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TREATMENT OF ACUTE CEREBRAL ISCHEMIA USING ANIMAL MODELS: A META-ANALYSIS

Peng-Fei Wang[1],
Yu Zhou[1],
Huang Fang[1],
Sen Lin[2],
Yan-Chun Wang[1],
Yong Liu[1],
Jun Xia[3],
Guy D. Eslick[4],
Qing-Wu Yang[1]*

Abstract

Background: There are numerous potential treatments assessed for acute cerebral ischemia using animal models. This study aimed to assess the effect of these treatments in terms of infarct size and neurobehavioral change. This meta-analysis was conducted to determine if any of these treatments provide a superior benefit so that they might be used on humans. Methods: A systematic search was conducted using several electronic databases for controlled animal studies using only nonsurgical interventions for acute cerebral ischemia. A random-effects model was used. Results: After an extensive literature search, 145 studies were included in the analysis. These studies included 1408 treated animals and 1362 control animals. Treatments that had the most significant effect on neurobehavioral scales included insulin, various antagonists, including N-methyl-D-aspartate (NMDA) receptor antagonist ACEA1021, calmodulin antagonist DY-9760e, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist YM872, and antiviral agents. Treatments providing the greatest effect on infarct size included statins, sphingosine-1-phosphate agonist (fingolimod), alcohol, angiotensin, and leukotrienes. Treatments offering the greatest reduction in brain water content included various agonists, including sphingosine-1-phosphate agonist fingolimod, statins, and peroxisome proliferator-activated receptor gamma (PPAR-γ). Treatment groups with more than one study all had high heterogeneity ($I^2 > 80\%$), however, using meta-regression we determined several sources of heterogeneity including sample size of the treatment and control groups, the occlusion time, but not the year when the study was conducted. Conclusions: Some treatments stand out when compared to others for acute cerebral ischemia in animals. Greater replication of treatment studies is required before any treatments are selected for future human trials.

Keywords

• Acute cerebral ischemia • Animal studies • Brain water content • Infarct size • Meta-analysis • Neurobehavioral scales

[1]Department of Neurology, Xinqiao Hospital, The Second Affiliated Hospital, The Third Military Medical University, Chongqing, China

[2]Department of Development and Regeneration Key Laboratory of Sichuan Province, Department of Histoembryology and Neurobiology, Chengdu Medical College, Chengdu, China

[3]Systematic Review Solutions, China

[4]Department of Surgery, The University of Sydney, Nepean Hospital, Penrith, Australia

Introduction

Acute cerebral ischemia is a substantial cause of morbidity and mortality among humans [1, 2]. The majority of these ischemic events occur in the middle cerebral artery. However, there are many clinical variations associated with the presentation and management of this important vascular disease. Treatment options and outcomes among humans vary widely with no single therapy available providing optimal outcomes [3].

There are numerous experimental animal models aimed at determining a novel treatment for acute cerebral ischemia [4, 5]. These laboratory-based studies are conducted under strict control conditions. The number of these types of studies have increased over the last decade [6]. Much of the information available on the pathophysiological mechanisms associated with focal cerebral ischemia was provided by animal models [6-9].

Currently, none of the hundreds of treatment options found from animal studies has been

reported to be effective in a phase III human clinical trial [10]. A greater sense of urgency is required to isolate and replicate novel treatments for acute cerebral ischemia in animals, so that these agents may undergo randomized clinical trials among human patients [11-13]. There have been several meta-analysis of animal studies focused on specific treatment options for intracerebral hemorrhage and stroke [14].

The objectives of the present study were to:
• Systematically review the collated the experimental evidence for various treatments for acute cerebral ischemia in animal models;
• Determine if there was a treatment that was clearly superior in improving (a) the neurobehavioral outcomes; (b) infarct size; and (c) brain water content.

