Randomized clinical trial

Randomized clinical trial of the use of glyceryl trinitrate patches to aid arteriovenous fistula maturation

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Background: **Arteriovenous fistulas are critical for haemodialysis, but maturation rates remain poor. Experimental and anecdotal evidence has supported the use of transdermal glyceryl trinitrate (GTN) patches. The aim of this RCT was to determine whether use of a GTN patch aids arteriovenous fistula maturation.**

Methods: **Patients referred for arteriovenous fistula formation were eligible. The GTN or placebo patch was applied immediately after surgery and left *in situ* for 24 h. The primary outcome measure was the change in venous diameter at 6 weeks after fistula formation. The secondary outcome measure was clinical fistula patency at 6 weeks.**

Results: **Of 200 patients recruited (533 screened), 101 were randomized to the placebo group and 99 to the GTN group. Of these, 81 and 86 respectively completed surgery, and had follow-up data available at 6 weeks. Improvements in venous diameter were similar in the two groups: mean(s.d.) increase 2·3(1·9) mm in the placebo group compared with 2·2(1·8) mm in the GTN group ($P = 0·704$). The fistula failure rate did not differ significantly between the two groups: 23 per cent for placebo and 28 per cent for GTN ($P = 0·596$).**

Conclusion: **GTN transdermal patches used for 24 h after surgery did not improve arteriovenous fistula maturation. Registration number: NCT01685710 (http://www.clinicaltrials.gov).**

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Introduction

For patients with end-stage renal failure requiring haemodialysis, an arteriovenous fistula (AVF) has clear advantages over both grafts and central venous catheters. These include decreased rates of infection, reduced need for radiological intervention, and a resulting survival benefit[1,2]. However, unlike both grafts and central venous catheters, an extended period of maturation is required before use.

AVF maturation is unpredictable; interventions that improve maturation rates have not been demonstrated reliably[3]. Rates of primary fistula failure vary widely, but are reported to range from 20 to 50 per cent[4,5].

Fistula maturation relies on vascular remodelling with both arterial recruitment and venous dilatation. This, in turn, results in increased blood flow through the anastomosis and into the draining vein. Flow-mediated venous dilatation occurs via wall shear stress-stimulated endothelium-derived pathways and nitric oxide generation. The magnitude of increased flow rate in the early post-operative period is critical to maturation; flow increases of 10–20-fold are critical in promoting maturation[6,7].

Factors that affect AVF maturation relate to the vein, the artery and the patient. Although many factors can influence the maturation of an AVF, most are surrogate markers of endothelial function and ability to generate early flow-mediated dilatation. A recent meta-analysis[8] found that non-modifiable factors such as age, diabetes, hypotension, arterial diameter, arteriosclerosis, venous diameter and venous distensibility affected AVF maturation. The only modifiable factors were timely referral for AVF creation and the routine use of preoperative ultrasound imaging.

Generally, pharmacological and interventional therapies have been disappointing in promoting maturation, with no significant effects observed[9]. Far-infrared therapy has the potential to improve patency and maturation, with a proposed mechanism of stimulation of nitric oxide[10]. In experimental settings locally applied nitrate (glyceryl trinitrate, GTN) therapy has also shown promise[9,11].

GTN is a nitrate-based vasodilator that also prevents platelet aggregation. It is used widely in clinical settings as a coronary vasodilator in ischaemic heart disease, where it can be administered effectively via sublingual or transdermal routes. The application of GTN transdermal patches on to newly created AVFs is practised on an *ad hoc* basis, particularly where there are concerns about maturation. Little evidence supports this practice, although Akin and colleagues[11] demonstrated that a locally applied GTN transdermal patch increased blood flow through the fistula after 24 h, and proposed that this application might improve maturation.

The aim of this study was to evaluate the effect of GTN transdermal patches on AVF maturation in a randomized, double-blind, placebo-controlled trial.

