

Amphetamine increases blood pressure and heart rate but has no effect on motor recovery or cerebral haemodynamics in ischaemic stroke: a randomised controlled trial (ISRCTN 36285333)

Nikola Sprigg,¹ MRCP; Mark R Willmot,¹ MRCP; Laura J Gray,¹ MSc; Alan Sunderland,² PhD; Valerie Pomeroy,³ PhD; Marion Walker,⁴ PhD; Philip M W Bath,¹ MD FRCP

Stroke Trials Unit,¹ School of Psychology,² and Department of Ageing and Rehabilitation,⁴ University of Nottingham, UK; Centre for Rehabilitation and Ageing³, St. George's Hospital Medical School, University of London, UK

Corresponding author:

Professor Philip Bath
Division of Stroke Medicine
University of Nottingham
Nottingham City campus
Nottingham
NG5 1PB

Tel: 0115 823 1765

Fax: 0115 823 1767

Email: philip.bath@nottingham.ac.uk

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ABSTRACT

Background: Amphetamine enhances recovery after experimental ischaemia and has shown promise in small clinical trials when combined with motor or sensory stimulation. Amphetamine, a sympathomimetic, might have haemodynamic effects in stroke patients, although limited data have been published.

Methods: Subjects were recruited 3-30 days post ischaemic stroke into a phase II randomised (1:1), double blind, placebo-controlled trial. Subjects received dexamphetamine (5mg initially, then 10mg for 10 subsequent doses with 3 or 4 day separations) or placebo in addition to inpatient physiotherapy. Recovery was assessed by motor scales (Fugl-Meyer, FM), and functional scales (Barthel index, BI and modified Rankin score, mRS). Peripheral blood pressure (BP), central haemodynamics and middle cerebral artery blood flow velocity were assessed before, and 90 minutes after, the first 2 doses.

Results: 33 subjects were recruited, age 33-88 (mean 71) years, males 52%, 4-30 (median 15) days post stroke to inclusion. 16 patients were randomised to placebo and 17 amphetamine. Amphetamine did not improve motor function at 90 days; mean (standard deviation) FM 37.6 (27.6) vs. control 35.2 (27.8) ($p=0.81$). Functional outcome (BI, mRS) did not differ between treatment groups. Peripheral and central systolic BP, and heart rate, were 11.2 mmHg ($p=0.03$), 9.5 mmHg ($p=0.04$) and 7 beats/minute ($p=0.02$) higher respectively with amphetamine, compared with control. A non-significant reduction in myocardial perfusion (Buckberg Index) was seen with amphetamine. Other cardiac and cerebral haemodynamics were unaffected.

Conclusion: Amphetamine did not improve motor impairment or function after ischaemic stroke but did significantly increase BP and heart rate without altering cerebral haemodynamics.

INTRODUCTION

Modern concepts in stroke recovery now include the brain's capacity to undergo dynamic plastic change.¹ This plasticity is exploited by rehabilitation which is effective at improving outcome, and it might be possible to enhance this recovery further using pharmacological means,² an approach that has been referred to as 'pharmacological rehabilitation'.^{3,4}

In experimental models cerebral ischaemia results in a catecholamine deficit, whilst drugs that negatively regulate central neurotransmitters, such as haloperidol, (a dopamine receptor antagonist), have detrimental effects on outcome in both experimental and clinical stroke.^{5,6} It has been hypothesised that increasing catecholamines could facilitate recovery following stroke, and that centrally acting neurotransmitters might modulate plasticity.^{7,8}

Amphetamine, a sympathomimetic drug, has been shown to accelerate the recovery of motor function in experimental models of stroke when given in conjunction with task specific practice.^{5,9,10} However, timing and dose of administration appears important; high doses and early administration being associated with a poor outcome,^{5,11} whilst pre-treatment with amphetamine led to increased ischemic insult.¹² The evidence in normal subjects¹³⁻¹⁵ and in clinical stroke is less clear,¹⁶⁻²⁷ numerous small trials, utilizing varying dosage and timing of treatment, showing conflicting results, overall demonstrating no evidence of benefit on motor recovery. Whilst treatment appears feasible and well tolerated, a trend to increased death in the treatment group exists on meta-analysis.²⁸ As such, there is currently no evidence to support the routine use of amphetamine.

