Transdermal delivery of glyceryl trinitrate: clinical applications in acute stroke

Abstract

Introduction

Glyceryl trinitrate (GTN), a nitric oxide donor, is a candidate treatment for the management of acute stroke with haemodynamic and potential reperfusion and neuroprotective effects.

Areas covered

Here we discuss the evidence to date from clinical trials and present and future possibilities for the clinical application of transdermal GTN in acute stroke. When administered as a transdermal patch during the acute and subacute phases after stroke, GTN was safe, lowered blood pressure, maintained cerebral blood flow, and did not induce cerebral steal or alter functional outcome. However, when given within the hyperacute phase (<6 hours of stroke onset), GTN reduced death and dependency, death, disability, cognitive impairment, and mood disturbance, and improved quality of life. However, in a large pre-hospital trial with treatment within 4 hours, GTN did not influence clinical outcomes.

Expert opinion

Transdermal GTN is an easy to administer BP-lowering therapy, which is safe when given after 2 hours of stroke onset, may improve outcome when initiated within 2-6 hours, but should be avoided (outside of a clinical trial) in the ultra-acute period within 2 hours of stroke onset. Further research needs to investigate the mechanisms of benefit or harm in ultra/hyperacute stroke patients.

Article highlights

- Transdermal glyceryl trinitrate (GTN) is safe when administered after 2 hours of stroke onset.
- Transdermal GTN may improve outcome if administered 2-6 hours after stroke onset, but may cause harm if used earlier.
- Further research is needed to investigate whether lowering BP in ultra-acute stroke is safe and efficacious.

1. Introduction

Nitric oxide (NO) is an obligate inorganic molecule in both human health and disease with anti-inflammatory, anti-leucocyte [1], anti-platelet [2,3], anti-proliferative (vascular smooth muscle cell) [4], neuroprotective, neurotransmitter, neuromodulator [5,6], pro-endothelial and vasodilatory properties. NO modulates blood brain barrier integrity, cerebral blood flow (CBF), auto- and chemo-regulation [7-9], and inhibits apoptosis [10]. Pre-clinical models of cerebral ischaemia have demonstrated the role of NO in a time-dependent manner. NO is synthesised from L-arginine by three forms of nitric oxide synthase (NOS) with differing resultant effects. NO production is increased via neuronal NOS (nNOS) activation for up to 30 minutes after middle cerebral artery (MCA) occlusion [11,12]. Endothelial NOS (eNOS) and nNOS activity increases in the first minutes following arterial occlusion and falls thereafter [13]. Up-regulation of inducible NOS (iNOS) occurs from 12 hours up to 7 days after ischaemia onset [14], whilst NO within cerebral tissue is undetectable during this period [11]. Intravenous L-arginine administered to rats following MCA occlusion improved penumbral blood flow and reduced infarct volume [15]. This effect was not seen in eNOS-deficient mice who developed smaller penumbral regions, larger infarcts and absent angiogenesis leading to further post-ischaemic injury [16-18]. Therefore, eNOS and eNOS-derived NO appear to be cytoprotective in focal ischaemia, whilst nNOS- and iNOS-derived NO have damaging effects on tissue survival with resultant poor neurological outcomes [12,19]. Although neurotoxic in acute stroke, iNOS and nNOS are involved in neurogenesis following stroke [20,21]. NO donors reduced infarct size in both permanent and transient pre-clinical models of ischaemia, and increased cerebral blood flow in permanent models, but only if administered soon after stroke induction [22].

Blood pressure (BP) is elevated in 75% of people with acute stroke at presentation [23] and is associated with worse functional outcome and increased death in both ischaemic and haemorrhagic stroke [24,25], stroke recurrence in ischaemic stroke [26] and haematoma expansion or rebleeding in intracerebral haemorrhage (ICH) [27]. Lowering elevated BP in acute stroke has long been debated and investigated. Resultant trials have led to treatment of raised BP in ICH being recommended [28].

