

# An experimental investigation of decompressive craniectomy in a rat model of hemispheric stroke treated with decompressive craniectomy

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## ABSTRACT

**Aims:** Acute ischemia can lead to severe edema in the brain, increased intracranial pressure and coma progression and death through cingular, uncal or tonsillar herniation in all the territories of the carotid artery. It is well established that cerebral and cardiovascular surgery patients benefit from decompressive craniectomy, although there is less data on how they do with regard to other forms of ischemia. In this study, we analyze the results of an experimental study on the decompressive craniectomy effects that occurs at various times after occlusion of the endovascular middle cerebral artery (MCA) in rats.

**Methods:** The endovascular occlusion procedure was done in 80 rats, resulting in focal ischemia. 4, 12, 24 and 36 hours after vessel occlusion decompressive craniectomies were done in 60 rats (each in groups of 15 rats). Decompressive craniectomy was not carried out on 20 specimens (control group). At day seven we used the number of infarcts and the neurological performance as endpoints.

**Results:** No animals infected with decompressive craniectomy died despite a mortality rate of 35 percent in untreated communities (mortality 0 percent). Both early or late treatment with a decompressive craniectomy dramatically improved neurologic function in both species. Compared to that animals that underwent endovascular occlusion of the per hour for 4 hours after their traumatic brain injury and did not have their brains decompressed, the infarction and neurological function showed statistically significant improvement after the 2 to 4 hours period ( $p < 0.01$ ) intervention. A new study has concluded that decompressive craniectomy care reduces mortality and increases the quality of life. Right after the outset of the formation of an occlusion, the infarct period is reduced. During a stroke treatment for head injury neurosurgeons may use neurochirons to decompress the brain.

**Conclusion:** Cerebral vascular insufficiency decompressive craniectomy works well after the vessel is clamped eliminates the infarction. Craniectomy performed within 4 hours of surgery will restore lives, neurological results are not improved or infarction levels are minimized just as effectively as craniectomy immediately after vessel occlusion. A randomized pilot study of the clinical support is provided for the concept of providing an immediate and aggressive treatment for those who have mid-grade internal carotid artery (ICA) and MCA occlusion neurosurgeons may play an important role in the treatment of patients with stroke by decompressive craniectomy.

**Keywords:** Craniectomy, cerebral infarction, ischemic cerebrovascular disorder, decompression

## INTRODUCTION

Ischemic cerebrovascular disorder, representing about 15 percent of all stroke casualties, represents the most common type of brain disease.<sup>1</sup> The MCA territory will trigger acute ischemia with a significant cerebral edema, high intracranial pressure and comatose and death in the worst-case scenario. While it has been established that isometrics, barbiturates and Tris buffers work to successfully treat ischemia-induced brain, none has been proved effective in the clinic.<sup>2,3</sup> While the treatment of large cerebellar infarctions with primary craniectomy is well established, retrospective, anecdotal case reports are available of only the treatment of patients for supratentorial ischemia. The preliminary results of an

open prospective trial were recently published to see how decompressive craniectomy affects mortality and morbidity. A time-dependent basis was found to reduce mortality and increase outcomes for patients with cerebral ischemia when a decompressive craniectomy was performed.<sup>4,5</sup> However this study only used 24 hours as a window period, following the occlusion of the MCA to carry out decompressive craniectomy after 1 and 24 hours have elapsed.<sup>6,7</sup> Craniectomy success is largely depends on the timing of the procedure. The optimal time for craniectomy, namely the removal of the cranium, remains undiscussed. Using an endovascular occlusion model, it was possible to examine how much of a decalcifying or

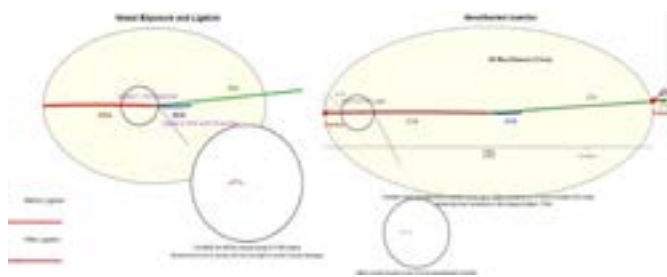
deoccluding craniectomy affected death, injury and the amount of oxygen or glucose deprivation in the endocrine system at different points after an occlusion of the cerebral vessels.