Despite well documented systemic effects of amphetamine,²⁹ in particular its effect of raising blood pressure (BP) and heart rate (HR), limited data exist regarding the effect of amphetamine on peripheral haemodynamics in patient with recent ischaemic stroke. One trial found that amphetamine increased BP and HR in stroke,³⁰ important as hypertension is a major risk factor for further stroke,³¹ and for a poor outcome.³² Furthermore, no data exist on the effect of amphetamine on central or cerebral haemodynamic in this population, despite recent evidence that these parameters can be related to outcome in acute stroke.^{33,34}

We performed a phase II trial assessing the effect of amphetamine on motor function, and cerebral and cardiac haemodynamics. We hypothesised that amphetamine would improve recovery from stroke when given with physiotherapy, and sympathomimetic actions would increase blood pressure and heart rate, and alter cardiac haemodynamics and cerebral blood flow velocity.

METHODS

Design

We performed a prospective, single-centre, double-blind, randomised placebo-controlled phase II trial of amphetamine in patients with recent ischaemic stroke. A sample size of 42 was required based on an unpublished meta-analysis of 4 small trials^{16, 17, 19, 25} which showed a beneficial effect of amphetamine on motor impairment assessed as the Fugl-Meyer motor scale: randomisation ratio of 1:1, mean treatment difference 16.2, with standard deviation 18.8, alpha = 0.05 and 80% power. The study was approved by the Nottingham Local Research Committee (October 2001), had a Medicines and Healthcare products Regulatory Agency Clinical Trial Authorisation (August 2001), and International trial number (ISRCTN 36285333), and was performed according to the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice guidelines.

Subjects

Previously independent (modified Rankin score, mRS <3) adult patients with recent ischaemic stroke (3-30 days post ictus) and motor weakness (arm and leg components of Scandinavian Stroke Scale, SSS < 6) were identified and enrolled from Nottingham City Hospital (NCH). Patients were recruited as early as possible after 3 days once they had become clinically stable. The principal exclusion criteria were contra-indications to amphetamine, including intracerebral haemorrhage, ischaemic heart disease, uncontrolled hypertension (>160/100mmHg), thyrotoxicosis and history of seizures; patients with dementia, coma, or pregnancy were also excluded. Full written informed consent was obtained from patients prior to randomisation, or assent taken from a relative/carer if the patient was incompetent, confused or dysphasic.

Intervention

Patients were randomised to receive either amphetamine or placebo using computerised minimisation on age, sex, baseline severity (SSS), and baseline Motricity Index upper extremity score. Dexamphetamine sulphate (initial 5mg dose followed by 10mg thereafter) or placebo was administered orally twice a week with alternating 3 or 4 day separations.^{17, 23, 24, 26, 35, 36} The dose of 10mg is unlikely to cause dependency or extreme vascular instability. There were a total of 11 doses covering a treatment period of 35 days. Treatment was given 1-2 hours before scheduled physiotherapy.

Outcome measures

The primary outcome was motor impairment as assessed by Fugl-Meyer (upper extremity) motor scale (FM) at day 90. Secondary outcomes included Motricity Index (upper limb) (MI), severity (SSS), Barthel Index (BI), modified Rankin Scale (mRS), extended activity of daily living (EADL), language skills (Sheffield screening test), cognition (mini-mental state examination), mood (Zung depression score), and quality of life (health state test); these were assessed at the end of treatment (day 35) and day 90. Discharge disposition and length of hospital stay were also recorded. Safety was assessed as mortality, serious adverse events (SAE), stroke recurrence (ischaemic or haemorrhagic), acute coronary syndrome (myocardial infarction, unstable angina), and symptomatic cardiac dysrhythmia during the study period.

