020*
	Saliva	2.18 (1.96-2.87)	2.64 (2.08-2.87)	3.18 (2.78-3.57)	2.56 (2.37-3.52)	.113

Note: Friedman *P* values are shown for significant changes over the time course (*). Timepoint 1: evening before the operation, timepoint 2: before anaesthesia induction, timepoint 3: intraoperatively after stent placement, timepoint 4: first postoperative day.

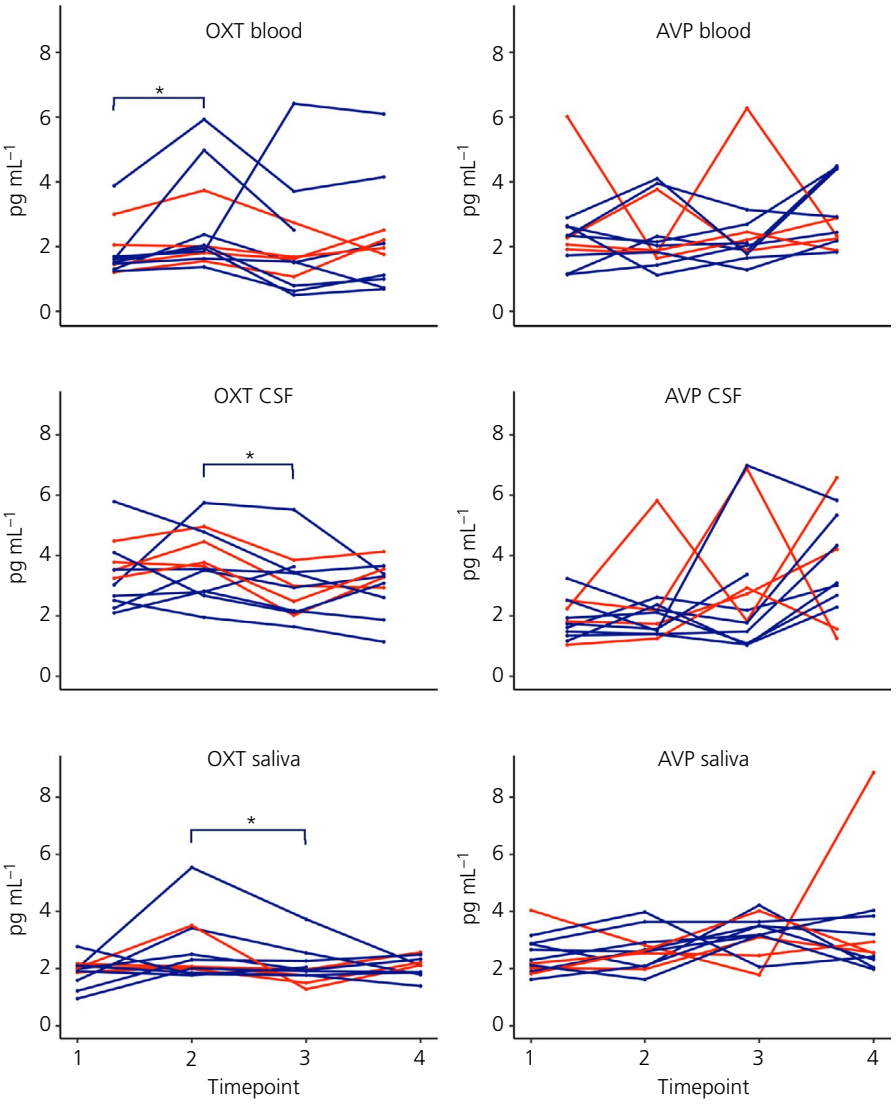

FIGURE 1 Oxytocin (OXT) and arginine-vasopressin (AVP) concentrations in the three compartments blood, cerebrospinal fluid (CSF) and saliva at the four timepoints and for the individual time course of each patient. Values of male patients are indicated in blue and female patients are indicated in red. The preoperative rise in OXT blood and the intraoperative decline in OXT CSF and saliva demonstrated statistical significance (*P < .05)

4 | DISCUSSION

The present study showed an intraoperative decrease in central OXT levels, which correlates well with saliva levels. Therefore, OXT saliva levels might present an adequate surrogate parameter for central OXT concentrations. Furthermore, postoperative AVP blood levels were negatively correlated with the postoperative HADS score.