Methods

Study protocol

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed, where possible, in performing

this systematic review [15]. A systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), and Google Scholar to October 18, 2013 was performed. The search terms included combinations of 'acute cerebral ischemia' or 'acute ischemic stroke' or 'brain ischemia' or 'carotid artery thrombosis' or 'stroke' or 'cerebrovascular disorders' or 'intracranial arterial diseases' or 'cerebral artery diseases' and 'animal model' which were searched as text word and with the 'explode' feature of medical subject headings (MeSH) turned on where possible, resulting in greater number of records retrieved. Only studies published in English were included. The reference lists of relevant articles were also searched for relevant studies. A search for unpublished literature was not performed.

Study selection

Studies that met the following inclusion criteria were used: 1. Only ischemic stroke was included (not haemorrhagic), 2. Animal studies only, 3. There had to be a control group, 4. A nonsurgical intervention was used, 5. The

middle cerebral artery (MCA) was used for occlusion, 5. Determined infarct size either as volume (mm³) or as percentage (%) for both treatment and control groups, 6. Determined neurobehavioral scores for both treatment and control groups, and 7. Determined brain-water content for both treatment and control groups.

Outcomes assessed

Three outcomes were to be assessed from these studies with one primary and two secondary outcomes. The primary outcome was neurobehavioral score and the secondary outcomes were (1) reduction in brain-water content and (2) the size of the infarct.

Data extraction

The data extraction was performed using a standardized data extraction form, collecting information on the publication year, sample size for treatment and control groups, country, animal type, statistical methods, occlusion time (mins), treatment, experimental time (days), neurobehavioral scores for treatment and control groups, infarct size for treatment and control groups, and brain-water content for treatment and control groups.

Quality assessment

No quality assessment was undertaken for these studies as none of them were randomized trials. The studies were comparative in nature and did not involve any forms of randomization, blinding or allocation concealment. Thus, we thought that quality assessment would be too subjective for animal studies designed in such a way.

Statistical analysis
Meta-analysis

The studies compared the treatment group with the control group. The control group was either labeled as a control or sham. The primary outcomes assessed were neurobehavioral scores, with secondary outcomes (structural measures) either infarct volume or brain water content. Treatment and control groups were compared using a standard difference in means (std diff mean) for infarct volumes, neurobehavioral scores, and brain-water content using a random effects model [16].

Assessment of heterogeneity

Heterogeneity was tested using the I^2 statistic, which represents the percentage of the total variability across studies which are due to heterogeneity [17]. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively.

Meta-regression

A mixed-effects meta-regression model was used for the meta-regression analysis. Meta-regression was conducted to assess if we could identify any potential causes for any heterogeneity that may be present. The main factors analyzed using meta-regression were sample size of the treatment group, sample size of the control group, the occlusion time, and the year of publication for neurobehavioral score, infarct volume and brain water content.

Publication bias

The publication bias was quantified using the Egger's regression model [18], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that would need to be missed for the observed result to be nullified to statistical non-significance at the $p < 0.05$ level [19]. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, with n being the number of studies included in the meta-analysis. All analyses were performed with Comprehensive Meta-Analysis software (version 2.0, 2005), Englewood, NJ, USA.

Results

Search strategy

From 23053 studies initially identified, 145 met the inclusion criteria (Fig. 1) [20-160]. Studies were excluded for the following reasons: no control group, abstract only, no data, hypothermia studies, genetic study, inappropriate study design, neonates, global ischemia, duplicates, language, radiology study, and cell-based studies.
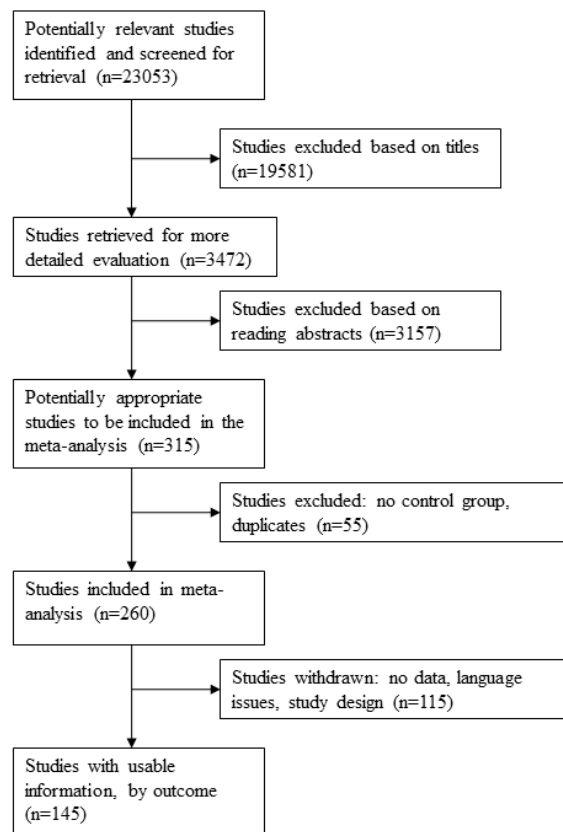