Haemodynamic measures

Cerebral and cardiac measurements were made immediately before and 90 minutes after both the first (dexamphetamine 5mg) and second treatment (dexamphetamine 10mg) doses. Peripheral systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were measured with a validated digital readout oscillometric device (Omron HEM-705CP, Illinois, US). Pulse pressure (PP = SBP - DBP) and rate pressure product (RPP = HR x SBP) were calculated from measured parameters.³⁷ Central BP, mean arterial pressure (MAP), compliance (augmentation index, AI) and myocardial perfusion (Buckberg index, BUI³⁸) were assessed by applanation tonometry pulse wave analysis (SphygmoCor Px, Australia) at the radial artery. Cardiac output

and peripheral vascular resistance were measured by Portapres (NO-TPD Biomedical Instrumentation, Amsterdam, Netherlands).

The middle cerebral artery (MCA) was insonated bilaterally by transcranial Doppler (Nicolet EME Companion, Kleimoftheim, Germany)³⁹ and systolic flow velocity (SFV), diastolic flow velocity (DFV), mean flow velocity (MFV) and pulsatility index (PI) recorded. Estimated cerebral perfusion pressure (CPP) was calculated using a mean of contra-lateral and ipsilateral cerebral blood flow velocity as follows:^{40, 41} $CPP = (MFV / (MFV - DFV)) \times (MAP - DBP)$.

All clinical measurements were performed blinded to treatment assignment, and outcome measures were performed blinded to haemodynamic measures and treatment. Measurements were not adjusted for concurrent antihypertensive therapy (as with previous studies) since this was very variable depending, in part, on the supervising consultant's medical practice.

Statistical methods

Data are presented as mean (standard deviation, SD), median (interquartile range, IQR) or number (%), and were analysed using Fisher's exact test, student t test, Mann Whitney U test, or comparison by ANCOVA with adjustment for baseline values, as appropriate. All analyses were performed using SPSS (Apple Mac, version 11; SPSS Inc, Chicago, USA). Analysis was by intention-to-treat; significance was taken at $p < 0.05$.

RESULTS

Subjects

Thirty three patients (of an intended 42) were enrolled between September 2001 and December 2005 (figure 1); enrolment was concluded early due to the low recruitment rate. Patients were enrolled 15 days (range 4 - 30 days) after stroke. Patients assigned to amphetamine were more likely to be male than in the placebo group otherwise both groups were matched for age, baseline blood pressure and stroke severity (table 1).

Recovery

There was no difference between treatment groups in Fugl-Meyer scores (primary outcome) at day 90 (table 2). Similarly, there was no difference between groups in the secondary outcome measures of impairment (MI, SSS) or function (BI, mRS and EADL) at day 35 or day 90. Length of stay and discharge disposition did not differ between treatment groups (table 2). No differences were observed between the treatment groups in terms of language skills (Sheffield screening test), cognition (mini-mental state examination), mood (Zung depression score) or quality of life (health state test) (data not shown).

Haemodynamic measures

Both groups were well matched for baseline blood pressure (table 1), although patients assigned to placebo had a higher heart rate, whilst patients in the amphetamine group had higher cerebral blood flow velocities. Peripheral and central BP were 11.2/5.8 mmHg and 9.5/6.6 mmHg higher respectively after amphetamine than placebo (table 3). Pulse pressure was unaffected by amphetamine. Heart rate was significantly increased by 7-9 beats/minute after amphetamine (table 3). Rate pressure product was increased after amphetamine, with a trend to a reduction in myocardial perfusion (Buckberg Index) present after the second dose of amphetamine (table 3). Other cardiac haemodynamics, including vessel compliance, cardiac output and total peripheral resistance were unaffected by amphetamine. Similarly, amphetamine did not significantly alter middle cerebral artery blood flow velocity or estimates of cerebral perfusion pressure (table 3).

