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Dehydration and venous thromboembolism after acute stroke

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Summary

Background: Although it is widely assumed that dehydration predisposes to venous thromboembolism (VTE), there are no clinical studies to support this.
Aim: To evaluate the relationship between biochemical indices of dehydration and VTE after acute ischaemic stroke (AIS).
Design: Prospective observational study.
Methods: Unselected AIS patients ($n = 102$) receiving standard thromboprophylaxis with aspirin and graded compression stockings, underwent serial measurements of serum urea, creatinine and osmolality, and were screened for VTE using magnetic resonance direct thrombus imaging.
Results: Serum osmolality of >297 mOsm/kg, urea >7.5 mmol/l and urea:creatinine ratio (mmol:mmol) >80 a few days post-AIS were associated with odds ratios for VTE of, respectively, 4.7, 2.8 and 3.4 ($p = 0.02$, 0.05, 0.02) on multivariable analysis.
Discussion: Dehydration after AIS is strongly independently associated with VTE, reinforcing the importance of maintaining adequate hydration in these patients.

Introduction

It is widely assumed that dehydration predisposes to venous thromboembolism (VTE),[1] although there are no clinical studies to support this. Patients with acute stroke comprise an excellent group in which to examine this hypothesis, as hyperosmolar dehydration secondary to reduced water intake consequent upon dysphagia and/or obtundation is common, even in patients receiving supplementary fluids via nasogastric or parenteral routes.[2] We investigated the association between VTE and dehydration post-stroke, as part of a study in which we prospectively investigated the incidence and distribution of, and risk factors for, VTE (subclinical and clinical) after acute ischaemic stroke, using magnetic resonance direct thrombus imaging (MRDTI) as the diagnostic standard. This non-invasive technique detects met-haemoglobin in clot, providing a positive image of thrombus without the need for intravenous contrast, and is highly accurate for the diagnosis of both deep-vein thrombosis (DVT) and pulmonary embolism (PE).[3,4]

Methods

Following ethical approval, in-patients at St Thomas' Hospital with acute ischaemic stroke (AIS) (first or recurrent) were prospectively recruited

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over 21 months within 7 days of onset, irrespective of the degree of neurological impairment. Exclusion criteria were: primary intracerebral or subarachnoid haemorrhage; non-ambulatory prior to admission; moribund on admission; ongoing anticoagulant treatment or prophylaxis; contraindications to MRDTI; implanted lower-limb metal; and consent/assent not available. MRDTI was performed on a Siemens 1 Tesla unit using a T1-weighted magnetization-prepared 3D gradient-echo sequence, including a selective water-excitation sequence with inversion time chosen to null blood signal.[3,4] Lower limbs and pelvis were imaged in two segments by the body coil with a 500 mm field of view between 7 and 14 days post-stroke, then days 21–28. If DVT was identified, thoracic imaging was performed to detect PE using the body array coil with a 450 mm field of view and scanning in six segments, each incorporating a 16-s breath hold when possible. All scans were reviewed independently by JK and AM, who reached a consensus.

Patients were assessed clinically on recruitment (mean ± SD 2 ± 1.4 days post-stroke) then weekly (means ± SD 9 ± 1.9, 14 ± 2.7 and 21 ± 3.6 days post-stroke) and serum was collected at the same intervals into lithium-heparinized containers, then immediately stored at −80°C. Samples were analysed for urea, electrolytes, creatinine and osmolality *en masse* at the conclusion of the study. The biochemical indices of hydration studied were serum osmolality, serum urea and the serum urea:creatinine ratio (mmol:mmol). Osmolality was determined by the 'depression of freezing point' method (Advanced Micro, Advanced Instruments) and urea, electrolytes and creatinine measured using a Vitros 950 analyser (Johnson & Johnson). Stroke severity was recorded using the Barthel index (BI, ≤9 indicates severe disability).

Univariate associations between VTE, indices of dehydration and other clinical variables were investigated using logistic regression models. All factors were expressed as binary variables. For osmolality, these were >297 and ≤297 mOsm/kg (reference range 281–297 mOsm/kg); for urea, >7.5 and ≤7.5 (reference range 2.5–7.5 mmol/l); and for the urea:creatinine ratio (mmol:mmol), >80 and ≤80 (a ratio of >60 has been regarded as suggestive of dehydration in the absence of other explanations[5]—a figure of 80 was chosen arbitrarily, as most patients had ratios >60 around day 9). Multivariable logistic regression models were used to investigate for independent associations between VTE and significant explanatory factors in the univariate models. Indices of dehydration were entered into these models individually. The results of multivariable analysis for clinical factors were derived with osmolality entered as the index of dehydration. To confirm the appropriateness of the models chosen, BI and age were categorized in 5-unit and 5-year groups. Adding these to the multiple regression models as well as the binary categorization did not influence the results; nor did the addition of the exact BI and age.