4.1 | Perioperative time course

The main observation in the present study was a significant intraoperative decline in OXT CSF, as well as saliva levels. This can be interpreted as an adequate depth of anaesthesia, which was ensured using entropy monitoring. Therefore, we assume that patients were adequately shielded from stress and painful stimuli during the operation. The decline of central OXT levels in the present study is

TABLE 3 *P* values of post-hoc analysis (Wilcoxon)

Timepoint		1-2	1-3	1-4	2-3	2-4	3-4
OXT	Blood	0.031*	1	1	0.28	1	1
	CSF	1	0.50	0.48	0.023*	0.056	1
	Saliva	0.41	1	0.67	0.023*	0.74	1
AVP	CSF	0.79	0.54	0.068	0.89	0.070	0.34

*Significant changes ($P < 0.05$) between two timepoints in oxytocin (OXT) blood, cerebrospinal fluid (CSF), saliva and arginine-vasopressin (AVP) CSF

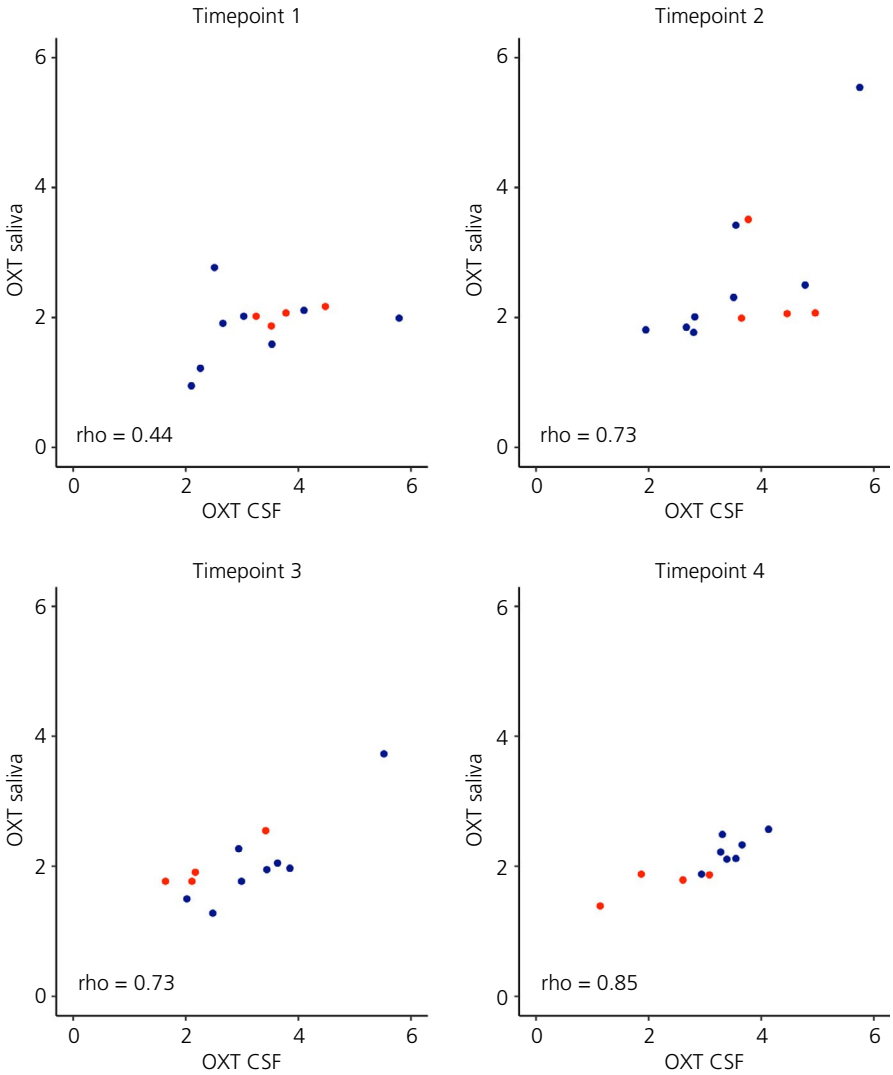

FIGURE 2 Correlations of oxytocin (OXT) cerebrospinal fluid (CSF) and saliva concentrations at the four perioperative timepoints and Spearman's rho values. Concentrations of OXT in CSF and saliva are depicted in pg mL^{-1}. Male patients are indicated in blue and females are indicated in red