Safety

No patients died during the course of the study, 1 patient each had a recurrent ischaemic stroke (placebo group) and transient ischaemic attack (placebo group) (table 4). There were no episodes of acute coronary syndrome, or symptomatic dysrhythmia or epilepsy. Serious adverse event rates did not differ between treatment groups (4 vs. 3, $p=0.69$) (table 4).

DISCUSSION

This phase II trial set out to assess the effect of amphetamine on functional outcome and haemodynamic parameters in patients with recent ischaemic stroke. The primary hypothesis that amphetamine would reduce motor impairment was not supported. Additionally, there were no effects on other measures of impairment, disability, mood and quality of life. Early studies of amphetamine after stroke suggested motor impairment might be reduced,^{16, 17, 19, 25} data we used to power the present trial. However, more recent studies have not supported this finding. Taking all the studies together (including that reported here), a meta-analysis reveals no evidence of efficacy, standardised mean difference (SMD) 0.12 (95% CI, -0.25 to 0.50) (figure 2a).

Amphetamine is known to have powerful effects on blood pressure and heart rate in normal subjects; indeed, a sympathetic surge resulting in hypertension is well recognised as a cause of stroke when recreational doses of the drug are taken.⁴² Unsurprisingly, amphetamine also increased peripheral blood pressure and heart rate in the present study, as has been found in earlier trials in patients with recent stroke.^{22, 26} Meta-analysis of these data show that amphetamine increases systolic BP (weighted mean difference) by 9.3 mmHg (95% CI, 3.3 to 15.3) (figure 2b) and HR by 7.6 beats per minute (95% CI, 1.9 to 13.4).

Other haemodynamic parameters are associated with stroke in epidemiological studies⁴³ and amphetamine appears to alter some of these. Central BP (rather than peripheral brachial BP) is more relevant to the cerebral circulation and amphetamine increased this. Rate-pressure product (the mathematical product of heart rate and systolic BP,⁴⁴ an index of myocardial work and associated with a poor outcome after stroke³⁴) was similarly increased with amphetamine. In parallel, the Buckberg Index (an estimate of myocardial perfusion) was decreased non significantly after amphetamine. Buckberg Index is affected by heart rate, with tachycardia resulting in shortened diastole and the potential for reduced coronary artery filling. Hence, the positive chronotropic effect of amphetamine may explain, in part, a tendency for myocardial perfusion to decrease.

Elevation of systemic blood pressure, in the presence of dysfunctional cerebral autoregulation (as occurs in acute ischaemic stroke), might lead to an increase in cerebral blood flow and, potentially, enhance recovery after stroke.³³ However, despite increasing blood pressure, no changes in middle cerebral artery blood flow velocity or estimated cerebral perfusion pressure were observed with amphetamine. Changes in cerebral blood flow with amphetamine have been demonstrated previously,⁴⁵ although these appeared to be region-specific and, therefore, are probably not detectable using global measures of flow and perfusion (as utilised here).

The lack of effect of amphetamine on recovery may be due to a number of reasons. First, enrolment in this study was terminated early due to a low recruitment rate (a problem seen in other trials with limiting inclusion criteria^{24, 46}) so the intended sample size was not achieved thereby leading to a potential type II error when viewed in the context of the pre-trial sample size calculation. This problem was compounded by the heterogeneous nature of recruited patients with widely varying impairment at baseline. Unfortunately, the limited sample size prevents stratification of data by prognostic baseline factors such as stroke syndrome, severity or time to recruitment. Furthermore, to date, no clinical study testing amphetamine in stroke has taken into account ischaemic lesion size or location.²⁷ Additionally, contemporary care of ischaemic stroke has evolved over the recruitment period of this study, which may also have introduced further heterogeneity. However, the management of blood pressure in acute stroke has not altered during this time. Second, no single outcome measure has been used in the existing amphetamine trials, so the potential for meta-analysis is limited and, again, a type II error may be present. In keeping with this, many of the outcome measures utilised demonstrate ceiling effects, although some studies have excluded patients with mild weakness in an attempt

