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Adverse Neurological Events after Sodium Tetradecyl Sulfate Foam Sclerotherapy – a prospective, observational study of 8056 treatments.

Authors

Huw OB Davies[1] hobdavies@doctors.org.uk (corresponding author)

Mike Watkins[2]

Richard Oliver[2]

Sarah Berhane[3,4]

Andrew W Bradbury[5]

[1] University Hospital of Wales, Heath Park Way, Cardiff CF14 4XW

[2] STD Pharmaceutical Products Ltd., Plough Lane, Hereford. HR4 0EL

[3] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

[4] Institute of Applied Health Research, University of Birmingham, UK

[5] University of Birmingham Department of Vascular Surgery, Netherwood House, Solihull Hospital, Birmingham, UK. B91 2JL

Key Words

STS, foam sclerotherapy, neurological events, migraine, stroke

Declaration of Conflicting Interests

None declared

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Abstract

BACKGROUND: Ultrasound guided foam sclerotherapy (UGFS) is a flexible and highly utilised tool in the treatment of varicose veins (VVs), both as a primary treatment and as an adjunct to other treatments. Concern remains regarding the risk of neurological adverse events (AEs) such as migraine, visual disturbance and serious adverse events (SAEs) such as cerebrovascular accident that have been reported after UGFS treatments.

AIM: To determine the incidence of neurological AEs and SAEs after UGFS

METHODS: A prospective, multicentre, post-authorisation safety study across Europe (both private and government) was performed between January 2015-2020. Neurological adverse events after UGFS with Fibrovein® (Sodium Tetradecyl Sulfate) 1 and 3% physician generated foam.

RESULTS: 8056 patients underwent treatment. There were 46 AE (including 5 SAEs), 30 (65%) SAEs were in female patients. Mean age was 55 years with mean body mass index (BMI) of 27. Univariable logistic regression demonstrate that UGFS only treatment (i.e. no adjunctive treatment), liquid-to-gas ratio, gas type and total foam volume (1% sodium tetradecyl sulfate, STS) were significantly associated with the odds of experiencing the outcome. Multivariable logistic regression model exhibits that migraine and total foam volume (1% STS) maintained statistical significance thus associated with the odds of adverse events.

CONCLUSIONS: This study demonstrates that UGFS with Fibrovein is safe with a very low incidence of neurological AEs and SAEs. Past history of migraine, use of physiological gas (O_2/CO_2) and increasing volumes of 1% foam increase the risk of AEs.

Introduction

Ultrasound-guided foam sclerotherapy (UGFS) is increasingly used worldwide in the treatment of chronic venous disease (CVD). Indeed, in a recent UK study [1], 50% of endovenous treatments were UGFS. Endothermal ablation and UGFS are recommended above open surgical treatment for varicose vein (VV) by National Institute for Health and Care Excellence (NICE) Clinical Guideline 168 [2].

Whilst most complications of UGFS are generic to other endovenous techniques for example recurrence and deep vein thrombosis (DVT), UGFS has been associated with neurological adverse events (AE) including headache, migraine or visual disturbance or serious adverse events (SAEs) for example transient ischaemic attacks (TIA) or stroke. Several papers [3-7], have cited low rates of neurological adverse events up to a 2.7% incidence [8]. There have been several putative mechanisms for this; microbubbles and/or vasoactive compounds travelling from right to left sides of the heart via a patent foramen ovale (PFO) and thus entering the arterial circulation and consequently entering the cerebral circulation with or without crossing blood brain barrier. It is postulated the resulting ischaemia from this is generated by occlusion of small vessels by microbubbles or vasoactive compound causing intense vasospasm.

Despite these papers, the exact incidence of neurological AEs and SAEs after UGFS is unknown. This study sought to address this and define the neurological safety profile of UGFS using sodium tetradecyl sulfate (STS), Fibrovein® (STD Pharmaceuticals Ltd., Hereford, for treatment of CVD and attempted to identify risk factors for the development of neurological events post UGFS.

Methods

Patients treated using UGFS with STS 1% and 3% foam (1% and 3% hereafter refer to STS foam concentrations) were recorded prospectively at multiple sites across the United Kingdom and France (Appendix 1). Treatments were performed in a mixture of government (NHS) and private healthcare settings. Non-patient identifiable treatments performed were recorded on a proforma after each UGFS treatment session. The data recorded was purely

observational and did not impact upon patient treatment. Treatment sheets were collated onto a secure database centrally at the University of Birmingham Department of Vascular Surgery.

Inclusion criteria were adults (aged 18 years or over), non-pregnant, non-breast feeding patients with CVD requiring treatment with UGFS as either a primary treatment or as an adjunct to another venous procedure. Those aged under 18, pregnant, breast feeding or having another contraindication to treatment with STS foam were excluded (e.g. anaphylaxis or previous adverse event).