Methods

The study received ethical approval from the National Research Ethics committee (12/WM/038). Medicines and Healthcare Regulatory Agency approval was also obtained, and the study was carried out according to the principles of the declaration of Helsinki and in accord with the International Council for Harmonization Good Clinical Practice Guidelines (EudraCT 2012-003756-36). The study was also registered, and the full study protocol is available on the Clinicaltrials.gov website (NCT01685710).

Study design

The study was a randomized, double-blind, placebo-controlled trial. Recruitment was undertaken from April 2013 to May 2015. All patients undergoing AVF formation at Queen Elizabeth Hospital, Birmingham, UK, were screened for the inclusion criteria and, if appropriate, approached to participate in the study. Potential study participants were sent information before their vascular access clinic appointment. The initial approach was made by a member of the research team. Consent to participate was formally taken on the morning of surgery and, following this, randomization was undertaken.

Inclusion and exclusion criteria

Inclusion criteria for the study were: consecutive patients undergoing primary radiocephalic or brachiocephalic arteriovenous fistula formation; aged over 18 years; and able to consent.

Exclusion criteria were: complex vascular access procedures (redo brachiocephalic and radiocephalic fistulas, brachiobasilic fistulas, prosthetic grafts); cardiovascular dysfunction (hypotension: systolic BP below 90 mmHg), documented obstructive cardiomyopathy, severe aortic stenosis (gradient over 40 mmHg), confirmed myocardial infarction within the past 6 months; anaemia (haemoglobin concentration below 80 g/l); history of migraine; current use of sildenafil or other nitrates; nitrate allergy; closed-angle glaucoma; chronically raised intracranial pressure; history of hypothyroid disease; pregnancy; and prisoners.

Randomization and blinding

Patients who gave informed written consent were randomized to receive either a GTN patch or a placebo patch. Randomization was undertaken by Birmingham Clinical Trials Unit using a varying block length randomization technique. This was undertaken via telephone on the day of surgery following formal consent to participate. After randomization the patch (treatment or placebo) was dispensed by the pharmacy.

All patients and members of the study group involved in treating the patients (fistula assessment, surgery and follow-up) were blinded to the randomization. Although the placebo patches were not identical to the GTN patches, they were extremely similar visually, and following application were covered with standard dressing for the 24 h.

Intervention

As part of standard care, all patients were assessed in a dedicated vascular access clinic before surgery imaging was undertaken, including assessment of the artery at the proposed fistula site and measurement of the venous diameter of the potential fistula site without a tourniquet. The preoperative and postoperative ultrasound assessment was done in a standardized manner by clinical staff. The same ultrasound machine was used for all measurements throughout the study. In line with unit policy, fistulas were not attempted on veins smaller than 2 mm in diameter.

Surgery was carried out as standard end-of-vein to side-of-artery anastomosis. The majority of operations were performed under local anaesthetic by either a consultant, an associate specialist or a registrar. The GTN

patch or the placebo patch was applied immediately at the end of the operation to a standardized location on the arm 5 cm proximal to the anastomosis, thus avoiding the surgical incision.

All patches were applied by a member of the research team not involved in follow-up assessment of the patient. Patients were instructed to remove the patch 24 h after operation.

All patients in the study were contacted 1 week after surgery, to determine subjective side-effects of the GTN patch or placebo. Patients were followed up at 6 weeks after surgery to assess fistula maturation. This included ultrasound assessment of the fistula and measurement of the venous diameter 5 cm distal to the anastomosis.

Outcome measures

The primary outcome measure was change in venous diameter at 6 weeks after surgery. The secondary outcome measure was primary patency of the fistula at 6 weeks. Data on adverse events and side-effects were also collected.

Statistical analysis

The study was powered based on an estimated standard deviation for the primary outcome of 2 mm. The target for recruitment was 200 patients in total, and drop-out rates were estimated to be 10 per cent, so it was assumed that 90 patients per group would be included in the final analysis. Based on these values, the minimum detectable difference of an independent-samples *t* test between the two groups was 1 mm at 80 per cent power and with an α level of 5 per cent.