to overcome this.^{17, 21, 24, 27} Third, suboptimal dose regimes might have been tested; the regime utilised here (and pioneered by others^{17, 23, 24, 26, 35, 36}) was driven by concern for potential adverse effects. It is possible that higher and more frequent doses are required, as tested in experimental models.^{5, 9, 47, 48} Fourth, treatment was started between 4 and 30 days after stroke onset. Similar studies have failed to address the issue of most favourable time to recruitment and the optimal therapeutic window remains to be elucidated. Finally, perhaps amphetamine has no overall effect on recovery, reflecting a balance between potential benefit and harm. Amphetamine might enhance plasticity, thus reducing impairment, whilst also increasing risk factors for a poor outcome. For example, elevating BP and heart rate will increase myocardial work load (rate-pressure product), as seen here, whilst tachycardia will reduce myocardial perfusion (Buckberg Index), a pattern which is likely to promote cardiac events, particularly since many patients with stroke have existing heart disease (whether clinical or occult). Although experimental data supporting the use of amphetamine, whether in animals or normal volunteers, has involved subjects with normal coronary vasculature,^{14, 15, 49} a trend to increased death in stroke patients has been noted previously²⁸ (although not seen in the present study) which supports this hypothesis.

We did not show any benefit of amphetamine therapy on recovery after ischaemic stroke although a moderate treatment effect, whether beneficial or hazardous, cannot be excluded. Amphetamine increased peripheral and central BP, heart rate, myocardial work rate and tended to reduce myocardial perfusion. In contrast, it had no effect on other central haemodynamic measures or middle cerebral artery blood flow velocity. Combining these data with those of previous studies, we find no evidence that amphetamine improves motor recovery, perhaps because it induces potentially hazardous effect on systemic haemodynamic parameters. Any future trials of amphetamine should further study its effects on haemodynamic measures.

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CONFLICT OF INTEREST STATEMENT

No company manufacturing amphetamine or developing it for stroke was involved in the conception, execution, analysis, or interpretation of the study, and none has commented on the manuscript.

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TABLE 1

Baseline characteristics of patients. Number (%), or mean (standard deviation)

Characteristic	Placebo (n = 16)	D-amphetamine (n = 17)
Age (years)*	73 (11)	69 (12)
Male (%)*	4 (25)	11 (65)
Time to treatment (days)	15 (7)	15 (8)
Clinical stroke syndrome (%) ⁵⁰		
Lacunar	6 (38)	8 (47)
Partial anterior circulation	5 (31)	4 (24)
Total anterior circulation	5 (31)	5 (29)
TOAST aetiological group (%) ⁵¹		
Small vessel disease	3 (19)	6 (35)
Large artery disease	2 (13)	2 (12)
Cardio-embolic stroke	2 (13)	4 (24)
Previous stroke (%)	2 (13)	3 (18)
Previous transient ischaemic attack (%)	2 (13)	2 (12)
Diabetes mellitus (%)	3 (19)	4 (24)
Prior hypertension (%)	5 (31)	6 (35)
Atrial fibrillation (%)	3 (19)	4 (24)
Baseline severity		
Scandinavian stroke scale *	37 (14)	34 (12)
Motricity Index *	39 (38)	37 (37)
Baseline haemodynamics		
Systolic blood pressure (mmHg) *	128.8 (17.6)	130.3 (18.3)
Diastolic blood pressure (mmHg)	75.6 (9.4)	76.4 (14.0)
Heart rate (bpm)	75.0 (10.1)	70.0 (15.4)

BPM: beats per minute. * Minimisation variables

TABLE 2

Functional outcome by treatment group. Frequency (%), mean (standard deviation), or median (interquartile range); comparison by student T test,* ANCOVA with adjustment for baseline, Mann-Whitney U Test,[†] or Chi square test[‡]

