Short-duration hypothermia after ischemic stroke prevents delayed intracranial pressure rise

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Keywords: Hypothermia, intracranial pressure, ischemic stroke

Word count: 4610 words

Conflicts of Interest/Disclosures: None to declare
Abstract

Background
Intracranial pressure elevation, peaking 3-7 days post-stroke is well-recognised following large strokes. Data following small-moderate stroke is limited. Therapeutic hypothermia improves outcome after cardiac arrest, is strongly neuroprotective in experimental stroke and is under clinical trial in stroke. Hypothermia lowers elevated intracranial pressure (ICP), however rebound ICP elevation and neurological deterioration may occur during rewarming.

Hypotheses
1. Intracranial pressure increases 24 hours after moderate and small strokes. 2. Short duration hypothermia-rewarming, instituted before ICP elevation, prevents this 24 hour ICP elevation.

Methods
Long-Evans rats with 2 hours middle cerebral artery occlusion (MCAo) or outbred Wistar rats with 3 hours MCAo had ICP measured at baseline and 24 hours. Wistars were randomised to 2.5 hours hypothermia (32.5°C) or normothermia, commencing 1 hour after stroke.

Results
In Long-Evans rats (n=5), ICP increased from 10.9±4.6 mmHg at baseline to 32.4±11.4 mmHg at 24 hours, infarct volume was 84.3±15.9 mm³. In normothermic Wistars (n=10), ICP increased from 6.7±2.3 mmHg to 31.6±9.3 mmHg, infarct volume was 31.3±18.4 mm³. In hypothermia-treated Wistars (n=10), 24 hour ICP did not increase (7.0±2.8 mmHg, p < 0.001 v. normothermia) and infarct volume was smaller (15.4±11.8 mm³, p < 0.05).

Conclusions
We saw major ICP elevation 24 hours after stroke in two rat strains, even after small strokes. Short duration hypothermia prevented the ICP rise, an effect sustained for at least 18 hours after rewarming. The findings have potentially important implications for design of future clinical trials.
Introduction
Stroke remains the third leading cause of death and a major cause of morbidity worldwide (1). Clearly, better widely applicable acute therapies are needed. Catastrophic intracranial pressure elevation has been associated with death in large acute stroke (2, 3). However the association between size of stroke and degree of ICP elevation is not strong (4). Typically in large strokes, ICP peaks between 2-5 days post stroke (2). Data on ICP in small stroke in humans is not available. In experimental stroke, there is surprisingly little data available on ICP changes, however the work of Kotwica et al. (1991) (5), suggests that an initial ICP peak at 24 hours is seen after both medium and large strokes (relative infarct size, % hemisphere, in large stroke: 25-36 %, in small stroke: 9-15 %). In the larger strokes ICP had a secondary peak at 3 - 4 days, whereas in the medium-sized strokes it normalised over this period.

Hypothermia results in reduction of ICP and it has been used to achieve therapeutic ICP reduction in stroke, traumatic brain injury and hepatic encephalopathy (6-8). A major limitation to hypothermia therapy is that rewarming after 12-72 hours of cooling often results in rebound ICP elevation with subsequent neurological deterioration. This is more prevalent with rapid rewarming (9). Consequently most protocols rewarm over ≥ 12 hours (10, 11). However prolonging the duration a patient is exposed to hypothermia increases the risk of adverse effects such as immunosuppression and pneumonia (9).

Therapeutic mild-moderate hypothermia is also a proven neuroprotective therapy in human global brain ischemia – post cardiac arrest and neonatal hypoxia ischaemia (12-14); however, benefit has not as yet been proven in focal brain ischaemia (stroke). Importantly, hypothermia appears to have the strongest evidence base of any neuroprotective strategy in experimental stroke (15). However, clinical trials have been hampered by the logistical challenges of prolonged cooling (12- 72 hours) in stroke patients, and concerns about iatrogenic complications (16). This extensive cooling period largely limits its use to centres with available intensive care facilities. In stark contrast to the clinical literature, the majority of studies in experimental stroke induce hypothermia for ≤ 3 hours (17). Somewhat surprisingly, there is very little data regarding the effect of hypothermia on ICP in experimental stroke.