Details recorded were patient variables: age, gender, body mass index (BMI), primary/recurrent VVs as well as classification of affected vein (e.g. great saphenous vein), previous DVT, Clinical Etiological Anatomical Pathophysiological (CEAP) 'C' grade and patient medical history (smoking, diabetes, hypertension, TIA, stroke and known PFO). Treatment variables were also recorded: method of foam preparation (e.g. Tessari technique, double syringe etc, see Table 1), concentrations (3% and 1%) and volumes used, STS to gas ratio (e.g. 1ml STS liquid to 3ml gas is recorded as 1:3 ratio), gas used (air/ O_2/CO_2 /other), number of injection sites, aliquot size, concomitant treatment (e.g. radiofrequency) and compression regime/duration.

If a patient suffered an AE or SAE – as defined by the European Medicines Agency [9], the treating clinician was asked to fill in a separate proforma providing further details. These were also recorded at the University of Birmingham Department of Vascular Surgery and forwarded on (anonymously) to the qualified person for pharmacovigilance at STD Pharamceutical Products for central reporting. Yearly reports were submitted to the European Union electronic Register of Post-Authorisation Studies (EUPAS8260).

Using the UK NHS Health Research Authority online decision tools (www.hradecisiontools.org.uk), this observational post authorisation safety study is not classed as research requiring ethical approval.

Statistical analysis was undertaken using Stata/SE 16.0 (StataCorp, Texas, USA). Continuous variables were presented as median and interquartile range and categorical variables as counts and percentages. Patients with and without adverse events were compared using the t-test/Mann-Whitney test (for continuous variables) or Pearson's chi-squared test/Fisher's exact test (for categorical variables). The maximum number of candidate parameters for developing the multivariable model given the size of the dataset were determined using a method proposed by Riley et al [10]. The amount of missing data for each variable was summarised and reported. Multiple imputation by chained equations [11-13] was performed to handle missing data in the candidate variables. Skewed variables that could not be transformed closer to normality were imputed using predictive mean matching (PMM) [14, 15]. The number of imputed datasets to be generated was chosen such that it is equal to the percentage of patients with missing data in any of the candidate variables. The distributions of the imputed variables were visually checked and compared with observed data. Univariable and multivariable logistic regression analysis were undertaken to analyse the effect of each variable on the odds of experiencing adverse events. Model estimates from each imputed dataset were combined into one pooled estimate using Rubin's Rules [16]. A multivariable logistic regression model was built using a stepwise backward selection of variables at the significance level of p=0.157 (corresponding to selection based on AIC) with multivariable fractional polynomials (MFP) being used to model non-linear relationships in continuous variables. The "best" functional form for the continuous variable was thus chosen as part of the variable selection. Outliers and influential observations were identified using standardised Pearson's residuals, deviance residuals and Pregibon leverage statistics plotted against observation number (for each imputed dataset). The impact of excluding any outliers and influential observations on the model parameters were examined.

For comparison with the imputed results, univariable and multivariable logistic regressions were also performed on patients with available data for the candidate variables (complete case analysis).

Results

Demographics

A total of 8056 treatments sessions (bilateral treatments were included as one treatment session), 10,274 legs, were recorded during the study duration (January 2015to December 2020), 5261 treatments (65%) were in female patients. Mean age was 55 years (interquartile range, IQ – 45-66) with mean body mass index (BMI) of 27 (IQ – 23.7 – 30.9). 2385 patients had undergone previous UGFS. Patient pre-procedural past medical history (PMHx)/co-morbidities are recorded in Table 1, comparing demographics between those who experienced no adverse events and those who experienced adverse events. Patients with adverse events had higher proportion of a history of migraine, migraine with aura, UGFS only treatment, CO2/O2 gas type as well as higher foam volume (1% concentration) compared to those with no adverse events (Table 1).

Missing data and data imputation

Fourteen percent (14.3%) of patients had at least one of the candidate variables missing. As a result, 15 imputed datasets were generated (M=15).

Univariable logistic regression

Results from the univariable logistic regression (Table 2) show that UGFS only treatment, liquid-to-gas ratio, gas type and total foam volume (1%) were significantly associated with the odds of experiencing an adverse event. Notably, patients with migraine had 18-fold higher odds of adverse events compared to those without, whereas use of CO2/O2 foam was associated with a 5.4-fold increase in the odds of an adverse event compared to air. Similarly, each one millilitre increase in total foam volume (1%) was associated with a 4% increase in the odds of adverse events.