	Placebo (n=16)	D-amphetamine (n= 17)	2P
Day 35			
Fugl-Meyer score ^{§*}	33.5 (28.2)	35.9 (26.4)	0.81
Motricity Index [§]	46.1 (37.9)	47.5 (36)	0.26
Scandinavian Stroke Scale	40.2 (12.5)	39.1 (14.3)	0.33
Barthel Index	11.5 (7.3)	12.5 (5.8)	0.57
Modified Rankin Scale	3.2 (1.5)	3.5 (0.9)	0.59
Extended ADL *	18.1 (21.4)	14.6 (14.1)	0.58
Day 90			
Fugl-Meyer score *	35.2 (27.8)	37.6 (27.6)	0.81
Motricity Index	35.3 (40.9)	51.2 (36.8)	0.74
Scandinavian Stroke Scale	41.1 (13.8)	42.9 (11.8)	0.42
Barthel Index	12.9 (7.4)	14.3 (7.3)	0.20
Modified Rankin Scale	2.9 (1.4)	3.2 (1.0)	0.46
Extended ADL *	25.3 (25.2)	22.3 (19.9)	0.71
Discharge disposition (%)[‡]			
Institution	4 (25%)	2 (11.8%)	0.49
Home	8 (50%)	12 (70.6%)	
Length of stay (days) [†]	67 (39-93)	63 (48-92)	0.75

ADL: Activities of Daily Living

[§] Upper extremity

TABLE 3

Haemodynamic and cerebral blood flow measures 90 minutes following first (5mg, day 0) and second (10mg, day 4) doses of dexamphetamine. Mean (standard deviation), 95% confidence intervals (CI); comparison by ANCOVA with adjustment for baseline.

	Control 90 mins post	Dexamphetamine 90 mins post	Difference	95% CI	p
Day 0					
Peripheral					
Systolic blood pressure	124.4 (16.2)	136.8 (21.1)	11.2	1.1, 21.4	0.03
Diastolic blood pressure	72.9 (7.4)	79.0 (16.2)	5.8	-3.0, 14.5	0.19
Pulse pressure (mmHg)	51.5 (18.7)	57.8 (16.0)	6.0	-6, 18.3	0.33
Central					
Systolic blood pressure	110.9 (12.6)	122.0 (19.6)	9.5	0.64, 18.3	0.04
Diastolic blood pressure	73.7 (7.3)	80.0 (16.1)	6.1	-2.5, 14.7	0.16
Heart rate (bpm)	73.3 (11.4)	75.4 (17.1)	7.0	1.8, 12.6	0.02
Rate-pressure product	9047 (1503)	10322 (2879)	1579	453, 2705	0.08
Buckberg Index	168.9 (34.8)	170.9 (52.1)	-12.8	-33.0, 7.3	0.20
Augmentation index	130.1 (17.2)	130.7 (24.9)	-2.7	-13.7, 8.3	0.62
Ipsilateral-MCA velocity	25.6 (11.8)	29.4 (12.3)	-2.3	-9.8, 5.3	0.51
Contralateral-MCA velocity	29.7 (18.0)	30.9 (11.9)	1.3	-13.8, 16.2	0.84
Cerebral perfusion pressure	27.2 (12.4)	40.5 (16.2)	10.5	-4.98, 25.9	0.17
Day 4					
Peripheral					
Systolic blood pressure	127.3 (25.2)	131.7 (19.2)	7.0	-3.7, 17.7	0.19
Diastolic blood pressure	75.1 (17.0)	77.2 (12.6)	6.8	-2.0, 16.4	0.16
Pulse pressure (mmHg)	52.2 (20.4)	54.5 (17.5)	0.3	-9.2, 9.8	0.95
Central					
Systolic blood pressure	115.4 (21.7)	118.6 (18.6)	6.6	-3.6, 16.7	0.20
Diastolic blood pressure	75.7 (17.1)	78.0 (12.7)	7.2	-2.3, 16.8	0.13
Heart rate (bpm)	71.2 (10.7)	77.7 (22.6)	9.0	2.1, 15.9	0.01
Rate-pressure product	9111 (2402)	10106 (2794)	1620	419, 2822	0.01
Buckberg Index	166.1 (27.5)	167.4 (59.0)	-19.4	-41.6, 2.9	0.09
Augmentation index	139.8 (22.1)	134.8 (23.4)	-2.2	-18.2, 13.7	0.78
Ipsilateral-MCA velocity	25.8 (10.5)	28.5 (12.4)	3.3	-7.6, 14.2	0.40
Contralateral-MCA velocity	37.1 (11.1)	33.3 (19.6)	-0.4	-18.9, 18.2	0.97
Cerebral perfusion pressure	27.2 (9.7)	33.8 (17.5)	3.1	-11.0, 17.2	0.64
MCA middle cerebral artery velocity					

