Pre-hospital transdermal glyceryl trinitrate for transient ischaemic attack: data from the RIGHT-2 trial

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ABSTRACT

Background: Ambulance trials assessing interventions in suspected stroke patients will recruit patients with currently active symptoms that will resolve into transient ischaemic attack (TIA). We assessed the safety and efficacy of glyceryl trinitrate (GTN) in the pre-specified subgroup of patients with TIA in the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2).

Methods: RIGHT-2 was a pre-hospital-initiated multicentre randomised sham-controlled blinded-endpoint trial that randomised patients with presumed ultra-acute stroke within 4 hours of symptom onset to transdermal GTN or sham. Final diagnosis was determined by site investigators. The primary outcome was shift in modified Rankin scale (mRS) scores at 90 days analysed using ordinal logistic regression reported as adjusted common odds ratio (cOR) with 95% confidence intervals (CI). Secondary outcomes included death or dependency (mRS >2).

Results: 109 of 1149 (9.5%) patients had a final diagnosis of TIA (GTN 57, sham 52) with mean age 73 (13) years, 19 (17.4%) had pre-morbid mRS >2, and onset to randomisation was 80 [49, 105] minutes. GTN lowered blood pressure by 7.4/5.2 mmHg compared with sham by hospital arrival. At day 90, GTN had no effect on shift in mRS scores (cOR for increased dependency 1.47, 95% CI 0.70-3.11), but was associated with increased death or dependency (mRS >2): GTN 29 (51.8%) vs. sham 23 (46.9%), OR 3.86 (95% CI 1.09-13.59).

Conclusions: Pre-hospital ultra-acute transdermal GTN did not improve overall functional outcome in patients with investigator-diagnosed TIA compared with sham treatment.

INTRODUCTION

Pre-hospital trials involving presumed stroke patients will recruit a mixed population including those with cerebral ischaemia whose symptoms subsequently resolve within 24 hours, diagnosed as transient ischaemic attack (TIA). A recent systematic review found 8% of patients recruited into pre-hospital stroke trials had a final diagnosis of TIA,(1) but few trials have reported their recruited TIA population in detail.

The UK-based Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) assessed transdermal glyceryl trinitrate (GTN) patch vs. sham in 1149 patients with presumed, paramedic-assessed acute stroke within 4 hours of onset.(2) Overall, there was a significant interaction by final diagnosis on the effect of GTN on outcome (p=0.014). Here, we present a pre-specified subgroup analysis of the 109 (9.5%) RIGHT-2 participants with a final diagnosis of TIA.

METHODS

Study design
RIGHT-2 was a UK-based, prospective, multicentre, paramedic-delivered, sham-controlled, participant- and outcome-blinded, randomised trial.(2-5) Patients were eligible if they: presented <4 hours of presumed stroke symptom onset to a trial-trained paramedic; had systolic blood pressure (SBP) ≥120 mmHg; and Face-Arm-Speech-Time (FAST) score of ≥2. Exclusion criteria included: nursing home resident; Glasgow coma scale (GCS) <8/15; hypoglycaemia (<2·5 mmol/l); or seizure. Full inclusion and exclusion criteria are outlined elsewhere.(2) The trial received ethical approval from the national research ethics committee (IRAS: 167115), was adopted by the National Institute for Health and Care Research Clinical Research Network and was registered (ISRCTN26986053). Participants had routine clinical brain imaging assessed centrally using standardised scores.

Treatment
Patients were randomised 1:1 to transdermal GTN patch (5 mg, Transiderm-Nitro® 5, Novartis, Frimley UK) or sham patch (DuoDERM® hydrocolloid dressing, Convatec, Flintshire UK). The first treatment was administered by a paramedic in the ambulance and three further daily treatments were given in hospital, placed on the shoulder/back and changed daily. The patch was removed if a non-stroke diagnosis was made (stroke mimic or TIA) or the patient was discharged prior to the end of the 4 day treatment period.

Clinical outcome measures
The primary outcome was death and dependency assessed using the 7-level modified Rankin Scale (mRS, 0=normal to 6=died) at 90 days by telephone performed centrally by trained assessors masked to treatment allocation.(6) If the participant was unable, information was collected from a relative/carer or by post.