Preliminary studies in our laboratory to investigate rebound ICP elevation following hypothermia treatment of stroke revealed some unanticipated results, leading to the hypotheses that: 1. ICP rises consistently at 24 hours after any stroke, not only after large hemispheric stroke, and 2. A brief period of body cooling commenced soon after stroke may prevent subsequent ICP elevation. Our aims were to measure ICP 24 hours after stroke in 2 different rat strains and to determine the effect of a short duration of moderate hypothermia on ICP, and infarct and oedema volumes 24 hours post-stroke.

Materials and Methods

Animals
Surgery was performed on male Long-Evans (n = 6, Client Service Centre, Monash University) and outbred Wistar rats (n = 37, Animal Services Unit, University of Newcastle) weighing 290-450 g. All experimental animal procedures used in this project were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and were approved by the Animal Care and Ethics Committee of the University of Newcastle.

Experimental Protocols
A small study (Part I) was conducted in Long-Evans rats, a strain that has large infarcts with this model, to investigate the effect 2 hours temporary MCAo on intracranial pressure. Since similar ICP effects were seen with small and large infarcts, for ethical reasons we conducted pilot studies in Wistar rats, which have much smaller strokes. These data showed a similar dramatic ICP rise with smaller strokes than the Long-Evans (data not shown). Since similar results were obtained in Wistars, the prospective studies of the effects of hypothermia on ICP were performed in this strain (Part II).

ICP was monitored at baseline, during stroke surgery and again at 24 hours post-stroke before sacrifice for histology. Infarct volume in Wistar rats is known to be dependent on the supplier (18-20), and our previous data shows small lesion sizes using rats from our supplier, even with permanent arterial occlusion (114 ± 50 mm³) (20, 21). Therefore, this strain was used to determine ICP following small strokes, and the effects of short duration hypothermia. Randomisation to hypothermia, or normothermia under anaesthetic, was performed 1 hour after stroke surgery in Wistar rats.

**Anesthesia and Monitoring**

Anaesthetic and surgical protocols were as previously reported (21). In brief, rats were anesthetised with isoflurane (5% induction, 2% maintenance) in 60:40 %, N₂:O₂. Incision sites were injected subcutaneously (s.c.) with 2 mg/kg 0.05% Bupivacaine (Pfizer, Australia). Core body temperature was regulated via a thermocouple rectal probe (RET-2, Physitemp Instruments Inc, USA) and warming plate (HP-1M, Physitemp). Temperature was also recorded every 5 minutes for 24 hours post-stroke using a datalogger (SubCue, Calgary, Canada) inserted into the peritoneal cavity at the beginning of the surgery. Blood gases were monitored periodically from 0.1 ml blood samples taken from a right femoral arterial line. This line was also used for arterial blood pressure monitoring. Prior to recovery, an additional Bupivacaine injection (0.3 ml 0.05%, s.c) and rectal Panadol (250 mg/kg) were administered for overnight pain relief and saline was administered (2 x 2.5 ml, s.c.) to replace fluid losses. Following surgery the animals were returned to their cages with free access to food and water, with cages placed half over a heat-mat to allow animals to self-thermoregulate during recovery.

**Intracranial Pressure Measurement**

ICP was measured using a SAMBA microcatheter (SAMBA Sensors, Sweden), as previously described (22). In brief, the catheter was sealed in an epidural position inside a fluid-filled hollow screw inserted in the parietal bone. Correct positioning was confirmed by observation of pulse and respiratory wave amplitudes and ICP response to abdominal compression. Cerebral perfusion pressure (CPP) was calculated using the formula CPP = Mean Arterial Pressure – Mean ICP. At 24 hours post-MCAo, animals were re-anaesthetised for 1 hour of ICP recording prior to sacrifice. The left femoral artery was cannulated, physiological monitoring equipment was reattached and the ICP catheter reinserted and sealed.