TABLE 4

Number of patients suffering serious adverse events (SAE) by treatment group. Frequency (%); comparison by Fisher's Exact test.

Event	Placebo	D-amphetamine
Recurrent stroke	1	0
Transient ischaemic attack	1	0
Pneumonia	0	1
Depression	1	1
Venous thromboembolism	0	1
Fall/fractured wrist	1	0
Total patients suffering a SAE	4	3

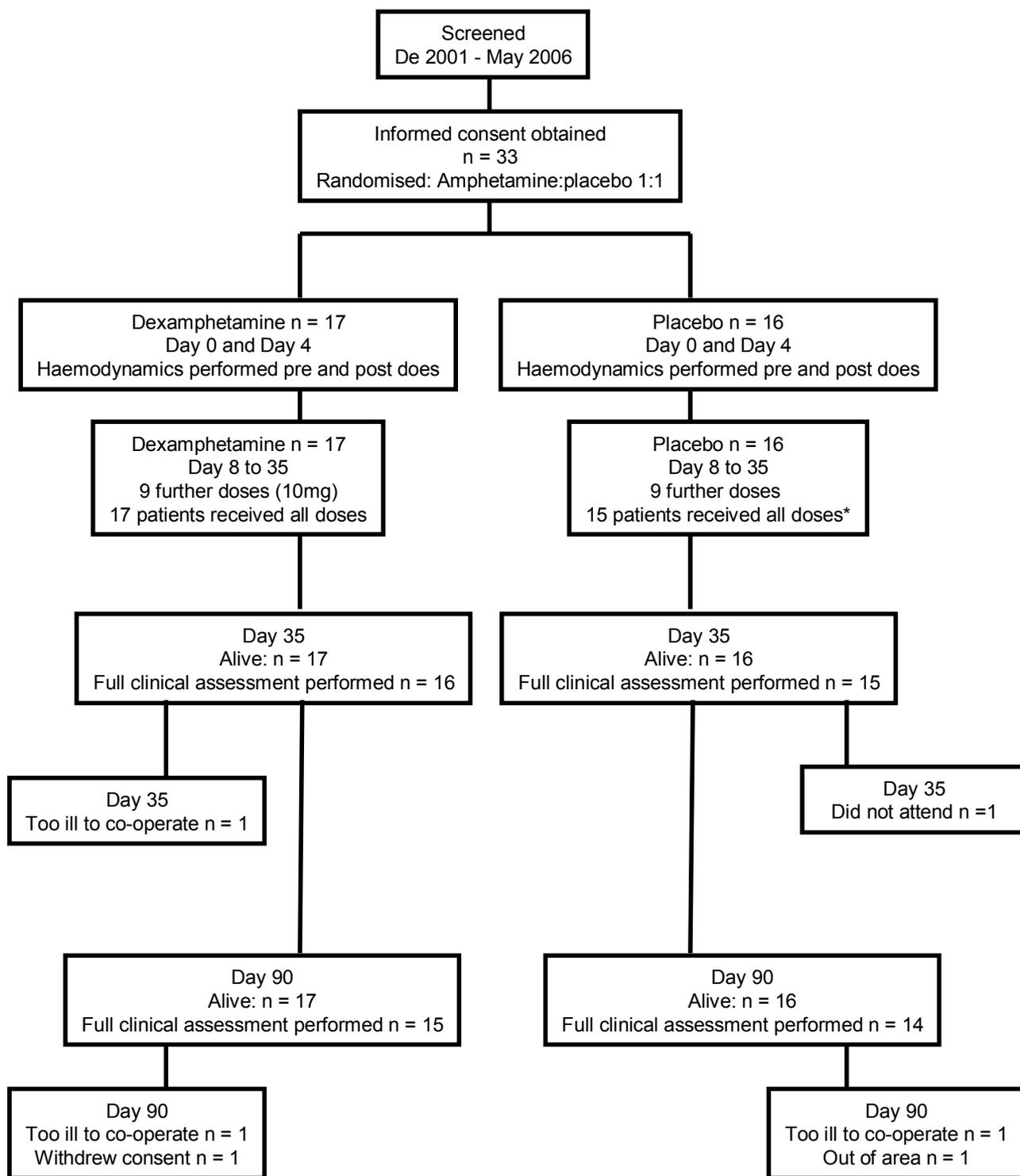
Figure Legends:

Figure 1: Trial Design

Figure 2a: Meta-analysis of amphetamine on motor impairment: Updated forest plot (meta-analysis) of effect of amphetamine on improvement in motor score

Figure 2b: Meta-analysis of amphetamine on blood pressure: Updated forest plot (meta-analysis) of effect of amphetamine on systolic blood pressure

Figure 1



*One placebo group patient did not receive final dose after an episode of agitation following the penultimate dose

Figure 2a

Review: Amphetamine for stroke recovery
 Comparison: 01 Recovery
 Outcome: 07 Improvement in motor score

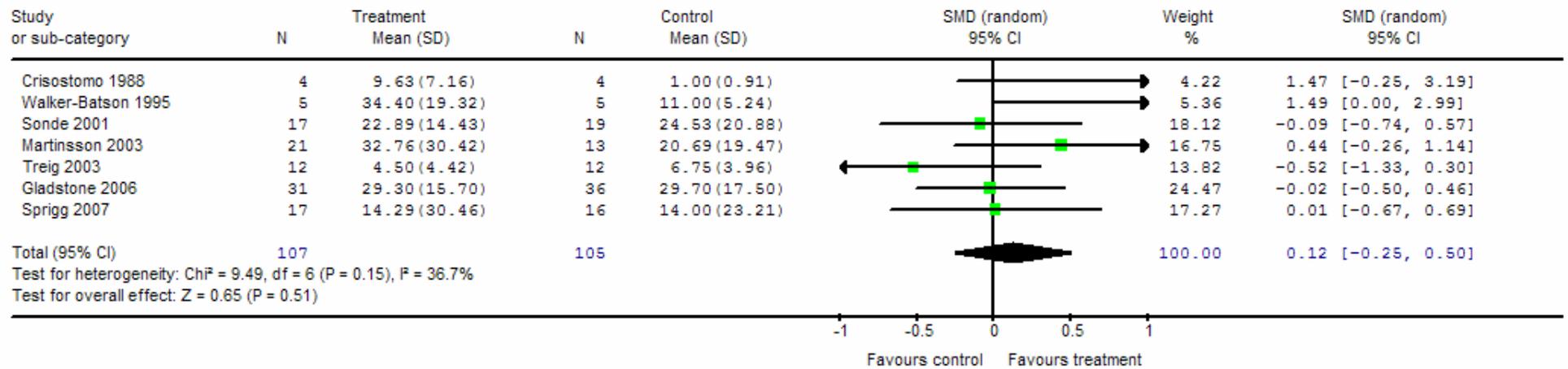


Figure 2b

Review: Amphetamine for stroke recovery
 Comparison: 01 Recovery
 Outcome: 13 Systolic blood pressure