Due to the variety of potentially beneficial effects of NO described above and the low levels of endogenous NO in stroke [29,30], supplementation through administration of NO donors might be beneficial but remains unclear. In contrast, diaspirin cross-linked

haemoglobin lowers vascular NO levels [31] and was associated with poor neurological outcome in acute stroke. Therefore, lowering NO may worsen outcomes in acute stroke, whilst increasing NO may be beneficial [32]. Based on these pre-clinical data, the NO donor glyceryl trinitrate (GTN) has been assessed in stroke patients. Of note, GTN does not have significant intravascular effects on leucocytes [33] and platelets. Transdermal delivery of GTN in stroke patients provides easy application and removal without the need for swallowing assessment or intravenous access. GTN patches are used in the management of hypertension and ischaemic heart disease with peak plasma concentrations reached in 1-2 hours of application[34] and rapid fall in plasma concentrations when removed [35]. Importantly, in comparison to sublingual administration, transdermal preparations are less likely to cause rapid and large falls in BP. Although intravenous GTN is used to lower BP in acute stroke, there is limited data on this route of administration. In contrast, transdermal GTN has been extensively investigated in stroke patients in ultra-acute (first few hours), hyper-acute (<6 hours), acute (6-48 hours) and subacute (>48 hours) time periods from stroke onset. Here, we discuss the evidence to date and current and future potential clinical applications of transdermal GTN in acute stroke.

2. Transdermal GTN and acute stroke

Transdermal GTN has been assessed in acute and subacute stroke patients in three small phase II randomised studies. As well as lowering peripheral and central BP, GTN reduced 24 hour BP, peak systolic BP, pulse pressure and pulse pressure index. Although GTN marginally increased heart rate, it was associated with improved vascular compliance. GTN did not influence intracranial pressure, cerebral blood flow and velocity, or induce cerebral steal (Table 1) [36-40]. Intravenous sodium nitroprusside, another nitric oxide donor, has antiplatelet properties [41], whilst GTN did not influence platelet function in the GTN-1 trial [36]. The safety and efficacy of transdermal GTN were assessed in the large Efficacy of Nitric Oxide in Stroke (ENOS) trial [42].

Between 2001 and 2014 ENOS enrolled 4011 patients from 173 centres in 23 countries worldwide with acute stroke within 48 hours of onset and systolic BP 140-220 mmHg; participants were randomised to transdermal GTN patch (5 mg) or no patch daily for 7 days. Patches were sourced from a variety of manufacturers but no differences in safety or efficacy were noted. All participants received standard acute stroke care including stroke unit admission, thrombolysis and secondary prevention

where appropriate. GTN lowered BP by 7.0 / 3.5 mmHg compared to no GTN at day 1 and administration was safe with no increased reporting of serious adverse events. The primary outcome of functional outcome was assessed by telephone at day 90 using the modified Rankin Scale (mRS), a seven level scale ranging from zero = no symptoms, through increasing levels of dependency, to six = death. Overall, GTN did not influence functional outcome at day 90 (adjusted common odds ratio [acOR] 1.01, 95% confidence intervals [CI] 0.91-1.13), nor any secondary outcomes [42]. However, in a pre-specified subgroup of participants randomised within six hours of stroke ictus (ENOS-early), those randomised to GTN had a favourable shift in mRS at day 90 (acOR 0.51, 95% CI 0.32-0.80), less death, disability (Barthel index) and mood disturbance (Zung depression scale), and improved cognition (telephone Mini-Mental State Examination) and quality of life scores (EuroQol health utility status and visual analogue scale) [43]. Similarly, the small (n=41) ambulance-based Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) found that transdermal 5 mg GTN administered within four hours of ictus improved mRS at day 90 [44].

A 2017 Cochrane review and an individual patient data meta-analysis in 2016 using data from five completed transdermal GTN trials in acute stroke (GTN-1/2/3, ENOS, RIGHT, n=4197) re-iterated that treatment within six hours of stroke onset (n=312) was associated with improved functional outcome and secondary clinical outcomes across a range of domains, but beyond this GTN had a neutral effect[45,46]. These findings were based upon high-quality evidence as assessed by GRADE criteria [46]. This potential time-dependent treatment effect was seen in both ischaemic and haemorrhagic stroke. Those participants with ICH randomised to GTN within 6 hours of onset had significant improvements in functional outcome, cognition, disability, mood and quality of life at 90 days compared with those randomised to no GTN [47]. Additionally, GTN appeared to have an additive effect with alteplase in those patients with ischaemic stroke; these participants had a significant shift to less death and dependency [45].