**Experimental Stroke and Hypothermia**

Thread occlusion of the middle cerebral artery was performed using a silicone-tipped monofilament passed via the external carotid artery, according to our established method (21, 23), with a minor variation to shorten the length of the silicone tip of the occluding thread to 3-4 mm.

After 1 hour of MCAo Wistars were randomised by sealed numbered envelope to hypothermia or normothermia. Hypothermia-treated animals were cooled to 32.5 °C using
70% ethanol evaporation with a sprayer and a fan. Hypothermia was maintained for 2.5 hours, followed by controlled rewarming to 37 °C over 2.5 hours. Normothermic animals were maintained at 37 °C under anaesthesia for the same time intervals.

**Neurological Testing**
Prior to 24 hour post-stroke monitoring, animals were tested for stroke induced neurological deficits. The forelimb flexion, torso twist and lateral push tests were used to assess this and a total neurological deficit score given out of 6 (higher score indicating greater deficit) (24, 25).

**Histological Analysis**
At 25 hours brains were processed for hematoxylin and eosin staining and histological analysis of infarct and oedema volumes using standard methodology (21). Images were scanned at high resolution using a digital slide scanner (Aperio, USA) and analysed by an investigator blind to treatment. Infarct (corrected for oedema) was calculated by subtracting the measured inter-hemispheric volume difference (oedema volume, ipsilateral – contralateral) from the measured infarct volume for each slice. Oedema was calculated by infarct volume minus the corrected infarct volume.

**Exclusions and Statistical Analysis**
Sample size calculations were performed using SPSS v21.0 (IBM, USA) prior to the commencement of the Long-Evans study (for a 15 mmHg difference in ICP), and the Wistar study (for a 30% difference in infarct volume) based on pilot data. Animals were excluded prior to randomisation if there were major deviations from the protocol, such as significant intraoperative oxygen desaturations, blood loss or temperature fluctuations. Additionally, evidence of subarachnoid hemorrhage upon brain removal after perfusion fixation was a pre-specified exclusion criterion, since this may alter both stroke outcome and ICP. Animals that died before final ICP measurement were by necessity excluded from outcome analyses but are fully reported. All physiological and histological data were analysed by an investigator blinded to treatment allocation.

Analysis of co-variance (ANCOVA) was performed using STATA/IC 11.1 for Windows (StataCorp, USA) to test whether treatment had a significant overall effect on the primary outcome of change in intracranial pressure at 24 hours, and on the secondary outcome of cerebral perfusion pressure, adjusting for baseline values. Other statistical tests were performed using GraphPad Prism™ Version 4.02 for Windows (GraphPad Software, USA). Student's t-tests were used to compare differences in infarct volumes and oedema volumes between groups. Significant differences were accepted at the $p < 0.05$ level. Student’s t-tests were also performed on physiological parameters for illustrative purposes, to highlight changes from baseline and between treatment groups; $p$-values are reported with no correction for multiple comparisons. Unless otherwise stated, data is expressed as mean ± standard deviation (± SD).

**Results**
A total of 5 Long-Evans, and 10 each of hypothermia-treated and normothermic control, and 2 normothermic sham surgical Wistar rats were included. A total of 16 animals were excluded: 8 pre-randomization, 6 due to subarachnoid hemorrhage (SAH) detected at post mortem (1 Long-Evans), and 2 post-randomization due to malfunction of homeothermic heat mat (1 hypothermia, and 1 normothermia Wistar). Of the six SAH animals, three normothermic animals died, and SAH was detected at post mortem (including the excluded Long-Evans rat). Three hypothermic-treated animals survived to 24 hours, however SAH was
detected at post-mortem. In these animals, there was no significant difference in ICP at 24 hours compared to baseline values (8.3 ± 2.9 mmHg, v. 10.5 ± 4.7 mmHg, respectively).

**Infarct volume and intracranial pressure 24 hours post-stroke**

In Long-Evans rats (n = 5), mean oedema-corrected infarct volume was 84.3 ± 15.9 mm³ (range 61-105 mm³). ICP increased from 10.9 ± 4.6 mmHg at pre-MCAo baseline, to 32.4 ± 11.4 mmHg at 24 hours (Figure 1). In normothermic Wistar rats, oedema-corrected infarct volume was 31.3 ± 18.4 mm³ (Figure 4A). ICP increased from 6.7 ± 2.3 mmHg at baseline to 31.6 ± 9.3 mmHg at 24 hours (Figure 2B).