Figure 1. Flowchart of the literature search strategy.

Study characteristics

The majority of the studies used rats as the animal model (n = 125, 89%), followed by mice (n = 13, 9%), with the remaining studies used cats, dogs, rabbits, and gerbils. The median number of treated/control animals used in each outcome group was: infarct (10 vs. 10; range 3 - 83 vs. 3 - 78), neurobehavioral score (10 vs. 10; range 3 - 83 vs. 3 - 78), and brain water content (8.5 vs. 8.5; range 3 - 24 vs. 3 - 24).

Neurobehavioral outcome

There were 85 studies assessing neurobehavioral outcomes across 41 different treatments. The sample size of the neurobehavioral outcome studies was (treatment, n = 1026 vs. control, n = 991), with the median number in each study equal to ten in both treatment (range: 3 - 83) and control groups (range: 3 - 78).

The overall effect of all the treatments on neurobehavioral scores was (std diff mean -0.68). For all the studies, including those with (n = 1) the treatments which provided the greatest impact on neurobehavioral scores were insulin (std diff mean -11.20), various antagonists, including N-methyl-D-aspartate (NMDA) receptor antagonist ACEA1021, calmodulin antagonist DY-9760e, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist YM872, (std diff mean -4.00), antiviral agents (std diff mean -3.30), peroxisome proliferator-activated receptor gamma (PPAR-γ) (std diff mean -3.18) and angiotensin (std diff mean -2.50) (Fig. 2). Interestingly, over two-thirds of treatment groups (73%) showed an improved neurobehavioral score compared with control groups.

For groups with more than 2 studies, the overall effect of all the treatments on neurobehavioral scores was (std diff mean –1.07). In this sub-group analysis, the treatments which provided the greatest effect on neurobehavioral scores were insulin (std diff mean -11.20), PPAR-γ (std diff mean -3.18), various inhibitors (dipyridamole - inhibitor of cGMP phosphodiesterase and of cellular reuptake of adenosine into platelets, red blood cells and endothelial cells, SNJ-1945 - inhibitor of calpain, N(G)-nitro-L-arginine methyl ester (L-NAME) - inhibitor of nitric oxide synthase, riluzole - inhibitor of NMDA and 2-(aminomethyl)phenylacetic acid/kainate, AMPA/kainate, receptors) (std diff mean -1.46), erythropoietin (std diff mean -1.45), and hyperbaric oxygen (std diff mean -1.30) (Fig. 3).

There were differences in the scoring systems used to determine the change in neurobehavioral outcomes. The most commonly used neurobehavioral scoring systems were those of Bederson (n = 23)