Initially, standardized differences were calculated for a range of demographic and disease-related factors, in order to quantify the degree of difference between the study groups. For continuous variables, these were calculated by dividing the difference in means by the pooled standard deviations. For rates, the absolute difference in proportions was divided by the pooled standard deviation, which was represented by $p \times (1 - p)$, where p is the proportion of patients being considered.

The change in venous diameter between the preoperative and 6-week postoperative measurements was calculated for each patient, and compared between groups using independent-samples *t* tests. Fisher's exact test was used to compare the fistula failure rate between the two groups.

Post hoc subgroup analyses were also performed. A treatment-by-subgroup-interaction approach was used to test whether there were any subgroups of patients who benefited significantly from the use of GTN. A separate model was produced for each of the baseline demographic and treatment factors, which included the factor being considered, alongside the study group (placebo or GTN) and an interaction term. General linear models were used to assess the change in venous diameter outcome, and binary logistic regression to evaluate fistula failure rates.

Multivariable models were also produced, considering all of the demographic and treatment factors for inclusion, and using a forwards stepwise approach, to identify any other factors that were significantly associated with either outcome. Patients with missing data for baseline characteristics were excluded from the subgroup analyses in a pairwise fashion.

All analyses were carried out using SPSS® version 22 (IBM, Armonk, New York, USA). $P < 0{\cdot}050$ was deemed indicative of statistical significance throughout.

Results

A total of 533 patients were screened, of whom 60 did not meet the inclusion criteria. Of the 473 who did, 131 were excluded (87 because of a medical contraindication, 43 owing to pre-existing nitrate use and 1 prisoner who was not available for standard follow-up). Of the remaining 342 potential participants, 40 were not assessed in the correct clinic, 41 declined to participate, three were already participating in another study, ten were excluded on logistical grounds, and for ten patients the reason was unclear. From the remaining group, 38 were not required as recruitment to target had been achieved (*Fig. 1*).

The remaining 200 patients were randomized to the two groups (99 placebo and 101 GTN). Once the full target was complete the study stopped recruitment, and closed once the last patient had attended follow-up. Surgery was abandoned in 12 patients (6 per group), and one patient in the placebo group withdrew consent for further follow-up. Surgery was abandoned during the procedure owing to concerns about the vein because of poor distension on flushing, patency concerns or inability to find the vein that had been identified before operation. An additional 11 patients in the placebo group and nine in the GTN group were excluded from the main analysis, as follow-up data were not available. After these exclusions, the total sample size for analysis was 81 in the placebo and 86 in the GTN group. Although some patients discontinued their intervention early (6 placebo, 8 GTN), all were included on the basis of intention to treat. Early discontinuation was predominantly due to local complications, or headache.

Postoperative ultrasound assessments were not performed in patients whose AVF failed. For these patients