TABLE 4 Patient Hospital Anxiety and Depression Scale (HADS) scores

		HADS preoperative		HADS postoperative	
Age	Sex	Anxiety	Depression	Anxiety	Depression
52	Female	12	7	13	5
79	Female	12	5	5	4
71	Female	4	2	4	3
69	Female	2	3	9	9
71	Male	6	2	2	1
82	Male	3	0	6	2
66	Male	4	3	3	4
74	Male	5	2	3	1
82	Male	2	4	na	na
84	Male	2	4	9	7
76	Male	2	6	1	4
68	Male	6	5	7	6

Note: Patient age (years), sex and HADS scores pre- and postoperative.

in accordance with several experimental studies. Zierer[16] described decreased neuropeptide concentrations in the posterior pituitary in rats anaesthetised with ether. Although changes in hypothalamic OXT and AVP mRNA levels could not be found after isoflurane anaesthesia,[17] down-regulation of AVP and OXT gene expression in the hippocampus as an effect of sevoflurane anaesthesia has been demonstrated by Pan et al.[18] These results are consistent with the findings of Zhou et al,[19] who also showed that sevoflurane decreases OXT and AVP mRNA in the hippocampus. Additionally, Zhou et al[19] described an association of down-regulation of OXT and AVP in the brain with impaired social recognition memory function and social discrimination ability. Whether the intraoperative decline of central OXT levels in the present study is a result of direct pharmacological effects of sevoflurane or indirectly caused by lowered stress levels because of anaesthesia remains to be assessed in further studies.

Regarding the perioperative course of OXT in the blood, concentrations immediately before induction of anaesthesia were significantly higher than concentrations on the evening before the operation. However, a concordant significant preoperative rise in CSF and saliva levels could not be shown. It appears reasonable to assume that movement from the ward to the operation theatre and anticipation of a major surgical procedure caused a high level of emotional stress that might have been accompanied by OXT release because it has been reported previously that OXT release is part of the psychosocial stress response.[20] The existing literature suggests that central and peripheral OXT secretion as a result of stressful stimuli is mostly coupled.[5,21] Therefore, it is unlikely that OXT release as a result of an emotional stressor occurs only in the blood circulation and not within the CNS.[22] After axonal or dendritic release, OXT fulfils its action on OXT-receptors in various brain regions.[3,23] Subsequently, OXT diffuses via the extracellular fluid in the ventricular system.[3] Therefore, changes in OXT concentrations in lumbar spinal fluid might be detected with some delay. This might explain why, in the present study, changes in OXT levels of lumbar CSF were too small to show significant changes simultaneous to peripheral OXT release. However, this consideration remains necessarily speculative.

Regarding AVP in the three compartments blood, saliva and CSF, the detected fluctuations did not demonstrate statistical significance, although we did observe a trend for higher postoperative AVP CSF levels compared to the preoperative state. Because AVP exerts a crucial role in regulating water homeostasis and blood pressure, its central and peripheral secretion can be influenced perioperatively by numerous factors that differ from patient to patient.[24,25] Individuals are differently affected by preoperative food and fluid deprivation, extracellular volume depletion, intraoperative blood loss and fluctuations in arterial pulse pressure, especially in major vascular surgery where patients always show a hormonal stress response.[26] Intraoperatively, on the other hand, the anaesthesiologist uses close monitoring to maintain blood pressure and urine output targets in patients undergoing vascular surgery who are at high risk for adverse cardiac and renal outcome. Therefore, fluid and norepinephrine administration were individually adjusted to each patient, avoiding hypovolaemia and maintaining sufficient perfusion pressure. Haemorrhagia and extreme hypovolaemia which are strong stimuli for AVP release[27,28], were largely avoided in our patients. This might be one explanation for the lack of significant perioperative fluctuations in AVP concentrations.