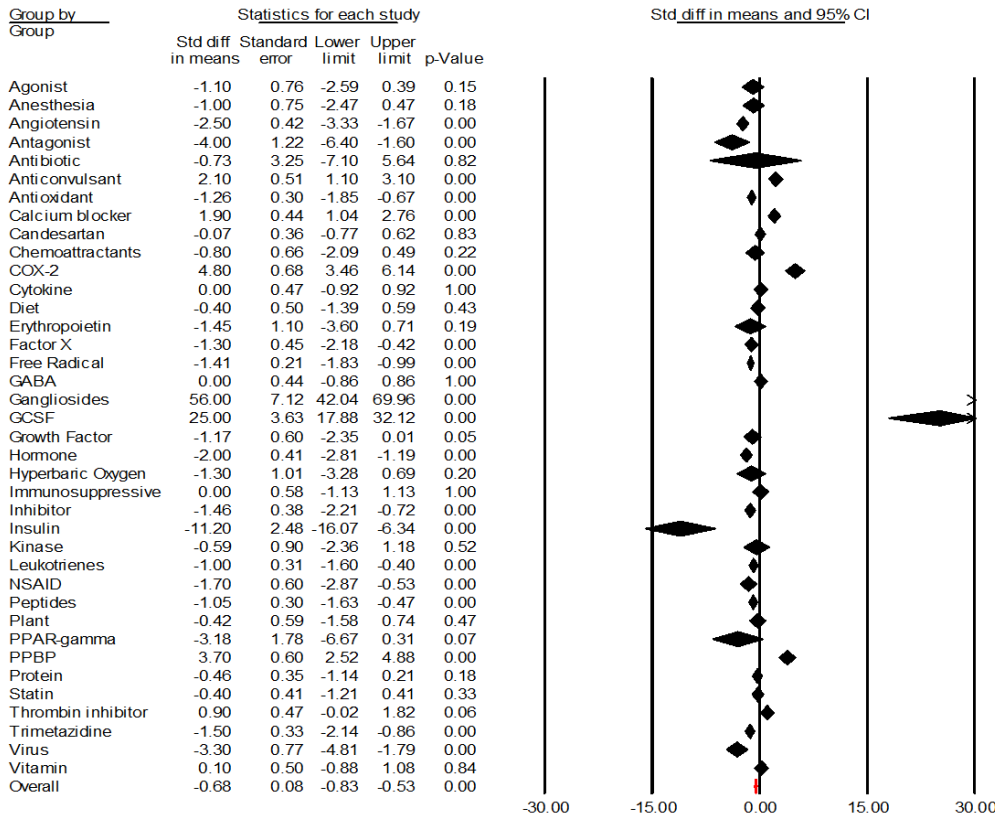| Group by Group	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Agonist	-1.10	0.76	-2.59	0.39	0.15
Anesthesia	-1.00	0.75	-2.47	0.47	0.18
Angiotensin	-2.50	0.42	-3.33	-1.67	0.00
Antagonist	-4.00	1.22	-6.40	-1.60	0.00
Antibiotic	-0.73	3.25	-7.10	5.64	0.82
Anticonvulsant	2.10	0.51	1.10	3.10	0.00
Antioxidant	-1.26	0.30	-1.85	-0.67	0.00
Calcium blocker	1.90	0.44	1.04	2.76	0.00
Candesartan	-0.07	0.36	-0.77	0.62	0.83
Chemoattractants	-0.80	0.66	-2.09	0.49	0.22
COX-2	4.80	0.68	3.46	6.14	0.00
Cytokine	0.00	0.47	-0.92	0.92	1.00
Diet	-0.40	0.50	-1.39	0.59	0.43
Erythropoietin	-1.45	1.10	-3.60	0.71	0.19
Factor X	-1.30	0.45	-2.18	-0.42	0.00
Free Radical	-1.41	0.21	-1.83	-0.99	0.00
GABA	0.00	0.44	-0.86	0.86	1.00
Gangliosides	56.00	7.12	42.04	69.96	0.00
GCSF	25.00	3.63	17.88	32.12	0.00
Growth Factor	-1.17	0.60	-2.35	0.01	0.05
Hormone	-2.00	0.41	-2.81	-1.19	0.00
Hyperbaric Oxygen	-1.30	1.01	-3.28	0.69	0.20
Immunosuppressive	0.00	0.58	-1.13	1.13	1.00
Inhibitor	-1.46	0.38	-2.21	-0.72	0.00
Insulin	-11.20	2.48	-16.07	-6.34	0.00
Kinase	-0.59	0.90	-2.36	1.18	0.52
Leukotrienes	-1.00	0.31	-1.60	-0.40	0.00
NSAID	-1.70	0.60	-2.87	-0.53	0.00
Peptides	-1.05	0.30	-1.63	-0.47	0.00
Plant	-0.42	0.59	-1.58	0.74	0.47
PPAR-gamma	-3.18	1.78	-6.67	0.31	0.07
PPBP	3.70	0.60	2.52	4.88	0.00
Protein	-0.46	0.35	-1.14	0.21	0.18
Statin	-0.40	0.41	-1.21	0.41	0.33
Thrombin inhibitor	0.90	0.47	-0.02	1.82	0.06
Trimetazidine	-1.50	0.33	-2.14	-0.86	0.00
Virus	-3.30	0.77	-4.81	-1.79	0.00
Vitamin	0.10	0.50	-0.88	1.08	0.84
Overall	-0.68	0.08	-0.83	-0.53	0.00