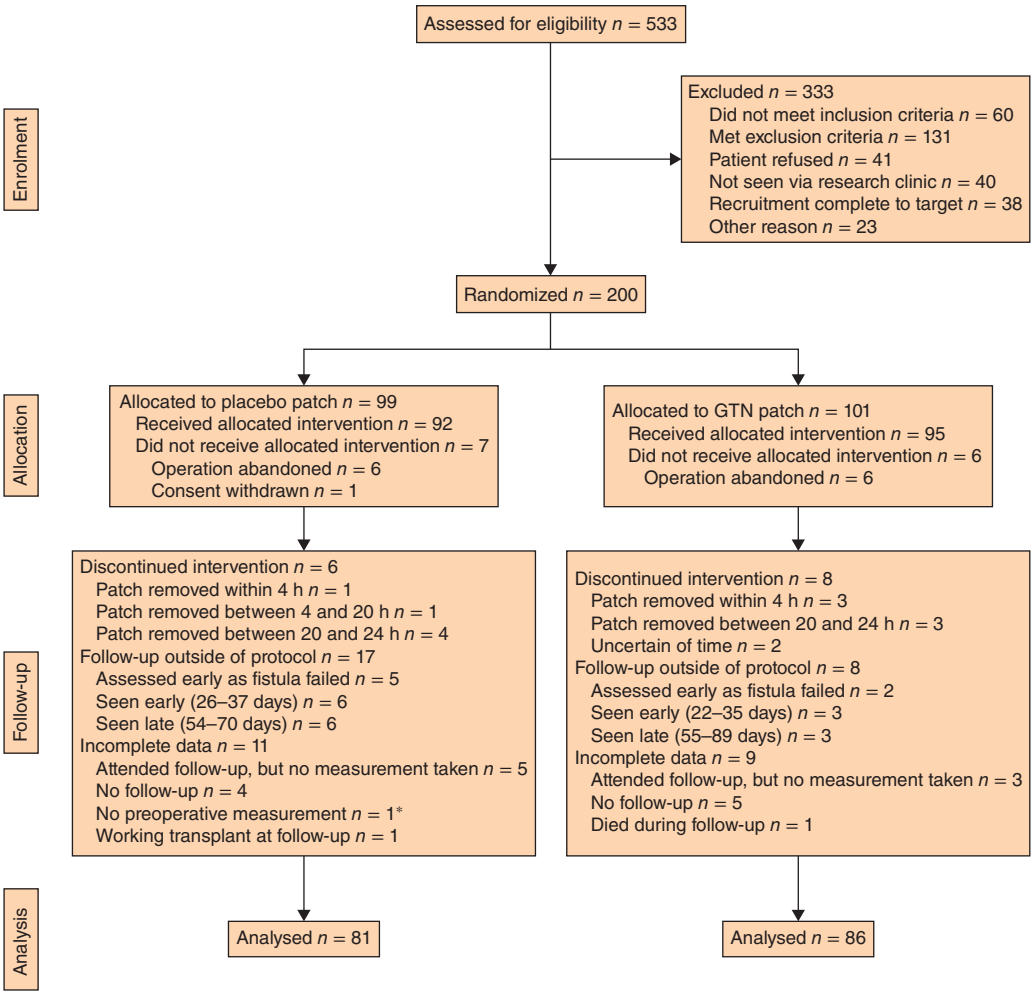

Fig. 1 CONSORT diagram for the trial. *Patient excluded from sensitivity analyses

a last-measurement-carried-forward approach was to estimate postoperative venous diameter, using their original measurement (*Fig. 1*).

Comparisons between study groups

The demographics of the two groups are reported in *Table 1*. The two groups were well matched, with the majority of the standardized differences being within ± 0·15.

The increase in venous diameter at 6 weeks did not differ significantly between the groups, with a mean(s.d.) increase of 2·3(1·9) mm in the placebo group, compared with 2·2(1·8) mm in the GTN group ($P = 0·704$) (*Table 2*). This gave a mean difference between the groups of −0·1 (95 per cent c.i. −0·7 to 0·5) mm. The fistula failure rates were also similar in the two study groups, at 23 per cent for placebo and 28 per cent for GTN ($P = 0·596$), giving a relative risk for failure of 1·2 (95 per cent c.i. 0·7 to 2·2).

Side-effects, reported at 1 week after surgery, occurred at similar rates in the two groups (*Table 3*).

Statistical power

The *a priori* power calculation returned a sample size of 90 patients per group, and a standard deviation in the primary outcome of 2 mm, which differed from the values actually observed in the study. For this reason, a *post hoc* power calculation was performed, based on the final sample size (81 *versus* 86) and the observed deviation (1·9 mm). For these variables, the minimum detectable difference between the groups was found to be 0·8 mm for 80 per cent power and an α level of 5 per cent, which was consistent with the *a priori* power calculation.

