Post Authorisation Safety Study final report for Fibrovein 3% and 1%

EU PAS register number: EUPAS8260

1. Abstract:

Title

A voluntary non interventional post-authorisation safety study (PASS) [as defined by Directive 2001/83/EC (DIR) Art 1(15)] to define the incidence of and potential risk factors for procedure-related neurological adverse events (AE) in patients undergoing ultrasound guided foam sclerotherapy (UGFS) for the treatment of lower limb varicose veins (VV) using Fibrovein 3% and 1% (sodium tetradecyl sulfate, STS, injection) incorporating a drug utilisation study.

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Keywords

Foam sclerotherapy, neurological adverse events

Rationale and Background

Across Europe, patients with lower limb varicose veins (VV) were increasingly being treated without surgery. In the UK, the National Institute of Clinical and Health Excellence (NICE) had recommended endothermal ablation (ETA) and ultrasound-guided foam sclerotherapy (UGFS) in preference to surgery for the treatment of VV.

(http://www.nice.org.uk/Guidance/QS67)

(http://www.nice.org.uk/guidance/CG168)

Randomised controlled trials and observational studies had indicated that the incidence of procedure-related neurological adverse events (AE) (including visual disturbance, migraine, transient ischaemic attack (TIA) and stroke) during and following UGFS was very low.

However, their exact incidence and cause had not yet been defined.

Fibrovein 3% and 1% were granted a UK license for the treatment of VV by means of UGFS in 2012 as part of a DCP (UK/H/2775/001-4/DC).

One of the post approval commitments was to perform a voluntary non-interventional PASS to assess the incidence and potential risk factors for procedure-related neurological AE.

Nested within this study was a drug utilisation study to examine the “real world” use of Fibrovein for UGFS.

Research questions and objectives

Research Questions:

1. What was the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam?
2. To what extent, if any, were these procedure-related neurological AE associated with identifiable patient and treatment characteristics?
3. Post-marketing authorisation (PMA), how is UGFS with Fibrovein 3% and 1% being used in the “real world” to treat lower limb VVs (nested drug utilisation study)?

Objectives

To:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam

2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study)

Study Design

This was a non-interventional prospective, multicentre, PASS of patients undergoing UGFS for lower limb VV incorporating a nested drug utilisation study.

The study was purely observational and had no impact on the:

1. Decision to treat with UGFS
2. Nature of any aspect of the UGFS treatment provided
3. Management of any procedure-related neurological AE

Furthermore:

1. The results of the PASS are not generalisable to patients having UGFS using other sclerosants or to other types of VV treatment
2. No access to medical records was required and patient identifiable data was be recorded outside the clinical care team

For these reasons, the NHS Health Research Authority (HRA) did not consider this type of non-interventional PASS study to:

1. Be "research" (http://www.hra-decisiontools.org.uk/research/)
2. Require NHS Research Ethical Committee (REC) approval (http://www.hra-decisiontools.org.uk/ethics/)
3. Require NHS R&D Management permission (http://www.hra.nhs.uk/documents/2013/09/approval-of-medical-devices-research-version-2-april-2008.pdf)

Setting

Place: public and private hospitals in the UK, France

Data collection period: 1 January 2015 to 31 January 2020

Inclusion criteria: all non-pregnant, non-breast-feeding patients aged 18 years or over, undergoing Fibrovein UGFS (either alone or in combination with another modality such as endothermal ablation) for varicose veins

Exclusion criteria: patient under 18 years of age; not undergoing Fibrovein UGFS as part of their varicose veins' treatment; pregnancy, breast-feeding

Sampling: none, all suitable patients were included

Subjects and study size

Persons: non-pregnant, non-breastfeeding, patients aged 18 years or over, undergoing Fibrovein UGFS for lower limb varicose veins

Study size: 10,274 legs treated in 8,058 sessions.