The safety of transdermal GTN in acute stroke has also been assessed in important patient subgroups. Although there is concern that BP lowering may compromise cerebral perfusion and worsen outcome in the context of carotid stenosis, in a secondary analysis of the ENOS trial, GTN appeared safe in both ipsilateral and bilateral stenosis. Further, participants with ≥70% ipsilateral stenosis who received

GTN had a favourable shift in mRS as compared to those randomised to no GTN (OR 0.56, 95% CI 0.34 to 0.93, p=0.024)[48]. Dehydration is a common finding in patients with acute stroke and antihypertensive medication can have accentuated effects on BP in such patients. However, in 310 ENOS participants with baseline blood markers of dehydration, GTN was safe in those with biomarker evidence of dehydration with no precipitous drops in BP [49]. Of note, patients felt to be clinically dehydrated were unlikely to have been enrolled into ENOS. Nevertheless, this analysis is reassuring and supports the use of GTN prior to blood markers of dehydration being available.

3. Transdermal GTN and ultra-acute stroke

Given the findings from ENOS-early and RIGHT, the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) trial was performed to assess the safety and efficacy of transdermal GTN within four hours of stroke onset [50]. RIGHT-2 was a UK multicentre, paramedic-delivered, ambulance-based, prospective, randomised, sham-controlled, blinded-endpoint trial that recruited 1149 participants with presumed stroke within 4 hours of onset and systolic BP >120 mmHg; participants were randomised to a daily GTN 5mg patch or sham dressing given for 4 days. Patients were randomised at a median of 71 mins after ictus, and 52% had an ischaemic stroke, 13% ICH, 26% stroke mimic and 9% transient ischaemic attack (TIA). At hospital admission, GTN lowered BP by 5.8 / 2.6 mmHg as compared with sham. Due to the high proportion of patients with a stroke mimic, a hierarchical analysis of the primary outcome of mRS at day 90 was planned a priori, first in those with a stroke or TIA, and then in the whole population. Although it was feasible for paramedics to recruit patients into a UK pre-hospital stroke trial, GTN did not influence the primary or secondary clinical outcomes at day 90 in either analysis [50].

The discrepancy between RIGHT-2 and prior data warrants further discussion. RIGHT-2 was different in design to ENOS-early recruiting patients much earlier (71 min vs. 257 min), with different inclusion criteria resulting in a population of older patients with more pre-morbid dependency, previous stroke, ischaemic heart disease and diabetes. Further, to reduce excess time for paramedics, RIGHT-2 utilised simple block randomisation and did not use computer-based minimisation as in ENOS. Therefore, there may have been baseline imbalances not apparent with current pre-hospital scoring systems. This may explain why GTN was associated with improved clinical outcomes in those with stroke mimics; a finding which could also represent

chance. RIGHT-2 also used a 4-day treatment period whilst previous trials used 7 days with higher rates of adherence and recruited patients with broader baseline BP (systolic BP >120 mmHg in RIGHT-2 vs. 140-220 mmHg in ENOS).

In a RIGHT-2 subgroup analysis of those participants with ICH (n=145), there was a tendency towards worse clinical outcome in those randomised to GTN; these participants had larger haematoma and more mass effect on admission imaging at a median of 2.3 hours after onset and 1.2 hours after treatment. This continued on day 2 imaging, whereby GTN was associated with larger haematoma and increased perihaematomal oedema and midline shift as compared to those randomised to sham. Without imaging pre-randomisation, it is difficult to establish whether those randomised to GTN had larger haematoma prior to treatment or were more likely to undergo haematoma expansion with GTN. In such a small subgroup, these results should be regarded as preliminary. Ongoing studies assessing transdermal GTN (Multicentre randomised trial of acute stroke treatment in the ambulance with a nitroglycerin patch [MR-ASAP]: ISRCTN99503308) and intravenous urapidil (Intensive ambulance-delivered blood pressure reduction in hyperacute stroke trial-4 [INTERACT-4]: NCT03790800) in the pre-hospital arena should shed further light on whether using GTN, or BP-lowering therapy more broadly, is safe in ultra-acute ICH.