Table 1 Baseline demographic comparisons between the two intervention groups of patients undergoing vascular access surgery

	Placebo ($n=81$)	GTN ($n=86$)	Standardized difference
Preoperative venous diameter (mm)*	3·4(0·9)	3·3(0·9)	−0·11
Age (years)*	60·4(15·0)	60·3(15·8)	0·00
Sex ratio (M : F)	49 : 32	55 : 31	0·08
Ethnicity			
White	56 (69)	50 (58)	−0·23
Asian	16 (20)	28 (33)	0·30
Black	6 (7)	8 (9)	0·07
Mixed/other	3 (4)	0 (0)	−0·29
Smoking history			
Never smoked	59 of 80 (74)	53 of 85 (62)	−0·26
Previous smoker	16 of 80 (20)	25 of 85 (29)	0·21
Current smoker	5 of 80 (6)	7 of 85 (8)	0·08
Established RRT	34 (42)	39 (45)	0·06
Fistula type			
Brachiocephalic	33 (41)	34 of 85 (40)	−0·02
Radiocephalic	48 (59)	51 of 85 (60)	0·02
Artery			
Biphasic	5 of 77 (6)	6 of 85 (7)	0·04
Triphasic	72 of 77 (94)	79 of 85 (93)	−0·04
Aspirin	22 (27)	16 (19)	−0·19
Warfarin	4 (5)	3 (3)	−0·10
Antiplatelets	5 (6)	3 (3)	−0·15
Diuretics	38 (47)	36 (42)	−0·10
Beta-blocker	31 (38)	25 (29)	−0·19
Calcium antagonist	37 (46)	37 (43)	−0·06
Diabetic on insulin	10 of 57 (18)	12 of 60 (20)	0·05
Diabetic managed by tablet/diet	3 of 57 (5)	4 of 61 (7)	0·08
ACE inhibitor or ARB	13 (16)	17 (20)	0·10
Cholesterol	41 (51)	36 (42)	−0·18

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). GTN, glyceryl trinitrate; RRT, renal replacement therapy; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Sensitivity analysis

As some patients had been excluded from the analysis owing to lack of follow-up, and others had been analysed using a last-measurement-carried-forward approach, owing to failed AVF, a set of sensitivity analyses were performed to ensure that bias had not been introduced.

The first of these analyses included all patients who completed surgery (91 placebo, 95 GTN). For patients who were lost to follow-up before the 6-week assessment, the preoperative venous diameter measurement was carried forwards, assuming that their venous diameter did not change after surgery. This analysis returned similar results to the main analysis, with mean changes in venous diameter of 2·0(1·9) mm in the placebo group and 2·0(1·8) mm in the control group ($P=0·818$), giving a mean difference of −0·1 (95 per cent c.i. −0·6 to 0·5) mm.

Table 2 Comparison of outcomes between the placebo and glyceryl trinitrate groups

	Placebo ($n=81$)	GTN ($n=86$)	P
Change in venous diameter (mm)			
Mean(s.d)	2·3(1·9)	2·2(1·8)	0·704†
Mean difference*	−0·1 (−0·7, 0·5)		
Fistula failure			
Rate	19 (23)	86 (28)	0·596‡
Relative risk*	1·2 (0·7, 2·2)		

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †GTN, glyceryl trinitrate. Independent-samples t test; ‡Fisher's exact test.

Table 3 Comparison of side-effects between the placebo and glyceryl trinitrate groups

	Placebo ($n=81$)	GTN ($n=86$)
Alteration to taste	1	0
Faintness/dizziness	1	0
Haematoma	1	1
Headache		
Mild	2	5
Severe	1	1
Nausea	1	0
Pain		
In fistula	4	1
In hand	1	0
Swollen arm	2	0
Itch	0	3

There were no statistically significant differences. GTN, glyceryl trinitrate.