Variables and data sources

Variables

Outcome of interest: procedure-related neurological AE

Exposures: 1% and/or 3% Fibrovein used as foam

Patient variables:

1. Age
2. Gender
3. Height, weight, and body mass index (BMI)
4. Primary versus recurrent VV
5. Co-existing deep venous disease / history of deep vein thrombosis (DVT)
6. CEAP clinical grade (C1-C6)
7. Type of VV: great saphenous vein (GSV), small saphenous vein (SSV), and anterior accessory saphenous vein (AASV), tributary veins
8. History of migraine / transient ischaemic Attack (TIA) / stroke / diabetes mellitus (DM) / hypertension (high blood pressure, BP)
9. Smoking status
10. Known to have a patent foramen ovale (PFO) (symptomatic or asymptomatic)
11. Previous Fibrovein UGFS

Treatment variables:

1. Unilateral vs. bilateral
2. Method of preparation of Fibrovein foam
3. Concentration of Fibrovein used
4. Fibrovein to gas ratio
5. Gas used: air vs. physiological gases (O_2/CO_2)
6. Volume of each concentration of Fibrovein used
7. Number of injection sites
8. Aliquot size (volume of foam injected at each injection site)
9. Concomitant surgical and non-surgical treatments for VV
10. Compression regime and duration following UGFS

Data sources:

The occurrence (and if present the type, severity, duration, treatment [where required] and clinical outcome) or absence of procedure-related neurological AE associated with Fibrovein UGFS for lower limb VV, together with patient and treatment characteristics, was collected using Fibrovein PASS Proforma 1 (Appendix 1) at the end of each UGFS treatment session.

Each separate UGFS treatment session generated a separate proforma.

In patients undergoing bilateral treatment a Fibrovein PASS Proforma 1 was completed for each leg.

UGFS was used either as the sole treatment for the patient's VV or in combination with another treatment modality.

In keeping with post-marketing pharmacovigilance (PV) requirements, in addition to completing Fibrovein PASS Proforma 1, co-investigators were asked to contact the UK co-ordinating centre should a serious adverse event (SAE) occur at the time of the UGFS or if they become aware that a SAE has occurred subsequently. SAE details were recorded on Fibrovein PASS Proforma 2 (Appendix 2).

SAE were defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those which:

- Result in death
- Are immediately life threatening
- Require in-patient hospitalisation or prolongation of existing hospitalisation

- Result in persistent of significant disability / incapacity or substantial disruption of the ability to conduct normal life functions
- Result in a congenital abnormality or birth defect
- Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Co-investigators were provided with instructions on how to complete the Fibrovein PASS Proformas 1 and 2 and telephone help was available during normal office hours from the UK Co-ordinating Centre.

Results

The table below compares the patient demographics and past medical history of patients who did and did not experience an adverse event. The statistical significance was calculated using two tailed t-tests for continuous data and Pearson's chi-squared test for categorical variables.

Statistical analysis was also performed on the other variables collected e.g. CEAP classification, treatment type, vein treated etc. The only variable suggesting a significant difference between patients who did and did not experience and adverse event was the volume of foam injected and this is analysed further below.

Patient Demographics – comparing no adverse event to patients experiencing an adverse event			
Variable	**No AE n=8,010**	**With AE n=46**	**p-value**
Age – median (IQR)	56 (46, 66) n=7,713	54 (46, 59.3) n=44	0.170
Female, n (%)	5,231 (66.2%) n=7,901	30 (65%) n=46	0.890
Male, n (%)	2,670 (33.8%) n=7,901	16 (35%) n=46	0.890
BMI – median (IQR)	26.8 (23.7, 30.9) n=4,158	26.9 (23.4, 30.3), n=32	0.537
Past Medical History			
Migraine, n (%)	543 (6.8%), n=8,010	26 (56. 5%), n=46	<0.0001
Migraine with aura, n (%)	186 (2.3%), n=8,010	21 (45.7%), n=46	<0.0001
Transient Ischaemic Attack (TIA), n (%)	68 (0.3%), n=8,010	2 (4.3%), n=46	0.011
Stroke, n (%)	47 (0.6%), n=8,010	0 (0%), n=46	0.602
Smoker, n (%)	392 (4.9%), n=8,010	0 (0%), n=46	0.124
Diabetic, n (%)	342 (4.3%), n=8,010	1 (2.2%), n=46	0.483
High Blood Pressure, n (%)	1,076 (13.4%), n=8,010	5 (10.9%), n=46	0.611
Deep Vein Thrombosis, n (%)	194 (2.4%), n=8,010	1 (2.2%), n=46	0.913
DVT same leg, n (%)	88 (1.1%), n=8,010	0 (0%), n=46	0.487
Known Patent Foramen Ovale, n (%)	5 (0.06%), n=8,010	0 (0%), n=46	0.865
Symptomatic PFO, n (%)	1 (0.01%), n=8,010	0 (0%), n=46	0.940