4. 'Time is brain' vs. 'too early'

Taking together all of the data for GTN in acute stroke, it is possible to build a potential time-dependent model. Previously, it was proposed that GTN might behave in a similar manner to reperfusion treatments such as thrombolysis and thrombectomy, i.e. GTN might be effective when given within 6 hours of onset but neutral when administered thereafter (Table 2). However, with the addition of RIGHT-2 into meta-analysis totalling 5005 patients, there now appears to be a U-shaped phenomenon whereby ultra-early treatment with GTN in under 2 hours of symptom onset is neutral (or even negative), treatment between 2 and 6 hours is beneficial, and treatment beyond 6 hours is neutral (Table 3, Figure 1). Overall, the pooled treatment effect of GTN is neutral and the time-dependent findings are primarily driven by the individual trial results discussed above.

The potential mechanisms driving these time-dependent findings, if real, can be postulated. In ICH, transdermal GTN may be harmful when given before hospital in the first two hours of symptom onset. Although GTN did not demonstrate antiplatelet

effects in the GTN-1 trial, NO has potent antiplatelet properties and GTN may therefore inhibit the platelet plugging phase, in addition to the vasoconstrictory phase, of haemostasis. When the vasoconstrictory and platelet plugging phases of haemostasis are complete (typically before 2 hours), BP lowering with GTN may be beneficial when administered between 2-6 hours after onset, perhaps through reducing haematoma expansion and perihaematomal oedema and so resulting in improved clinical outcomes. In ischaemic stroke patients, BP lowering in the context of large vessel occlusion prior to recanalisation may be harmful, reducing regional cerebral blood flow, extending the ischaemic core and thus reducing the potentially salvageable brain tissue. A subgroup analysis of the enhanced control of hypertension and thrombolysis stroke study (ENCHANTED) BP arm alluded to this; hyperacute intensive BP lowering of patients with large vessel occlusion undergoing thrombolysis was associated with worse clinical outcomes [51]. Further imaging analysis of RIGHT-2 and MR-ASAP should prove illuminating.

5. Current clinical applications of transdermal GTN in acute stroke

Given transdermal GTN's safety profile in hospital-based trials of acute stroke, it seems appropriate to consider using this medication in the following scenarios. First, systolic BP lowering to <185 mmHg in the context of thrombolysis in acute ischaemic stroke. Transdermal GTN may prepare patients for thrombolysis by lowering systolic BP below the licensed threshold of 185 mmHg. In RIGHT, there was a non-significant increase in both rates of and time to thrombolysis [44]. In the 2016 meta-analysis, those with ischaemic stroke who received thrombolysis had a significant shift to better functional outcome at day 90 in the presence of GTN [45]. Whether this effect is maintained beyond 90 days is unknown. Second, in hypertensive patients at 2-6 hours of stroke onset. ENOS-early demonstrated that treatment with transdermal GTN under 6 hours of onset improved multiple clinical outcomes in both ischaemic and haemorrhagic stroke [43]. Given the ease of application (and removal) of a topical patch without the need for intravenous access in the setting of dysphagia, transdermal GTN is a safe way to initiate BP lowering therapy until such access can be obtained.

6. Future clinical applications of transdermal GTN in acute stroke

The role of transdermal GTN in the setting of thrombectomy is unclear. Further data are needed to establish whether waiting until recanalisation has been achieved prior to lowering BP is a safer option. Imaging analysis assessing whether GTN influences

collaterals – a key determinant of outcome in large vessel occlusion – may provide insight into a population of stroke patients that may benefit. Given the subgroup analysis of ICH patients from RIGHT-2, transdermal GTN should only be used in the pre-hospital setting in the context of a clinical trial (as with MR-ASAP). On-going trials will help to understand whether BP lowering in the ambulance is safe in presumed stroke patients and to further elucidate the time dependent effects on outcome. The data pertaining to transdermal GTN in acute stroke have, thus far, been investigated by one group of authors. Importantly, on-going trials are being performed by different groups in different healthcare settings and regions of the world.