**Short duration hypothermia to 32.5°C prevents delayed ICP rise.**

Accurate temperature regulation was maintained in hypothermia-treated animals and controls (Figure 2A). Heart rate and respiratory rate were lower during hypothermia (Table 1). ICP traces revealed consistent pulse and respiratory waveforms. There were no major changes in ICP during the initial 6 hour monitoring, including during hypothermia. One animal had an 8.0 mmHg ICP rise during rewarming, to 15.5 mmHg at 6 hours. At 24 hours its ICP was 4.6 mmHg. There were dramatic increases in ICP at 24 hours in all normothermic animals. Intracranial pressure increased from 6.7 ± 2.3 mmHg at baseline to 31.6 ± 9.3 mmHg at 24 hours, whereas the ICP in hypothermia-treated animals was 5.4 ± 2.1 mmHg at baseline and 7.0 ± 2.8 mmHg at 24 hours. There was a significant main effect of treatment group, F(2, 17) = 31.87, p < 0.0001 (Figure 2B). There was no overlap in final ICP values between the two groups. This was despite equivalent core temperatures in the two groups at 24 hours, and for the preceding 18 hours (Figure 2A). Sham surgical animals showed no elevation of ICP.

There was no significant difference in mean arterial pressure between groups (Table 1). Therefore as predicted there was a significant main effect of treatment group on cerebral perfusion pressure at 24 hours, F(2, 16) = 14.73, p = 0.0002 (Figure 2C). There was significantly smaller mean oedema-corrected infarct volume in hypothermia-treated animals compared to normothermics (15.4 ± 11.8 mm³, v. 31.3 ± 18.4 mm³, p = 0.03). However among the normothermia animals there was no clear association between infarct volume and ICP. Oedema volumes calculated from histological sections showed a non-significant trend to be lower in the hypothermia-treated animals (2.8 ± 4.6 mm³, v. 17.1 ± 24.2 mm³ in normothermic animals, p = 0.08). Neurological deficit scores also showed a non-significant trend to be lower in the hypothermia-treated animals (2.5 ± 1.6, v. 2.2 ± 1.2 in normothermic animals, p > 0.05) (Figure 4B), however there was no association between neurological deficit scores and ICP (Figure 3).

**Discussion**

ICP is known to rise after large stroke, and hypothermia is well known to lower ICP (6). However this study has revealed several important novel results. First, quite dramatic elevations in ICP were seen following only small stroke in normothermic animals. Second, a short period of hypothermia early post-stroke had a prolonged effect moderating subsequent ICP long after rewarming. Hypothermia treatment completely abolished the dramatic rise in ICP seen at 24 hours in the normothermic animals, although no differences were seen between groups during the hypothermic interval.

The dramatic ICP elevations in normothermic animals were seen despite their small stroke sizes. Infarct and oedema volumes resulting from temporary MCAo were approximately 1/6th the maximal volume that can result from permanent occlusion in our hands, yet ICP elevation in the normothermic animals was dramatic. As already alluded to, we have been unable to
find data reporting ICP measurement 24 hours after small strokes, in either experimental animals or humans. Others have shown ICP elevation after moderate-large stroke in rat stroke models, peaking at 24-72 hours (5, 26). Baseline and post-stroke ICP values were similar to our results in the study that also monitored over the ipsilateral cortex (26), but lower in the study using infratentorial monitoring (5). ICP gradients between different cerebral compartments have been reported (27), so this may explain the apparent differences in measured pressures. Silasi et al. (26) reported ICP only in animals with massive infarction (228 ± 36 mm³). Kotwica et al. (5) studied a mixture of infarct volumes, though even the group with the smallest strokes in their study had reported hemispheric lesion volumes larger than those calculated from our data. Interestingly, Kotwica et al. (5), reported similar ICPs at 24 hours in the smaller and larger stroke groups, although some of the animals with larger strokes had a second, higher ICP peak at 3-4 days. The findings of the current study raise the question of whether the small volume of oedema seen could be responsible for such dramatic ICP elevation in the normothermic animals.