Multivariable logistic regression

The multivariable logistic regression model as a result of the backward selection of the candidate variables is shown in Table 3. It shows that migraine, total foam volume (1%) and gender maintained statistical significance thus associated with the odds of adverse events. In order to visualise the effect of these variables on the outcome, a plot of probability versus total foam volume (1%) according the migraine status and gender was produced and this was shown in Figure 1.

Neurological Adverse Event Cohort (AEC)

Of 46 patients in the AE and SAE cohort 30 patients were female, 16 were male with a mean age of 54 years and mean BMI of 26.9. 26 of the patients had history of migraines and 21 migraines with aura. Two had previous TIAs, one was diabetic, five were hypertensive and one had a previous DVT on the contralateral leg. No patients had known PFOs. 15 had previous UGFS treatments.

Neurological Adverse Event Descriptions

Forty six patients suffered AEs or SAEs, an overall incidence of 0.57%. The adverse events are presented below by type.

Patients experiencing a migraine/headache

Sixteen patients experienced a migraine/headache which equates to a 1 in 500 (0.2%) incidence of experiencing a migraine/headache. However, six of these patients received a volume of foam significantly higher than the maximum of 16mL recommended in the SmPC (Summary of Product Characteristics).

Ten patients who received a volume of foam within the SmPC recommendations experienced a migraine/headache which equates to a 1 in 833 (0.12%) incidence.

Overall, of the patients who experienced a migraine/headache 12/16 (75%) had a history of migraine. For those treated within the SmPC recommendations the history of migraine was 6/10 (60%).

Patients experiencing a migraine/headache plus visual disturbance

In this group all ten patients were treated within the recommended maximum foam volume giving a 1 in 833 (0.12%) chance of experiencing this AE. Nine patients had a history of migraine (90%).

In summary 26 patients had a migraine/headache with or without a visual disturbance of which 21 (80.8%) had a history of migraine. Taking the group of patients treated within the recommended foam maximum dose 14 (70%) had a history of migraine.

Patients experiencing a visual disturbance

Overall, 12 patients experienced just a visual disturbance with no migraine/headache a 1 in 667 (0.15%) chance. Of this group eight were treated within the recommended maximum dose of foam an incidence rate of 1 in 1,000 (0.1%).

A history of migraine was present in four patients (33%) with any volume of foam and two patients (25%) treated within recommended maximum dose of foam.

Neurological Serious Adverse Event Cohort

There were five serious adverse events (SAEs) (0.062%) and four neurological SAEs (0.049%). These included anaphylaxis in 47-year-old male patient (previous UGFS 8 years previously) who developed breathing problems requiring intubation two minutes after treatment with 12ml 3% STS foam. After six hours he was extubated and discharged the following day with no further adverse effects.

The 4 neurological SAEs were:

- 82 year old female with PMHx of TIAs (not on any medical therapy), 8-12 hours post treatment or recurrent GSV VVs with radiofrequency ablation and 8ml 1% STS foam, whilst at home, she developed transient numbness/weakness in left hand which fully resolved – was referred to stroke team for ongoing risk management.
- 32 year old female with PMHx of headaches (not migraines) had primary GSV VVs treated with 2ml 1% STS foam reported some right arm weakness immediately post treatment (with no reported headache/migraine). This resolved after 10-15 minutes. The treating team noted the patient was anxious during her treatment session.
- 55 year old male with PMHx of hypertension and hypercholesterolaemia primary GSV VVs were treated with 10ml 1% STS foam only. 20 days later he developed left arm

weakness (CT head demonstrated right internal capsule infarct) which fully resolved and was discharged after 5 days.

- 70 year old female with no PMHx was treated with 32ml 1% STS foam only to residual varicosities (previous truncal treatment with endothermal ablation). During application of stocking she developed left sided weakness and facial droop. CT head demonstrated possible air embolus in the right middle cerebral artery. The patient was treated with hyperbaric oxygen therapy and made an almost complete recovery (the long term sequalae being minor sensation loss in left shoulder and face).

Of the four neurological SAEs, three resolved entirely, leaving long-term sequalae in only one patient (0.012% treatments). There was no mortality in the study.

Discussion

The data demonstrates a wide range of treatment styles, utilising both UGFS as a stand-alone treatment modality and as an adjuvant therapy with all other commonly utilised endovenous treatment modalities. Patients from a large age range were treated across all groups of CEAP clinical class and numerous patterns of reflux. This demonstrates the flexibility of UGFS both as an independent and adjuvant treatment for VV. This flexibility is increasingly recognised in the importance of treating the small tortuous veins in the sub ulcer plexus which are otherwise unreachable with other treatment modalities.