4.2 | Correlations of CSF, blood and saliva levels

Physiological stimuli can trigger simultaneous central and peripheral neuropeptide release. On the other hand, some stressors may cause OXT and AVP release within certain brain regions that are not paralleled by secretion into the blood.[4] Therefore, it is reasonable to assume that blood is not always a suitable body fluid for characterising central neuropeptide actions. Under basal conditions, the correlation of OXT and AVP blood and CSF levels was shown to be weak, and central neuropeptide activity might be better represented by CSF concentrations.[14] Because CSF collection requires invasive procedures such as lumbar puncture, many studies use other body fluids as a surrogate. Saliva is easy to obtain and the neuropeptides in saliva are reliably measurable.[2,15] Therefore, salivary biomarkers increase in popularity and are used in a growing number of studies examining different patient populations.[29-31] In a recent study on neurocritical care patients, we demonstrated a moderate to strong correlation for OXT between the saliva and CSF compartment, whereas plasma OXT did not correlate well with CSF levels.[15] These results are confirmed in the present study, where we could demonstrate significant moderate to strong correlations for OXT saliva and CSF levels intraoperatively, whereas correlations between blood and CSF levels were mostly weak. Correlations between OXT saliva and CSF were moderate at timepoint 1, which represents basal conditions during the evening before the operation in the absence of external stimuli. At timepoints 2-4 with their assumed stressful conditions, we found strong correlations

TABLE 5 Correlations of anxiety and depression subscales of the pre- and postoperative Hospital Anxiety and Depression Scale (HADS) with oxytocin (OXT) and arginine-vasopressin (AVP) concentrations in the three compartments blood, cerebrospinal fluid (CSF) and saliva

			all		m		f	
			rho	p	rho	p	rho	p
Timepoint 1	Anxiety	OXT blood	–0,369	0,237	0,031	0,942	–0,738	0,262
		OXT CSF	0,036	0,912	–0,098	0,817	0,316	0,684
		OXT saliva	0,168	0,601	0,344	0,404	–0,211	0,789
		AVP blood	–0,387	0,215	**–0,872**	**0,005**	0,105	0,895
		AVP CSF	0,344	0,273	0,049	0,908	0,316	0,684
		AVP saliva	0,351	0,264	0,270	0,518	0,632	0,368
	Depression	OXT blood	–0,535	0,073	–0,285	0,494	–1	0,083
		OXT CSF	–0,096	0,768	–0,193	0,647	–0,200	0,917
		OXT saliva	0,236	0,461	0,349	0,396	–0,400	0,750
		AVP blood	0,513	0,088	0,627	0,096	0,200	0,917
		AVP CSF	–0,229	0,475	–0,446	0,268	–0,400	0,750
		AVP saliva	0,312	0,324	0,434	0,283	0	1
Timepoint 4	Anxiety	OXT blood	0,014	0,968	–0,072	0,878	0	1
		OXT CSF	–0,114	0,738	0,180	0,699	–0,400	0,750
		OXT saliva	0,103	0,763	0,054	0,908	–0,316	0,684
		AVP blood	**–0,671**	**0,024**	**–0,811**	**0,027**	0,400	0,750
		AVP CSF	–0,260	0,440	–0,450	0,310	0,400	0,750
		AVP saliva	0,023	0,947	–0,090	0,848	–0,400	0,750
	Depression	OXT blood	–0,207	0,542	–0,218	0,638	–0,400	0,750
		OXT CSF	–0,474	0,141	–0,255	0,582	–0,800	0,333
		OXT saliva	–0,452	0,163	–0,509	0,243	–0,632	0,368
		AVP blood	**–0,658**	**0,028**	–0,600	0,154	–0,200	0,917
		AVP CSF	–0,368	0,266	–0,546	0,205	0,200	0,917
		AVP saliva	0,446	0,169	0,691	0,086	0	1

Note: Spearman's rho and *P* values are shown for all patients (all) and for the male and female subgroups separately. Significant correlations are indicated in bold. Timepoint 1 = evening before the operation, timepoint 4 = postoperative

throughout for OXT saliva and CSF. These findings are plausible because correlations between neuropeptide concentrations in different compartments might vary depending on basal or stimulating conditions.[3] In conclusion, the results obtained in the present study encourage the use of salivary OXT concentrations as a surrogate parameter for central neuropeptide activity in the perioperative phase, although we can only speculate about the source and functions of OXT in saliva. Correlations between AVP levels in the compartments blood, CSF and saliva were usually weak in our small patient population, such that the role of salivary or blood AVP concentrations as a surrogate for central AVP activity remains undefined.

4.3 | Neuropeptide levels and HADS score

The HADS is a self-assessment scale that has been developed for detecting anxiety and depression in hospital outpatients. As early as the 1980s, the implementation of this scale into general hospital practice was proposed.[32] The scale is used broadly in the general population to detect anxiety disorders and depression[12] and has recently been used in a study assessing mental distress of vascular surgery patients undergoing abdominal aortic aneurysm repair.[33] Therefore, the HADS appeared to comprise a suitable instrument for measuring anxiety and depressive tendencies in our patient population.