Oedema may have effects by increasing ICP post stroke, but may also have important effects through local swelling and mass effect, which may be associated with brain herniation and death after stroke (4). Schwab et al. (4) studied 48 patients with large hemispheric stroke, and reported that although significantly elevated ICP (>35 mmHg) reliably predicted death, clinical signs of brain herniation preceded ICP elevation in all 39 non-surviving patients in their study. This suggests that in patients with large strokes, dramatic ICP elevation may be secondary to brain herniation (due to mass effect), not its primary cause. One may then ask, if ICP elevation does not cause brain herniation, is it important? We believe so, primarily due to potential effects on cerebral perfusion pressure (CPP): the difference between arterial and intracranial pressure. Perfusion of peri-infarct regions supplied by collateral vessels is already compromised and normal autoregulation impaired, such that perfusion of the penumbra is CPP-dependent. Due to its effect on CPP, ICP elevation post-stroke could well be the mechanism for secondary ‘collateral failure’ and stroke-in-progression. Clearly, this possibility requires further investigation.

Our second key finding was that a brief period of hypothermia exerts a prolonged effect on ICP. This is not an intuitive concept and has not previously been investigated. Studies in other brain injury models have shown minimal effect of hypothermia on ICP in the early phase post-injury (28), as also seen in our study. However ICP was not measured at later times after rewarming. The effect of short-duration hypothermia that we observed appears to be a “switch-like” mechanism, which completely prevented ICP elevation at 24 h. The exact mechanism has not yet been elucidated, however it has obvious potential clinical importance.

The results raise the intriguing possibility that for the use of hypothermia after stroke, “less may be more”. Therapeutic hypothermia in patients has traditionally been administered for 12-72 hours and carries significant logistical and technical challenges. Rebound ICP elevation can be a significant problem, and prolonged rewarming protocols have been instituted in many studies to try to avoid this. Prolonged hypothermia is associated with a degree of immunosuppression. This and the sedative effects of shivering suppressant medication may be a particular problem in stroke patients, due to their increased risk of pneumonia. A recent early phase trial reported very high rates of pneumonia in hypothermia-treated patients cooled for 24 hours + 12 hours rewarming (11). Shorter duration cooling may reduce such complications, and most of the supportive experimental studies have shown neuroprotection with short duration cooling (29). There is a wealth of data showing that infarct size and functional outcome are significantly improved by short duration hypothermia.
at both early (24 hours) and later (3-days post-stroke) (30). In the large meta-analysis of animal experimental stroke hypothermia studies, of 145 experiments, the median cooling duration was 180 minutes. Interestingly, in that study, a post-hoc analysis indicated that shorter duration cooling may be associated with better neuroprotection (17). Despite being the only paradigm tried in human studies, prolonged hypothermia has only been investigated in relatively few experimental focal ischemia studies, and there is little easily interpretable data directly comparing short versus long duration hypothermia. Yamamoto et al. (31) showed neuroprotection with either 22 or 3 h cooling, but only when this was begun prior to stroke induction (31, 32). Colbourne et al. (32, 33) have conducted several studies showing effectiveness of long-duration cooling, and one showing long-duration cooling was more effective than short, however in that study the short duration group were cooled for 12 hours, significantly longer than in the great bulk of experimental hypothermia research (33). In contrast, Markarian et al. (34) found greater neuroprotection with longer durations of hypothermia, however the longest durations tested were 3-4 hours. The findings of the current study suggest that short duration hypothermia, the dominant paradigm used in successful experimental studies, should perhaps be subject to trial in patients.

There were some unavoidable limitations to this study. There were differences in intraoperative physiological variables (particularly reduced heart and respiratory rates) during the cooling phase. This is largely unavoidable in hypothermia, since heart and respiratory rates and anaesthetic requirement drop considerably during this therapy. However there is no known way these factors could account for the dramatic differences seen in final ICP. The measurement of ICP beyond 24 hours, although desirable, was beyond the scope of this study and will be the focus of future investigations.