Results

We recruited 102 AIS patients. Mean follow-up was 21 days (SD 5.9). Mean age was 70.1 years (SD 11.9) and 47 (46.1%) were male. Fifty-eight patients (57.1%) sustained total or partial anterior circulation infarcts, 11 (10.8%) posterior circulation infarcts, 32 (31.4%) lacunar infarcts, and one patient could not be classified. VTE occurred in 41 (40.2%) patients and was predominantly subclinical (35/41 cases, 85%). Isolated DVT occurred in 29 (28.4%), DVT and PE in 11 (10.8%) and isolated PE in one (1%). All but three (7%) VTE-positive patients were identifiable on initial imaging (between days 7 and 14 post-AIS). Hence, only the association between indices of hydration at the first two time points (days 2 and 9) and VTE were examined. Mean serum osmolalities on days 2 and 9 were 291.6 (SD 7.9) and 292.2 (SD 8.7) mOsm/kg; mean serum ureas were 5.7 (SD 2.7) and 6.9 (SD 3.2) mmol/l; and median urea:creatinine ratios (mmol:mmol) were 60 (IQR 50.7–71) and 70.9 (IQR 55.7–91.4). The odds ratios (ORs) for VTE on univariate and multivariable analysis in patients with osmolalities of >297 mOsm/kg, ureas of >7.5 mmol/l and urea:creatinine ratios (mmol:mmol) of >80 are shown in Tables 1 and 2.

Discussion

Biochemical indices of dehydration measured a few days post-stroke were significantly associated with the development of VTE on univariate and multivariable analysis, with ORs of 2.8–4.7 on multivariable analysis. To our knowledge, this is the first study to demonstrate that dehydration is strongly independently associated with VTE in any group of patients. While there is no single 'gold standard' clinical or laboratory measure of hydration status, and while increases in the biochemical indices measured in this study can sometimes have alternative explanations, it is likely that they did broadly reflect hydration status.[2,5] The fact that there was only a non-significant trend towards an association on day 2, that indices tended to become more abnormal between days 2 and 9, and that the association on day 9 persisted on multivariable

Table 1 Unadjusted univariate associations between VTE, indices of dehydration at 2 and 9 days post-stroke and clinical factors assessed on day 2, using logistic regression models

Variable	OR	95%CI	*p*
Osmolality >297 mOsm/kg day 2 ($n=22$)	1.3	0.5–1.4	0.6
Urea >7.5 mmol/l day 2 ($n=16$)	1.6	0.5–4.7	0.4
Urea:creatinine ratio >80 day 2 ($n=11$)	2.9	0.8–10.8	0.1
Osmolality >297 mOsm/kg day 9 ($n=24$)	2.7	1.1–7.0	0.04
Urea >7.5 mmol/l day 9 ($n=34$)	3.5	1.5–8.4	0.004
Urea:creatinine ratio >80 day 9 ($n=37$)	5.5	2.3–13.4	<0.0001
Age >70 ($n=53$)	3.7	1.6–8.7	0.002
Barthel ≤9 ($n=54$)	10	3.8–26.4	<0.0001
Leg paresis ($n=76$)	5.2	1.6–16.6	0.005
Incontinent* ($n=36$)	3.9	1.7–9.2	0.002
Malignancy ($n=6$)	3.2	0.6–18.3	0.2
Atrial fibrillation ($n=24$)	3.3	1.3–18.6	0.01
Diabetes ($n=25$)	0.6	0.2–1.6	0.3
Hypertension ($n=57$)	2	0.9–4.5	0.1
Ischaemic heart disease ($n=16$)	0.4	0.1–1.5	0.2

All factors are expressed as binary variables. *Persistent or occasional incontinence, or catheterized.

Table 2 Associations between VTE, indices of dehydration on day 9 and clinical factors assessed on day 2, using multiple logistic regression models

Variable	OR	95%CI	*p*
Osmolality >297 mOsm/kg day 9 ($n=24$)	4.7	1.4–16.3	0.02
Urea >7.5 mmol/l day 9 ($n=34$)	2.8	1–7.8	0.05
Urea:creatinine ratio >80 day 9 ($n=37$)	3.4	1.2–9.6	0.02
Age >70 ($n=53$)	4	1.3–12	0.02
Barthel ≤9 ($n=54$)	8.1	2.2–30.1	0.002
Leg paresis ($n=76$)	2.5	0.6–10.4	0.2
Incontinent* ($n=36$)	0.5	0.2–1.9	0.3
Atrial fibrillation ($n=24$)	1.8	0.5–5.9	0.3

All factors are expressed as binary variables. Indices of dehydration were entered into the models one at a time along with age, Barthel index, leg paresis, incontinence and atrial fibrillation. Results for age, Barthel index, leg paresis, incontinence and atrial fibrillation are for multivariable analysis using osmolality as the index of dehydration. *Persistent or occasional incontinence, or catheterized.

analysis, indicates that dehydration was largely hospital-acquired and suggests that the association was causal. Although our data cannot discount the possibility that VTE was already present at entry, previous reports using serial ^{125}I fibrinogen scanning have shown that VTE is rarely present before the second day post-stroke, then becomes increasingly prevalent over the next few days.[6] This study reinforces the importance of maintaining adequate hydration in the acute phase of stroke.

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