At Day 4 (or hospital discharge, if earlier) trial treatment compliance, neurological status, in-hospital treatments and investigator-determined final diagnosis were recorded. At Day 90, pre-specified secondary outcomes were collected: Barthel index (BI) – activities of daily living; telephone mini-mental state examination (t-MMSE), telephone interview for cognition scale-modified (TICS-M) – cognition; animal naming –verbal fluency; health status utility (HSU) value calculated from European Quality of Life-5 dimensions-3 level (EQ-5D-3L), EQ-visual analogue scale (EQ-VAS) – quality of life; and Zung depression score (ZDS) – mood.(3, 7) Home-time was the number of days between discharge and Day 90. Safety outcomes included all-cause death.

Statistical analysis
The statistical analysis plan for the whole trial was applied to this pre-specified subgroup and performed by intention to treat.(4) The primary outcome was shift analysis of the 7-level mRS using ordinal logistic regression with adjustment for age, sex, premorbid mRS, baseline FAST score, SBP and time from onset to randomisation, reported as adjusted common odds ratio (cOR). The assumption of proportional odds was tested using the likelihood ratio test. We performed unadjusted, mean, per-protocol and imputed sensitivity analyses. For hypothesis-generation, heterogeneity of the treatment effect on the primary outcome was assessed in pre-specified subgroups by adding an interaction term to an adjusted ordinal logistic regression model. Other outcomes were assessed using adjusted binary logistic regression, Cox regression, ordinal logistic regression, multiple linear regression and analysis of covariance. A pre-

specified global outcome (comprising ordered categorical or continuous data for mRS, BI, ZDS, TICS-M and HSUV) was analysed using the Wei-Lachin test.(8, 9)

RESULTS

Of 1149 RIGHT-2 participants, 109 (9.5%) had a final diagnosis of TIA (GTN 57, sham 52). Among all patients with acute cerebral ischaemia (ischaemic stroke or TIA), TIA patients represented 15.9% (57/359) and 15.0% (52/347) of GTN and sham groups respectively. Baseline characteristics were balanced between treatment groups (Appendix Table 1): mean age 73 (13) years; white race 101 (92%); FAST score =3, 43 (39%); BP 161 (24)/92 (16) mmHg; time from symptom onset to randomisation 80 [49, 105] minutes; pre-event mRS >2, 19 (17%), GTN 0 [0,2] and sham 1 [0,2]. There were more female participants randomised to sham (28, 54%) than GTN (19, 33%), and more participants randomised to GTN had atrial fibrillation/flutter recorded in the ambulance (11, 24%) than sham (4, 10%).

Following hospital arrival, those randomised to GTN had a significantly lower GCS, non-significant trends to higher FAST and NIHSS scores, and numerically more total anterior circulation syndromes than sham participants (Table 1). Overall, baseline imaging features of brain frailty(10) were common - cerebral atrophy 99%; leukoaraiosis 45%; old vascular lesion(s) 72% - and when pooled as a score: 2 [2,3].

Compliance with the first treatment patch was 98%, 29% on day 2, with only 5% receiving all 4 days of trial treatment. Main reasons for non-compliance were non-stroke diagnosis (47, 43%) and hospital discharge (22, 20%). GTN lowered BP by 7.4/5.2 mmHg at hospital arrival, but thereafter there was no difference in BP between treatment groups. No participants with TIA received thrombolysis or mechanical thrombectomy.

The primary outcome (mRS) was available in 105 (96%) participants at day 90. The proportional odds assumption was not violated (p=0.70). There was no difference between GTN and sham groups in the shift analysis: GTN 3 [1,3] vs. sham 2 [1,3], cOR 1.47, 95% CI 0.70, 3.11, p=0.31 (Table 1, Figure 1). There were no statistically significant interactions of the effect of GTN in pre-specified subgroups. More patients randomised to GTN were dead or dependent (mRS >2) at day 90 than those randomised to sham: GTN 29 (51.8%) vs. sham 23 (46.9%), OR 3.86, 95% CI 1.09-13.59, p=0.036 (Table 1). These results were not altered by adding atrial fibrillation into statistical models.

Other outcomes at days 4 and 90 did not differ between GTN and sham, except mood which was better at day 90 in those randomised to GTN (Table 1).