Figure 2. Treatment studies assessed for neurobehavioral outcomes.

and Longa (n = 12), with 21 different scoring systems used across all studies.

Neurobehavioral scores differed across different geographical regions with the most significant improvement in neurobehavioral scores found in Australia (std diff mean -1.70), Middle East (std diff mean -1.41), North America (std diff mean -0.91), Asia (std diff mean -0.60) and Europe (std diff mean -0.48).

There was no publication bias present for the studies assessing neurobehavioral outcomes (p = 0.65).

Infarct size

There were 102 studies that determined infarct size across 46 different treatments. The sample size of the infarct studies was (treatment, n = 1369 vs. control, n = 1323), with the median number in each study equal to ten in both treatment (range: 3 - 83) and control groups (range: 3 - 78).

Overall, the effect of treatment on infarct size was (std diff mean -2.06). For all studies, including those with (n = 1), the treatments that reduced infarct size the most were statins (std diff mean -27.61), variuos agonists, including sphingosine-1-phosphate agonist fingolimod (std diff mean -18.34), alcohol (std diff mean -17.32), angiotensin (std diff mean -15.80), and leukotrienes (std diff mean -15.45) (Fig. 4). Nearly all studies (93%) showed a decrease in infarct size when compared to control groups.

For groups with more than 2 studies the overall effect of all the treatments on infarct size was (std diff mean -1.38). For groups of treatments with more than two studies those that reduced infarct size the most were statins (std diff mean -27.61), alcohol (std diff mean -17.32), angiotensin (std diff mean -15.80), anticonvulsants (std diff mean -11.35), and various antagonists, including NMDA receptor antagonist ACEA1021, calmodulin antagonist DY-9760e, and AMPA receptor antagonist YM872 (std diff mean -11.18) (Fig. 5).

Differences could also be observed in the infarct size by volume (mm³) (std diff mean -4.78) compared to percent infarct (std diff mean -1.89). There were also differences by the type of animal with rats (n = 85; std diff mean -3.50), cats (n = 4; std diff mean -2.97),
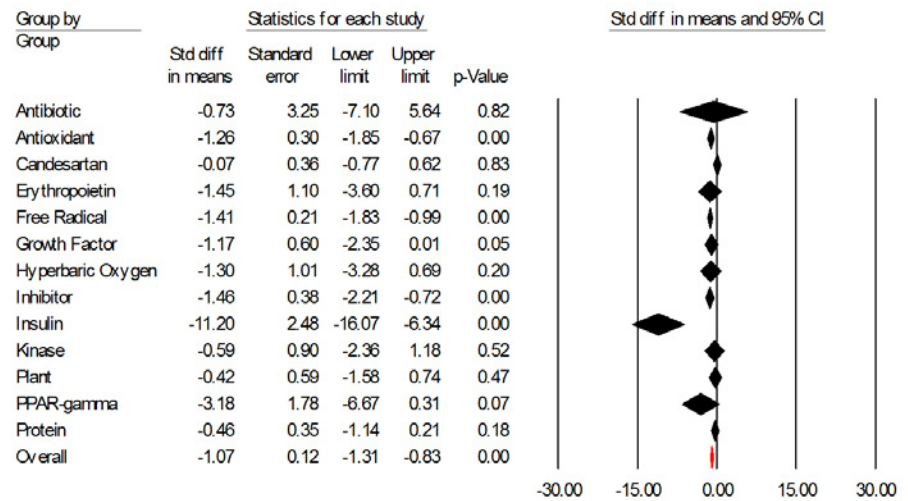