The results show that a history of migraine with or without aura ($p < 0.0001$) and TIA ($p = 0.011$) are significantly associated with the occurrence of an adverse event.

The table below shows that a history of migraine and TIA and the use of foam in excess of the SmPC recommendations, are associated with a greatly increased chance (odds ratio) of an adverse event.

Variable	Odds Ratio	Upper 95% CI	Lower 95% CI	p-value
History of migrane	17.92	32.32	9.94	0.000000
History of migraine/aura	35.33	64.26	19.43	0.000000
History of TIA	5.31	22.34	1.26	0.022615
Foam volume over 16ml	3.77	7.46	1.91	0.000154

There were twelve cases of an AE after volumes of foam in excess of SmPC recommendations was administered however ten of the patients also had a history of migraine. The data indicates that a high volume of foam alone is less of a predictor but high volumes in patients with a history of migraine is a very strong predictor of an adverse event.

Discussion

The study objectives as defined in the protocol were:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the post marketing authorisation “real world” use of Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study).

The study has achieved the objectives with data collected on 48 patient and treatment variables for over 8,000 treatment sessions and over 10,000 legs.

Incidence of procedure related adverse events

Looking firstly at defining the incidence of procedure related adverse events and comparing them with expected frequencies as defined in the SmPC.

There were 46 adverse events.

The events with the highest frequency were migraine/headache with or without visual disturbance/aura followed by visual disturbance alone. The results are slightly confused by some patients receiving much higher doses of foam than the recommended maximum of 16ml. Here the incidence will be discussed including the high doses but also without the high doses because it is important when comparing results with the SmPC that we consider the treatments that conformed to the SmPC recommendations.

The SmPC lists the frequency for migraine and headache using foam as ‘rare’ defined as >1 in 10,000 to < 1 in 1,000 (>0.01% to <0.1%).

Visual disturbance is not listed specifically in the SmPC but scotoma, scintillating scotoma is listed with a frequency of uncommon defined as >1 in 1,000 to < 1 in 100 (>0.1% to <1%).

The tables below compare the frequency of the adverse event with the expected frequency listed in the SmPC

Adverse event	Incidence all cases	Incidence normal dose	SmPC frequency
Migraine ± aura/ visual disturbance	19/8056 = 0.24%	15/8056 = 0.19%	>0.01% to <0.1%
Headache ± visual disturbance	8/8056 = 0.099%	5/8056 = 0.062%	>0.01% to <0.1%
Scotoma/visual disturbance	NA	10/8056 = 0.12%	>0.1% to <1%
Key point - the incidence of migraine is higher than the frequency listed in the SmPC			

Looking at the other adverse events there were two cases of stroke, one TIA, one arm weakness (hemiparesis) and one allergic reaction all of which are listed as very rare (<10,000). There were two vasovagal cases which is listed as rare (>1 in 10,000 to < 1 in 1,000).

Adverse event	Incidence including high doses	Incidence normal dose	SmPC frequency
Vaso vagal e.g. fainting, confusion	NA	2/8056 = 0.025%	>0.01% to <0.1%
Allergic reaction	NA	1 in 8056	< 1 in 10,000
Weakness (hemiparesis)	NA	1 in 8056	< 1 in 10,000
Transient ischaemic attack	NA	1 in 8056	< 1 in 10,000
Stroke/CVA	2 in 8056	1 in 8056	< 1 in 10,000
Hyperventilation Carpo-pedal spasm	1 in 8056	NA	

Looking at the cases in more detail the vaso-vagal cases are within the frequencies listed in the SmPC.