7. Conclusions

Transdermal GTN is safe to lower elevated BP beyond two hours of stroke onset and may improve outcome when administered within two to six hours, but requires confirmation. When treatment is likely to be started within two hours, as in the pre-hospital setting, transdermal GTN should only be used in research trials whilst its safety is further tested in ultra-acute stroke. Future research may help to answer: whether to lower elevated BP in those with large vessel occlusion prior to thrombectomy; whether to lower elevated BP in ICH patients prior to hospital; and the time course of when, and if, to intervene, duration and with which agent.

8. Expert opinion

Transdermal GTN is an easy to administer BP-lowering therapy which safely reduces BP when given after 2 hours of stroke onset, may improve outcome when initiated within 2-6 hours, but should be avoided (outside of a clinical trial) in the ultra-acute period within 2 hours of stroke onset, particularly when given pre-hospital. Given its affordability and ease of application (and removal), transdermal GTN is an ideal agent to lower elevated BP in acute stroke patients 2-6 hours after onset. Further research needs to investigate the mechanisms of benefit or harm in ultra-acute intracerebral haemorrhage, ischaemic stroke or transient ischaemic attack. Such avenues may include imaging markers that GTN may influence such as collateral status in patients with large vessel occlusion, the timing of BP-lowering therapy in relation to mechanical thrombectomy, and the effects on BP variability by different antihypertensive agents. GTN may also complement other stroke treatment strategies such as anticoagulation reversal in ICH and treatments to reduce brain oedema following severe stroke.

On-going trials (MR-ASAP: ISRCTN99503308, INTERACT-4: NCT03790800) will help to answer whether lowering elevated BP is safe in ultra-acute stroke and ascertain whether certain groups of patients benefit whilst others may be harmed. In future, lowering of elevated BP in acute stroke may be dependent on stroke severity, stroke type, consideration of large vessel occlusion and other imaging markers, as well as co-morbidities, frailty and prior antihypertensive treatment. We may be able to target certain patient populations in acute stroke who may benefit from BP lowering; whether this will be agent-specific (e.g. transdermal GTN) or a more general effect of BP lowering, route-specific (intravenous, topical, enteral), time-dependent (early but not too early), will hopefully become clearer as the field of ultra-acute stroke research evolves.

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References of interest

*ref 42: ENOS trial of GTN vs. no GTN in 4011 acute stroke patients

**ref 43: ENOS-early: GTN vs. no GTN within 6 hours of stroke onset

**ref 45: Meta-analysis of GTN trials in acute stroke

*ref 46: Cochrane review of GTN trials in acute stroke

**ref 50: RIGHT-2 trial of GTN vs. no GTN in pre-hospital presumed stroke patients.

Table 1. Effects of GTN in stroke patients

	GTN-1 2001 [36]	GTN-2 2003 [37]	GTN-3 2006 [38]	RIGHT 2013 [44]	ENOS 2015 [42,52]	RIGHT-2 2019[50]
n	37	90	18	41	4011	1149
OTR (hrs)	99.2	55.1	72.2	1.6	26.0	1.2
Systolic BP (mmHg)	↓ 13 (7.8%)		↓ 23 (14%)	↓ 21	↓ 7	↓ 5.8
Diastolic BP (mmHg)	↓ 5.2 (5.4%)		↓ 4 (3%)	↓ 6	↓ 3.5	↓ 2.6
Heart rate (bpm)	No change	No change	No change	No change	↑ 1.4	
MAP (mmHg)		↓ 6.2%			↓ 4.7	
PP (mmHg)		↓ 3.9		↓ 16	↓ 3.6	
PPI					No change	
RPP (mmHg.bpm)				No change	↓ 278	
BP variability (SBP SD)	No change	No change	No change	↓ 7.2	↓ 0.4	
Augmentation index		Improved		Improved		
Cerebral blood flow velocity		No change	No change			
Cerebral blood flow			No change			
Zero flow pressure			No change			
Platelet function	No change					