Figure 3. Treatment groups with two or more studies assessed for neurobehavioral outcomes.
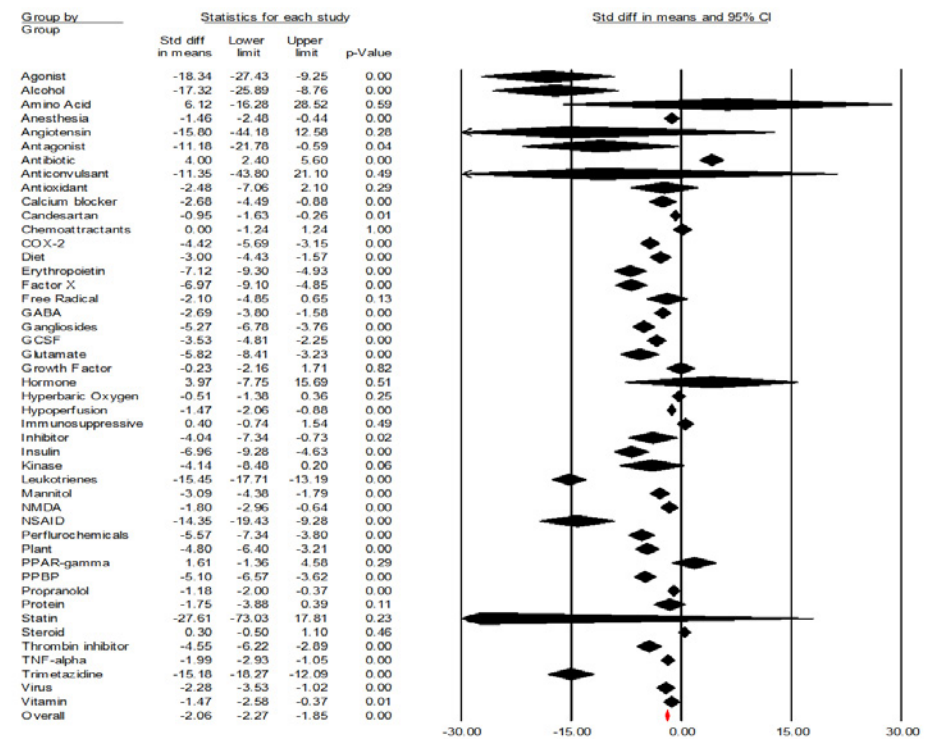

Figure 4. Treatment studies comparing infarct size.

mice (n = 10; std diff mean -1.61), dogs (n = 1; std diff mean -1.56), and gerbils (n = 2; std diff mean +4.28). In the rat only studies the most significant effect occurred for statins (std diff mean -27.61), alcohol (std diff mean -17.32), angiotensin (std diff mean -15.80), leukotrienes (std diff mean -15.45), and trimetazidine

(inhibits beta-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase) (std diff mean -15.18).

Infarct size varied by geographical regions with the most significant decrease in infarct size reported in Asia (std diff mean -4.49), Australia (std diff mean -4.68), Europe (std diff

mean -3.21), and North America (std diff mean -2.61).

There was publication bias present for the studies assessing infarct size (p < 0.001), and the fail-safe number was greater than 1000 (studies).

Brain water content

There were 15 studies that assessed brain water content for 13 different treatments. The sample size of the brain water content (treatment, n = 137 vs. control, n = 137), with the median number in each study equal to 8.5 in both treatment and control groups (range: 3 - 24).