There was one of each of the following adverse events, allergic reaction, weakness, transient ischaemic attack in the data set of 8,056 sessions and 10,274 legs. It is reasonable to propose that the listed frequency of very rare for these adverse events is commensurate with the data collated in this study.

Looking at the stroke cases it seems likely that one was not related to the sclerotherapy treatment. Cases reported in the literature tend to occur at the time of treatment or within 3-4 days whereas this one was 19 days after treatment. The patient's medical history included hypertension and elevated cholesterol. Given the late onset and patient history it therefore seems reasonable to exclude this case.

The second stroke case was definitely related to the treatment, but the patient received 32mL of foam which is twice the recommended maximum.

Given the mitigating factors in the two stroke cases it is reasonable to propose that the listed frequency of very rare for a stroke remains commensurate with the data collated in this study.

The case of hyperventilation leading to carpo-pedal spasm it was felt with this case that the patient suffered from anxiety which led to hyperventilation, this thinking is based on the fact that once the symptoms had been explained and the patients breathing was regulated there was a rapid resolution of the symptoms.

In summary the individual case data suggests the frequencies listed in the SmPC remain adequate for all of the adverse events except for migraine. The data suggests that the frequency for migraine should be changed from 'rare' to 'uncommon'.

Looking at the relationship between procedure related neurological AE and identifiable patient and treatment characteristics.

The statistical analysis identified three predictors that increase the likelihood of an adverse event occurring.

A history of migraine with or without aura, higher than recommended foam volumes and TIA.

Section 4.4 of the SmPC 'Special warnings and precautions for use' already lists migraine the recommendations in the SmPC are as follows:

'Previous migraine sufferers should be treated with care. Patients with previous migraine have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant. Use smaller volumes in patients with history of migraine.'

Based on this recommendation, the warnings regarding previous migraine sufferers and the need to be careful with the volume of foam injected is adequately covered in the current SmPC.

Regarding TIA as a possible predictor of an adverse event, it is not mentioned in the SmPC. However, there were only two patients with a history of TIA who experienced an adverse event. One experienced a headache the other experienced a visual disturbance (flashing lights). It is difficult to be certain that the adverse events were related to the patients having had a TIA previously however a special warning could be added to the SmPC.

Conclusion and impact on benefit-risk balance of the product

The study objectives were well met and the real-world frequencies of neurological adverse events following UGFS using 3% and 1% Fibrovein has been accurately determined.

The main conclusions are that the current SmPC lists the neurological adverse events and the frequencies listed accurately reflects the frequencies of occurrence with the exception of migraine.

The recommendation is that the frequency for migraine listed in the SmPC is changed from 'rare' to 'uncommon'.

A past medical history of migraine is a strong predictor for a neurological adverse event especially when larger volumes of foam are administered. A past medical history of migraine is addressed in the current SmPC as a special warning which urges caution and to use low volumes of foam.

The recommendation is to leave the special warning as it is.

A past medical history of a TIA was a significant predictor for a neurological adverse event. The current SmPC has no warnings regarding a past medical history of TIA.

The recommendation is to add a past medical history of TIA to section 4.4 'Special warnings and precautions for use' with a statement such as:

TIA

Patients with a past medical history of TIA should be treated with care.

Patients with previous TIA have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Large volumes of foam also are a strong predictor for a neurological adverse event especially where the patient has a history of migraine. Large volumes of foam on it own is not a particularly strong predictor. Most centres treated patients stayed within the SmPC recommended volumes of foam with only 610 sessions exceeding them.

Recommendation is that the current maximum dose listed in the SmPC (16ml) is safe and should remain the same and should not be increased or decreased.

Marketing Authorisation Holder

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