Stroke post UGFS has previously been reported as case studies and therefore previously it has only been possible to estimate this incidence. In this series the rate of neurological SAEs was extremely low. Of the four individual neurological adverse events only one (air embolus) was directly attributable to their UGFS treatment course. Indeed, stroke is a common phenomenon - there are over 100 000 strokes per year in the UK (approximately one every 5 minutes) [17]. Other patients having had previous cardiovascular or cerebrovascular disease it may have been incidentally related to their treatment. The young patient was felt to be extremely anxious and her right arm weakness may well have been related to this rather than a true neurological event. Previously post-UGFS stroke has either been reported immediately or up to 3-5 days post UGFS [18]. There is also data suggesting delayed stroke aetiology from

UGFS may result from paradoxical clot embolus [19] from DVT and patent foramen ovale. Although, the high prevalence of patent foramen ovale in the general population and the low reported incidence of neurological events after sclerotherapy should be noted, it remains as a potential causative factor for neurological adverse events post UGFS.

Whilst comorbidities were recorded, the low prevalence of smoking and diabetes may suggest some under reporting of patients' past medical histories. It therefore makes associating particular co-morbidities as risk factors for developing neurological AEs difficult. It seems however, that the majority of patients experiencing headaches/migraines with or without aura after treatment were considerably more likely to have a previous history of suffering these. Perhaps this lends support to the theory that these side effects are a result of endothelin release and generation of brain/retinal vasospasm (migraine patients are noted to have high levels of endothelin-1 during vasospastic phase) [20]. Although the pathophysiology of migraine is extremely complex and post-procedural migraine may simply be a response to environmental factors such as the stress of undergoing a procedure [21] rather than the sclerosant (or a vaso-active by-product of treatment) contributing as an exacerbator medication. The authors suggest given that previous history of migraine is associated with post procedural migraine – that patients should be counselled of this risk pre-procedurally.

The use of CO_2 rather than room air to make foam has been previously suggested as a method to reduce neurological adverse events [22, 23] though not all papers have demonstrated this [24]. In this study the use of physiological gases seemed to increase the risk of AEs. There were however, no SAEs with physiological gas preparation. However, given the extremely low incidence of SAEs delineating a difference in safety profile between physiological gas and room air would require an extremely large data set and a different study design. This low risk is perhaps counterbalanced by the potentially reduced therapeutic effect from swifter foam degradation with CO_2 [25]. It should be noted that the patients experiencing AEs following treatment with foam prepared with physiological gases were given large volumes of foam (8-52mL).

Overall, the average foam volumes were still below STS licensed maximum volume of 16ml [26], but greater volumes of STS foam were used in the neurological adverse event cohort

compared to the overall cohort. This was the case for both those treated with UGFS as sole treatment modality and those using UGFS as an adjunct treatment. The volume of 1% foam administered did seem to increase the likelihood of AE (Table 2,3, Figure 1). The results were not duplicated for 3% foam, however 58% of treatments used no 3% foam (compared to only 24% treatments using no 1% foam), which may have skewed results and prevented 3% total foam usage demonstrating similar increasing risk above the licensed maximum dosage. It is also possible that practitioners used lower sclerosant concentrations and thus increased volumes of foam in their treatments.

Previous work is not concordant on a link between foam volumes and AEs [22, 23, 27], however the Fibrovein licence and international guidelines do recommend limits [28]. Cardiac bubbles have been noted with doses as low as 1.5ml injected distally [29]. It should also be noted that both radiofrequency ablation and mechano-chemical ablation have both demonstrated the production of microbubbles (although there is an absence of reported neurological adverse events) [30].

Limitations

This is a pragmatic observational study. AEs and SAEs were self-reported and not necessarily diagnosed by a neurologist. The investigators were asked to report events, if patients suffered an event after discharge that was minor (e.g. headache), they may not mention this at follow up and so these events may have been under reported. There is also likely to be bias between public and private practice settings, where private patients are more likely to have prolonged post procedural care (rather than treatments commonly being performed in out-patient treatment rooms with immediate discharge in public setting) and therefore an increased number of post procedural events may be identified.

UGFS treatment techniques also vary between clinicians and certainly techniques between UK and French centres are likely to vary.

14.3% of treatments had missing data requiring multiple imputation for analysis. The analysis of treatments with complete datasets however did not significantly alter the results.

Conclusion

This is the largest cohort evaluated for neurological adverse events following foam sclerotherapy with STS thus far reported. This large cohort has allowed the identification of history of migraine and use of 1% foam (particularly volumes above the recommended maximum in the SmPC of 16ml of foam) as risk factors for neurological AEs.

Overall AE and SAE rate were similar or lower to those rates published in the literature. This implies that UGFS is a safe treatment for VVs with a low rate of neurological complications. Further work is required to delineate the exact pathogenesis of neurological AE to allow the reduction of this risk even further.

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