DISCUSSION

In this pre-specified subgroup analysis of the RIGHT-2 trial, 109 participants had an investigator-determined final diagnosis of TIA. Transdermal GTN lowered BP at hospital arrival, but did not effect the primary outcome of mRS at day 90.

Two phase III pre-hospital trials have assessed transdermal GTN in presumed ultra-acute stroke and found no overall benefit,(2, 11) with signals suggesting very early treatment with GTN in severe stroke could be harmful.(9, 11, 12) In contrast, the direction of treatment effect favoured GTN in mimics.(13) Lowering BP acutely during a TIA episode may compromise cerebral blood flow, extending any ischaemic insult, leading to worse clinical outcomes at hospital admission and extended to 90 days. Although current guidelines do not cover acute BP management in TIA, it is possible that subgroups may warrant different BP management strategies similar to ischaemic stroke.(14)

Overall, TIA participants had >60 minutes of symptoms with a demonstrable neurological deficit on hospital admission (mean NIHSS 3), although none received reperfusion therapies, perhaps due to their mild deficit. Length of hospital stay was >2 days, half were dependent at 90 days, with significant disability, cognitive impairment, reduced quality of life and low mood. Having a presumed transient event was not benign, perhaps reflecting their baseline clinical and brain frailty and potential for deconditioning in the context of an acute illness such as TIA.

There are limitations. First, although this subgroup analysis was pre-specified, there was no separate statistical analysis plan. Instead, the analyses followed the plan for the overall trial as we did previously for the other diagnostic groups.(9, 12, 13) Second, the clinical diagnosis of TIA was determined by site investigators and not centrally adjudicated, so some may have had an alternative diagnosis diluting any effects seen. Third, some TIA diagnoses may have been rendered using the time (symptoms <24h) rather than tissue (symptoms <24h and no new infarct) definition and would be considered ischaemic stroke under the tissue approach. Furthermore, the designation of TIA was made post-randomisation and so could represent an outcome i.e. randomised treatment may have shifted participants from being minor strokes to severe 'TIAs' or the reverse. Fourth, the high burden of brain frailty despite being independent according to baseline mRS may have limited any potential treatment effect on outcome. Given the challenges and inaccuracies with using mRS as a pre-stroke assessment tool, brain frailty could be used as a surrogate for baseline function, predicts clinical outcome after stroke, and could be used in stratification at randomisation and/or adjustment in analyses of future stroke trials.(10, 15) Last, the small sample size of this subgroup analysis without adjustment for multiplicity of testing, means the findings may reflect chance (particularly since some outcomes went in opposite directions), or measured/unmeasured baseline imbalances.

In summary, ultra-acute transdermal GTN given in the ambulance to patients with investigator-diagnosed TIA lowered BP by hospital arrival, but did not influence the shift analysis of mRS at day 90.

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CONTRIBUTORSHIP STATEMENT
JPA interpreted the data and wrote the first draft. LJW performed the analyses. All authors edited the manuscript. PMB conceived the trial and is corresponding author and guarantor for the study.

CONFLICTS OF INTEREST
JPA is supported, in part, by a Nottingham University Hospitals Research & Innovation award. PMB is Stroke Association Professor of Stroke Medicine and an emeritus NIHR Senior Investigator. TGR is a NIHR Senior Investigator. GM is the Stroke Association Edith Murphy Foundation Senior Clinical Lecturer (SA L-SMP 18\1000). JMW is supported by the UK Dementia Research Institute which receives its funding from DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. The remaining authors report no conflicts of interest.

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Table 1. Primary outcome & key secondary outcomes. Data are number (%), median [interquartile quartile range] or mean (standard deviation). Comparison by binary logistic regression (BLR), Cox proportional hazards regression (Cox), ordinal logistic regression (OLR), or multiple linear regression (MLR), with adjustment for age, sex, pre-morbid mRS, FAST, pre-treatment systolic blood pressure, and time to randomisation (unless stated). The effect of treatment for GTN versus sham is shown as common odds ratio (cOR), odds ratio (OR), hazard ratio (HR), or mean difference (MD), with 95% confidence intervals.