A second analysis included only patients with a successful surgical outcome (a functioning fistula), and who received both preoperative and postoperative vein assessments, leaving 62 patients in each group. The results for this subset of patients were also similar, with mean changes in venous diameter of 3·0(1·6) mm in the placebo group and 3·0(1·4) mm in the GTN group ($P=0·991$), giving a mean difference of 0 (95 per cent c.i. −0·5 to 0·5) mm.

Subgroup analysis

As the overall effect of GTN was not found to be significant, a set of *post hoc* analyses was performed to identify whether there were any subgroups that could potentially benefit from GTN. These analyses were not prespecified, so any significant findings would have to be interpreted in view of the increased false-positive rate of the analysis. A treatment-by-subgroup-interaction approach was used, with all of the factors from *Table 1* considered in separate

models, and both the change in venous diameter and the failure rate considered as outcomes. None of the resulting models had a significant interaction term, so there was no evidence that the effect of GTN was significantly associated with either outcome within any of the patient subgroups considered.

A second analysis was undertaken to test whether any of the factors considered had a significant impact on either of the outcomes. No factor was found to be significantly associated with the failure rate. A significant association was detected between venous diameter and the fistula type ($P < 0{\cdot}001$), with brachiocephalic fistulas having increases in venous diameter that were a mean of 1·3 (95 per cent c.i. 0·7 to 1·9) mm greater than those of radiocephalic fistulas.

Discussion

Transdermal GTN had no significant effect on AVF maturation in the present study. This finding is consistent with all previous well designed studies assessing a variety of medical adjunctive therapies in an attempt to improve venous maturation following vascular access surgery.

Although an early study of aspirin showed marginal benefit, subsequent studies of arteriovenous grafts for access showed no benefit in fistula patency for aspirin, dipyridamole or both[12,13]. Similarly ticlopidine (another antiplatelet drug) showed marginal benefit in a small study[14], although a larger randomized trial[15] showed no benefit, and clopidogrel also had no clinical advantage in a large multicentre RCT[16]. Other medical adjuncts tested include fish oil and a topically applied recombinant pancreatic elastase (PRT-201)[17], for which results were again disappointing[18,19].

The main outcome measure in all of these studies is fistula or graft thrombosis; primary failure and failure to mature are not separated. Maturation is used interchangeably as a standard outcome measure, despite diverse definitions.

Change in venous diameter is not a standard definition of maturation, but was used in the present study as it is easily and reproducibly measured, and can be compared individually with preoperative measurements, providing an internal control in each subject. Although this measure does not directly relate to clinical outcomes, a failure to increase in size will render the fistula unsuitable for dialysis. However, no clinical or statistically significant difference in venous diameter was found with the postoperative application of a GTN patch.

Although the study was not originally designed or powered to distinguish subgroup differences, an attempt was made to assess trends to guide future study design. This failed to demonstrate any group that benefited from the GTN patch treatment over placebo. All of these findings contributed to the conclusion that GTN patches have no benefit in aiding AVF maturation.

This study is limited as it was performed in a single centre. In addition, the study population was unselected and is generalizable only to the UK dialysis access population, which does, however, represent most international populations.

Another potential limitation of the study is selection bias in the analysis, as it could not include patients with no available postoperative data, or whose fistula failed before the 6-week follow-up. A range of sensitivity analyses was used to assess how differing approaches to these patients influenced the outcomes of the study. As these analyses gave consistent results it was concluded that, although bias may exist, it did not influence the overall findings of the study.

In the present study, the autologous AVF failure rate at 6 weeks was 23 per cent with placebo and 28 per cent after GTN, and is broadly consistent with other studies. This is slightly higher than the rate in the US Dialysis Access Consortium Study[20] which, although widely quoted as having a failure rate over 50 per cent, actually had a 15·8 per cent thrombosis rate within 6 weeks of fistula creation.

Although previous small, non-randomized studies have supported the use of GTN, this RCT provides no evidence to support the use of topical GTN in primary AVF formation.

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