## METHODS

The study was initiated with the approval of the Ankara University Medical Faculty Local Ethics Committee for Animal Experiments (Date: 05.09.2022, Decision No: 34). All procedures were carried out in accordance with the ethical rules and the principles of the animal experiments.

The strain of 68-Wistar rats, whose brains measured 270 to 320 g, was used to cause focal ischemia by the occlusion of the intraluminal suture discovered by Koizumi and colleagues. The study passed the animal safety committee. The anesthetics, xylazine (1.5 mg/100 g) and ketamine (4 mg/100 g) were given I/M to rats and before the start of procedure they were freely given water and food. The pH, hematocrit, partial pressure of O<sub>2</sub> and CO<sub>2</sub> levels were all held constant with a femoral artery catheter while doing surgery. To maintain the body temperature of the process, a heat-controlled heating pad held the rectal temperature at 37 degrees Celsius.

To occlude the OSA, a medium neck incision was made, exposing the right ECA and right CCA were exposed. This surgical procedure is illustrated in three main phases in the figure: placing the animal in a surgical position and making an incision on its skin as the first step; exposure and ligation of vessels during the second step where distal ECA and CCA were ligated while arteriotomy was performed; thirdly this illustrates proper placement through CCA arteriotomy of 4/0 nylon monofilament with silicone tip into ICA. In this operation, the filament extended to ACA such that it blocked PCA as well as origin of OSA. Additionally, these processes are visually indicated by means of diagram (Figure 1)



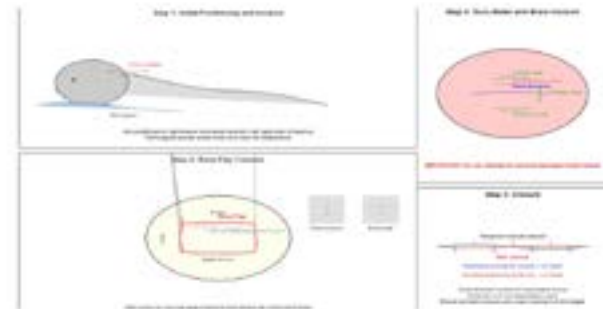
**Figure 1.** Vessel exposure, ligation, and monofilament insertion

Through a mid-neck incision; the right external carotid artery (ECA) and right common carotid artery (CCA) are exposed to occlude the MCA. To avoid bleeding, the CCA was ligated loosely distal to the arteriotomy with 4/0 silk and then the neck wound was quickly closed.

Decompressive craniectomy was carried out in four major stages: First, the animals were placed on their right side with their heads resting on cushions. The skin cut was approximately 3 cm long and situated over the right temporal muscle. Secondly, a bone flap of width 0.9cm, length 3cm and depth of 0.5cm was created. Thirdly a incision was made on the dura mater to reach the frontal and temporal lobes of the brain but it did not involve removing any brain tissues. Lastly, absorbable

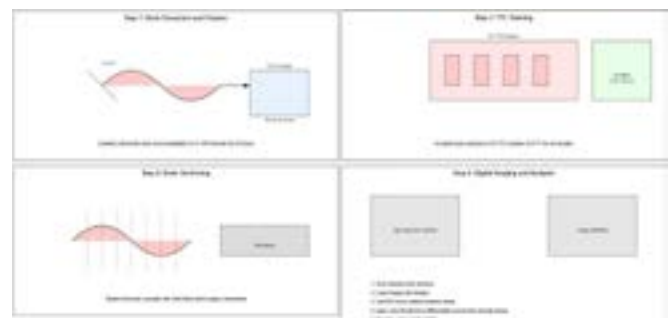
sutures closed up both the temporal muscle and skin. These steps are shown in detail in Figure 2 below.

20 animals haven't received any treatment since occlusion of MCA (Group A: control group). The right cerebral hemisphere in 60 rats was decompressed surgically by performing a craniectomy. At 4 hours in Group B, at 12 hours in Group C and subsequently at 24 and 36 hours in Groups D and E after MCA decompressive craniectomy was done. The 80 animals have been randomly divided among the various control and treatment groups (and assigned letters) by a computer-generated randomization method. At the end of the procedure, the temporal muscle and skin were closed.