The overall effect on brain water content was (std diff mean -1.44). Brain water content was most significantly reduced using various agonists, including sphingosine-1-phosphate agonist fingolimod (std diff mean -8.00), statins (std diff mean -5.00), PPAR-γ (std diff mean -4.29), various plants (std diff mean -3.22), and nonsteroidal anti-inflammatory drugs (NSAIDs) (std diff mean -2.50). All these groups contained only a single study except for plants which had four studies (Fig. 6). The majority of studies (85%) showed a reduction in brain water content. There was publication bias present for the studies assessing brain water content (p = 0.03). The fail-safe number was greater than 500 (studies).

Discussion

In this work, we presented the results of the comprehensive meta-analysis of 145 controlled animal studies, assessing 46 different treatments using 21 different neurobehavioral scales in 2692 animals. Overall, there were ten treatment groups that provided the greatest effect to the three neurological outcome groups (neurobehavioral, infarct size, brain water content). These treatment groups included insulin, various antagonists, including NMDA receptor antagonist ACEA1021, calmodulin antagonist DY-9760e, and AMPA receptor antagonist YM872, antiviral agents, statins, various agonists, including sphingosine-1-phosphate agonist fingolimod, alcohol, plants, angiotensin, leukotrienes, and PPAR-γ [32, 73, 89, 92, 115, 159].

Some treatments offered substantial improvements across multiple outcome
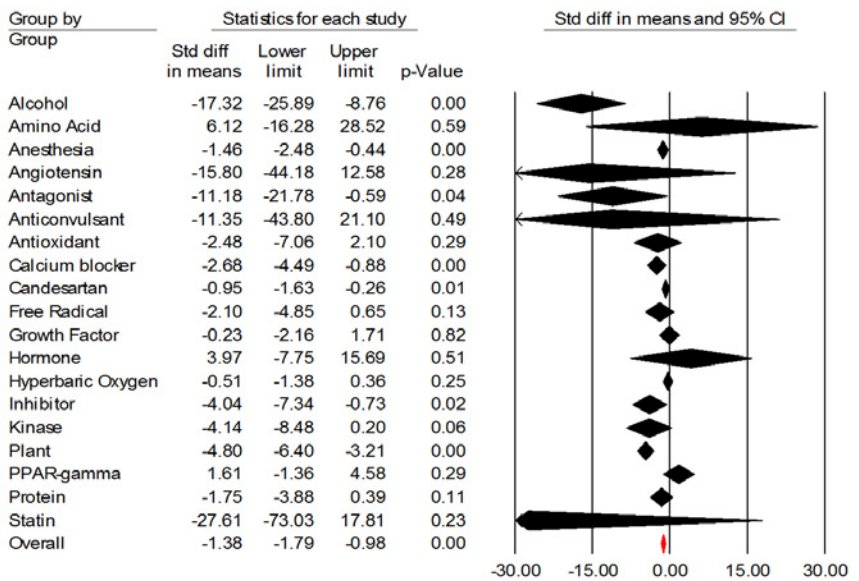

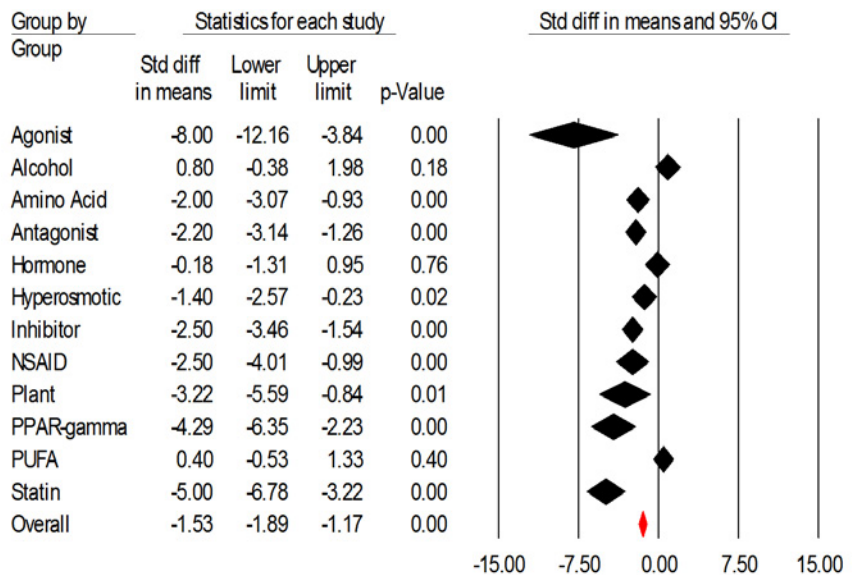Figure 5. Treatment groups with two or more studies comparing infarct size.