	N	GTN	Sham	OR/MD (95% CI), adjusted	p-value
N	109	57	52		
Day 90 mRS (0-6), primary outcome[a]	105	3 [1,3] (n=56)	2 [1,3] (n=49)	1.47 (0.7, 3.11)	0.31
Sensitivity analyses					
Unadjusted	105	3 [1,3]	2 [1,3]	0.96 (0.48, 1.9)	0.91
Mean mRS	105	2.2 (1.6)	2.2 (1.8)	0.36 (-0.05, 0.78)	0.089
mRS > 2 (%)	105	29 (51.8)	23 (46.9)	**3.86 (1.09, 13.59)**	**0.036**
Per protocol	94	3 [1,3]	2 [1,3]	1.55 (0.71, 3.41)	0.28
Imputation	109	3 [1,3]	2 [1,3]	1.63 (0.78, 3.42)	0.19
Admission					
NIHSS (/42)	88	3.4 (3.7)	2.3 (2.8)	0.93 (-0.28, 2.15)	0.13
FAST [/3]	89	1.3 (1)	0.9 (1)	0.37 (-0.03, 0.77)	0.067
OCSP, TACS (%)	94	8 (14.8)	2 (5)	3.13 (0.50, 19.79)	0.22
GCS (/15)[b]	103	14.7 (0.7)	14.9 (0.3)	**-0.31 (-0.51, -0.12)**	**0.002**
Day 90					
Death (%)	107	2 (3.5)	3 (6)	-	-
Disposition [/3][c]	100	1 [1,1]	1 [1,1]	0.64 (0.1, 4.11)	0.64
EQ-5D HUS (/1)[d,e]	99	0.6 (0.3)	0.6 (0.4)	-0.01 (-0.12, 0.11)	0.93
EQ-VAS[d,e]	96	63.7 (25.1)	57.7 (24.6)	3.56 (-5.02, 12.15)	0.42
Barthel Index (/100)[d]	98	86 (26.8)	79.6 (31.7)	2.04 (-5.74, 9.83)	0.61
TICS-M[d,e]	59	20.1 (7.2)	21 (9.8)	-0.73 (-3.64, 2.17)	0.62
t-MMSE[d,e]	59	17.5 (5.6)	16.4 (7)	1.14 (-0.99, 3.26)	0.29
Animal naming[d,e]	59	14.7 (7.3)	15.2 (9.3)	-1.41 (-4.81, 2.00)	0.42
Zung Depression Scale (/100)[d,e]	69	43.4 (20)	52.7 (24.7)	**-8.95 (-17.4, -0.54)**	**0.037**
Home time (days)	97	93.2 (32)	96.7 (29.8)	-5.76 (-17.2, 5.64)	0.32
Global analysis, Wei-Lachin[e]	59	-	-	-0.04 (-0.23, 0.15)	0.68

EQ-5D: EuroQoL-5 dimension 3 level; EQ-VAS: quality of life-visual analogue scale; FAST: face, arm, speech, time test; NIHSS: National Institutes of Health Stroke Scale; OCSP: Oxfordshire community stroke project; TACS: total anterior circulation syndrome; TICS-M: telephone interview cognition scale-modified; t-MMSE: telephone modified mini-mental state examination.

[a] Increased OR, i.e. >1, indicates a shift to worse functional outcome

[b] Analysed using non-parametric regression

[c] Disposition: home (score of 1), institution or in hospital (score of 2), died (score of 3) by day 90

[d] Death assigned: BI -5, animal naming -1, EQ-VAS -1, home time -1, tMMSE -1, TICS-M -1, EQ-5D HUS 0, GCS 2, NIHSS 43, ZDS 102·5
[e] Some participants with poor outcomes or dysphasia could not answer cognition, quality of life and mood questions

Figure 1. Shift in modified Rankin scale in 109 participants with a final diagnosis of transient ischaemic attack by treatment group – glyceryl trinitrate (GTN) versus sham. Comparison by ordinal logistic regression with adjustment for age, sex, pre-morbid modified Rankin Scale, face-arm-speech time test, pre-treatment systolic BP, and time to randomisation. The effect of treatment for GTN versus sham is shown as adjusted common odds ratio (cOR): cOR 1.47, 95% CI 0.70 to 3.11, p=0.31.