In conclusion, short-duration moderate hypothermia commenced shortly after onset of experimental stroke, had a profound, sustained, neuroprotective effect, preventing subsequent ICP elevation. This approach would be easier to apply in patients than most currently used protocols, and would potentially avoid the problem of rewarming-induced ICP elevation. Further preclinical testing is required before clinical proof of concept studies. However, perhaps in the case of hypothermia following neurological injury, less is more?

Acknowledgements/ Funding
We would like to thank the Faculty of Health Stores Workshop of the University of Newcastle for manufacture of bespoke surgical and anesthetic equipment. This work was supported by a NHMRC Program Grant, #454417, and research support from the Hunter Medical Research Institute from funds donated by the Greater Building Society. N. Spratt received a NHMRC training fellowship, #455632. L. Murtha received a student grant from the National Stroke Foundation (Australia). D. McLeod and N. Spratt received a project grant from the National Stroke Foundation (Australia).
References

Table 1. Physiological Parameters

<table>
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<tr>
<th>Parameter</th>
<th>Pre-MCAo</th>
<th>2h Post-MCAo</th>
<th>6h Post-MCAo</th>
<th>24h Post-MCAo</th>
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<tr>
<td>Temp (°C)</td>
<td>Normo.</td>
<td>37.2 ± 0.4</td>
<td>37.2 ± 0.1</td>
<td>37.3 ± 0.1</td>
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<td></td>
<td>Hypo.</td>
<td>37.4 ± 0.3</td>
<td>32.7 ± 0.2*</td>
<td>37.2 ± 0.3</td>
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<td>RR (BPM)</td>
<td>Normo.</td>
<td>63.9 ± 13.8</td>
<td>58.4 ± 11.7</td>
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<td>HR (BPM)</td>
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<td>454 ± 42†</td>
<td>382 ± 28</td>
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<td>347 ± 107*</td>
<td>380 ± 22</td>
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<td>MAP (mmHg)</td>
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<td>96.9 ± 8.8</td>
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<td>pO2 (mmHg)</td>
<td>Normo.</td>
<td>162 ± 30</td>
<td>187 ± 31†</td>
<td>173 ± 29</td>
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<td>Hypo.</td>
<td>148 ± 29</td>
<td>167 ± 59</td>
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<td>SpO2 (%)</td>
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<td>pCO2 (mmHg)</td>
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<td>Glu (mmol/L)</td>
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<td>9.8 ± 1.1</td>
<td>11.6 ± 2.6</td>
<td>9.5 ± 1.6</td>
</tr>
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</table>

Temp = temperature; RR = respiratory rate; HR = heart rate; MAP = mean arterial pressure; pO2 = partial pressure of oxygen; SpO2 = oxygen saturation; pCO2 = partial pressure of carbon dioxide; Glu = glucose; *p < 0.05 versus normothermia; †p < 0.05 versus pre-MCAo.

Figure Legends

Figure 1. Intracranial pressure (ICP) at 0 hours and 24 hours post-stroke in Long-Evans (individual data points, mean and s.d.).
Figure 2. Temperature, ICP and CPP in Wistar rats. A. Temperature profiles of experimental groups during hypothermia or normothermia. B. Intracranial pressure (ICP) 0-6 and 24-25 hours post-stroke in hypothermia-treated (open circles) and normothermic rats (filled circles). The shaded region represents the cooling interval. C. Cerebral perfusion pressure (CPP) following stroke. CPP was calculated for each animal as arterial pressure minus ICP. *p < 0.0001 for t-tests between respective hypothermia (open circles) and normothermia (filled circles) groups.
Figure 3. Intracranial Pressure (ICP) versus neurological score in Wistar rats. Linear regression showed no significant correlation between ICP and neurological score for either group: normothermia $p = 0.44$, hypothermia $p = 0.94$.

Figure 4. Infarct volume (A) and neurological scores (B) in normothermia and hypothermia treatment groups in Wistar rats.