Figure 6. Treatment groups comparing the effects of brain water content.

groups (neurobehavioral outcomes, infarct size and brain water content). For treatment responses that included all studies, even those with a single study within the treatment group, angiotensin showed improved outcomes in the neurobehavioral and ischemic groups. Statins and various agonists, including sphingosine-1-phosphate agonist fingolimod, had improved outcomes in both ischemia size and brain water content groups, while PPAR-γ showed improved outcomes in the neurobehavioral and brain water content groups. There was no overlap among treatment groups that contained two or more studies with insulin, PPAR-γ, various inhibitors (dipyridamole, SNJ-1945, L-NAME, riluzole), erythropoietin, and hyperbaric oxygen, showing the greatest effects for

neurobehavioral outcomes. Moreover, for the ischemic size the main treatments with two or more studies having an effect were statins, alcohol, angiotensin, anticonvulsants, and various antagonists, including NMDA receptor antagonist ACEA1021, calmodulin antagonist DY-9760e, and AMPA receptor antagonist YM872. There was only one treatment group in the brain water content outcome that had more than two studies, that was the plant group.

Further research should be conducted into these treatments as potential options for the management of acute cerebral ischemia among humans. Additional mechanistic evidence is required for these potential treatments [161, 162]. For example, recent human studies have reported that statins improve 2-year survival and 2-year functional outcome [163-165]. These data require replication in other populations and long-term follow-up to assess outcomes in these patients.

This study had a number of strengths. The PRISMA guidelines were followed, although no specific guidelines were followed for meta-analysis of animal studies. A thorough search was performed using multiple databases and we imposed no word restrictions. However,

studies that did not include a control group were excluded. The use of an internal control group is recognized as a more statistically robust way of study design. There were also some limitations to this study. The majority of treatment comparisons involved only single studies, of which very few studies had been replicated, thus providing limited comparative data. However, there were some treatments which had two or more studies and these have also been reported and should be reproduced. Those treatments which contained more than one study usually had high levels of heterogeneity and we elucidated some potential causes for this heterogeneity, including sample size of the treatment and control groups and the occlusion time. The year of publication was not a reason for heterogeneity. The statistical power of these studies was also limited. Publication bias was present for infarct size and brain water content comparisons. However, due to the comprehensive literature search strategy undertaken it is extremely unlikely that we missed hundreds of studies based on the fail-safe number.

The following are some recommendations to improve the outcome data provided by

these studies. Future studies for individual treatments should be replicated several times in order to provide more robust data. Studies should contain larger sample sizes in order to improve statistical power and the ability to detect small differences between treatment and control groups. Utilization of validated instruments used to assess neurobehavioral outcomes should be implemented and these should be limited to those used in studies more frequently. Standardization of the experimental protocol should also be undertaken to reduce potential bias and improve study quality.

In summary, this meta-analysis provides evidence that certain treatments improve neurobehavioral outcomes, infarct size and brain water content in animals. Future studies should aim to replicate the pathophysiological mechanisms reported in humans. Animal studies need to be substantially improved before treatments for acute cerebral ischemia can be translated into human randomized clinical trials.

Acknowledgment

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