A balanced activity of the OXT and AVP system within the CNS appears to be crucial for mental health, with central OXT and AVP effects on anxiety and depression-like behaviour being characterised in a number of studies.[4] However, the value of OXT and AVP as biomarkers in psychiatric disorders remains unclear because studies have demonstrated varied results and, in most cases, peripheral neuropeptide levels are determined.[11,34] As far as OXT is concerned, we found no correlation of blood, CSF or saliva concentrations with either the anxiety or depression score of the HADS. These results are not completely unexpected because, in a recent review, Engel et al[34] found very heterogeneous results concerning the role of endogenous OXT levels in human psychopathology. In their meta-analysis, basal OXT levels did not differ between depressive patients and healthy controls.[34] Studies on peripheral AVP levels in psychopathology also reveal inconsistent findings.[11] In the present study, we showed a significant inverse relationship of anxiety and depression scores of the HADS with AVP blood levels only in the postoperative setting and not preoperatively. Interestingly, these results are consistent with the findings of Sadlonova et al[35] who showed an inverse association of copeptin (CT-pro-AVP) levels in the blood and the HADS anxiety score in male, but not in female patients who had cardiovascular risk factors.[35] This matches our patient cohort, which was small, although the majority of patients were male, and the four women included were in the postmenopausal state. When analysing males and females

separately in the present study, only men showed significant negative correlations between HADS scores and AVP blood concentrations. Females even showed a non-significant positive correlation regarding AVP blood and the HADS anxiety subscale. Taken together, there might be sex differences in perioperative psychical alterations and these need to be confirmed in larger studies.

4.4 | Strengths and limitations

By contrast to former studies, we were able to repeatedly take CSF samples from a lumbar catheter during the perioperative course. This enabled us to quantify global OXT and AVP activity within the CNS and to compare central and peripheral neuropeptide concentrations, which are of particular interest because the number of patients with intraoperative CNS access is extremely limited, especially in patients without CNS pathologies.

Despite the relatively small sample size, we were able to detect significant fluctuations in central and peripheral OXT but not AVP concentrations in the perioperative course. Because patients suffering from aortic aneurysms are predominantly male, we were only able to include four women in the present study, which does not allow us to draw conclusions on sex effects. However, our study population consisted of men and postmenopausal women only, such that we can exclude oestrous cycle effects.

Surgery can never be considered as a standardised stimulus. However, we attempted to achieve conditions that were as uniform as possible. Patients were closely monitored to maintain blood pressure and urine output, and we included no patients who were receiving mass transfusion. To minimise the influence of SIRS,[36] we restricted our study population to endovascular surgery.

Finally, the results regarding perioperative psychopathology should be interpreted carefully as a result of the sample size and the lack of a long-term follow-up. However, the significant results of this pilot study support the need for additional larger studies that aim to clarify the association between the OXT/AVP system and perioperative post-traumatic stress disorder, especially with respect to identifying patients who are at risk. Post-traumatic stress disorder is frequent in patients undergoing major surgery and modulation of the central OXT/AVP system could provide a possible therapeutic approach.[7] At least for OXT, the results of the present study suggest that saliva is an adequate surrogate parameter for the central compartment in the perioperative setting, which facilitates the design of future studies.

5 | CONCLUSIONS

To our knowledge, we report the first study examining perioperative fluctuations in central and peripheral neuropeptide concentrations in the three compartments CSF, blood and saliva. This pilot study has revealed some interesting aspects: OXT CSF levels showed a significant intraoperative decline accompanied by concordant changes in saliva levels. Therefore, saliva OXT levels might present an adequate surrogate parameter for central OXT concentrations. Oxytocin blood levels rose preoperatively probably as a result of emotional stress caused by anticipation of a major surgical procedure. AVP blood levels showed a significant inverse relationship with anxiety and depression scores of HADS. Because females were under-represented in the present study, larger patient cohorts are required to investigate sex-specific effects.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

SMK was responsible for the study design, data acquisition and interpretation, and drafting of the manuscript. JM was responsible for data acquisition and critical feedback on the manuscript. BU was responsible for the data analysis and critical feedback on the manuscript. BJ was responsible for the data interpretation and critical feedback on the manuscript. AHP was responsible for the study design, data acquisition and interpretation, and critical feedback on the manuscript. The final version of the manuscript submitted for publication has been approved by all of the authors.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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