BP: blood pressure; bpm: beats per minute; GTN: glyceryl trinitrate; MAP: mean arterial pressure; PP: pulse pressure; PPI: pulse pressure index; RPP: rate pressure product; SBP: systolic blood pressure; SD: standard deviation

Table 2. Comparison of transdermal GTN with other treatments for acute stroke; odds ratio are for a worse outcome (i.e. numbers <1 suggest benefit)

Intervention	Time window	Primary outcome	Odds ratio (95% CI)	NNT
Aspirin [53]	<48 hrs	Death or dependency at least 30 days after stroke	0.95 (0.91, 0.99)	79
Alteplase [54]	0-3 hrs	mRS 0-1 (functional independence) at 3-6 months	0.57 (0.44, 0.74)	10
	3-4.5 hrs	mRS 0-1 (functional independence) at 3-6 months	0.79 (0.66, 0.95)	19
Thrombectomy [55]	<6 hrs	Ordinal mRS at 90 days (OR >1 = better outcome)	0.40 (0.28, 0.57)	2.6*
Transdermal GTN [43]	<6 hrs	Ordinal mRS at 90 days (OR <1 = better outcome)	0.51 (0.32, 0.80)	5.2*

CI: confidence interval; GTN: glyceryl trinitrate; mRS: modified Rankin Scale; NNT: number needed to treat; OR: odds ratio.
*number of patients needed to treat to move 1 patient by 1 level of the mRS

Table 3. Clinical outcomes with GTN in stroke by onset to randomisation. Data are number, mean difference, or odds ratio with 95% confidence intervals. Comparisons by binary logistic regression, ordinal logistic regression or multiple linear regression, with adjustment. Significant ($p<0.05$) results in bold.

		Onset to randomisation (hours)			
	All	**≤ 2**	**2.1 - 6**	**6.1 - 12**	**> 12**
Patients (N)	5005	708	440	439	3418
Death (%)	0.96 (0.82, 1.12)	1.19 (0.83, 1.72)	**0.59 (0.35, 0.99)**	1.22 (0.75, 1.98)	0.94 (0.77, 1.14)
mRS	1.01 (0.91, 1.11)	1.11 (0.84, 1.48)	**0.61 (0.43, 0.87)**	1.07 (0.77, 1.51)	1.05 (0.93, 1.18)
Barthel Index	1.31 (-0.42, 3.04)	-1.5 (-7.08, 4.07)	**7.71 (1.86, 13.56)**	0.43 (-5.84, 6.7)	0.95 (-1.02, 2.93)
TICS-M	-0.07 (-0.74, 0.60)	-0.89 (-2.88, 1.11)	1.64 (-0.37, 3.65)	0.07 (-2.2, 2.35)	-0.23 (-1.02, 0.57)
ZDS	0.07 (-1.29, 1.43)	-0.89 (-2.88, 1.11)	**-5.84 (-10.69, -0.99)**	0.7 (-3.95, 5.35)	0.47 (-1.10, 2.03)
HUS	0 (-0.02, 0.02)	-0.75 (-2.41, 0.92)	0.04 (-0.03, 0.1)	-0.01 (-0.08, 0.05)	0 (-0.02, 0.02)
EQ-VAS	0.28 (-1.35, 1.9)	1.81 (-2.72, 6.34)	5.23 (-0.41, 10.87)	-1.46 (-7.25, 4.34)	0.12 (-1.80, 2.03)

EQ-VAS: Euro-Quality of life visual analogue scale; HUS: health utility scale (derived from EQ-5D); mRS: modified Rankin Scale; TICS-M: telephone interview cognition scale; ZDS: Zung depression scale

Figure 1: Forest plot of day 90 mRS by time to randomisation (hours) GTN vs. no GTN