**Figure 2.** Surgical steps for decompressive craniectomy: positioning, incision, bone flap creation, dura mater incision, and closure

The ischemic study's brain tissue preparation and analysis were carried out in four steps: The first step involved removing the brain, which was then placed into a 10% formalin solution immediately for fixation lasting 24 hours. Afterward, the fixed brain was sliced using a micro-saw to create 2 mm thick sections during the second step. Subsequently, sectioned pieces of brains were incubated at 37°C for half an hour in TTC (2,3,5 triphenyl tetrazolium chloride) solution- this is third stage. Finally involved digital imaging and analysis where infarct areas are measured while total volume is calculated using these pictures. These steps are visually represented in figure 3 that gives visual representation for each step (Figure 3).



**Figure 3.** Brain tissue preparation and analysis: extraction, fixation, sectioning, TTC staining, and digital imaging

All of the surviving animals have been observed for 7 days to see whether they still have a neurological activity and their weight has been recorded according to a previously known protocol of Bredesen et al and has been standardized by Menzies and colleagues' (Table 1). All animals with ketamine and xylazine had been re-anesthetized and decapitated at the end of day seven. Their brain has been quickly cut and the 2 mm brain

slices have, before being fixed in a 10 per cent buffered formalin solution, been incubated for 30 minutes at 37°C in 4 percent solution of 2,3,5 triphenyl tetrazolium chlorides (TTC). When exposed to TTC, the normal tissue of the brain (with cellular membranes intact) becomes red and necrotic tissue becomes rosy and grey. The TTC has stained and then photographed five of the brain parts of each species. Once digital images have been captured, the infarction areas are measured using a monitor and software (1.41 IMAGE; Bethesda, Wayne Rasband, National Institutes of Health, MD). In each slice, an ischemic brain region is present and two millimeters of infarct volume has been stained for inflammation. At the time of the craniectomy, two of the writers who were not known about the decompressive craniectomy have made calculations and measurements. Evaluation was done twice, once on each side of the brain section and the average values were taken. Recent work by Lin et al. states that to prevent a misinterpretation of the severity of infarction, a correction factor must be calculated by contrasting the infarct hemisphere to a similar-sized non-infarcted volume.

Table 1. Neurological activity with scores

Score	Evaluation criteria
0	No obvious deficits
1	Flexion of contralateral forelimb
2	Diminished contralateral forelimb grip while animal is dragged by the tail
3	In all directions; spontaneous movement and contralateral circling solitary if animal is pulled by tail
4	Spontaneous contralateral circling
5	Demise

Study data was compiled on a PC (off-the-shelf, Stat View was used) with off-the-shelf, cost-effective software (Brain Inc. for the results) (Macintosh Quadra, Apple Computer Inc., Cupertino, CA). The Chi-square and the Kruskal-Wallis test were used to determine the rate of ischemia and test for neurological impairment. Since the probability was below 0.05, this was deemed significant

## RESULTS

In all of the intraoperative physiological parameters, there were no statistically significant variations between the five classes. The average body temperature of all animals was found to be 37.1°C ± 0.6°C (mean ± standard deviation). The arterial blood concentrations (PO<sub>2</sub> 125 ± 36 mm Hg; PCO<sub>2</sub> 34 ± 3.1 mm Hg; pH 7.40 ± 0.03) and hematocrit values have no significant changes.

### Mortality Rate

The 8 out of the 20 animals in the test group had a 40 % mortality rate from MCA of 24 to 48 hours of the procedure. Without exception, during the entire observation period, all the animals that underwent decompressive craniectomy survived, whether the procedure was performed early (4 hours after) or late (24 hours after) (mortality rate 0 percent). A few weeks/the subsequent few weeks a substantial difference existed between these two classes as shown by significant differences (p<0.01).

### Body Weight

Animal weights decreased in the study at the end of the week, the average weight of Group A was significantly lower than that of Group D (p<0.001). The findings are as a comparison of these weight shifts. Average neurological score of 3.8 after

7 days was obtained from the control group (group A). The average score for very early craniectomies (Group B) was 1.8; the score for animals that had a craniectomy was 2.4, 2.6, and 2.8 after 12 hours (Group C), 24 hours (Group D) and 36 hours (Group E). There has also been a statistically important difference between animals regulated and untreated (p<0.001), Groups B and Groups C, D and E (p<0.001). Table 2 shows the estimated infarction volumes for various treatment classes. The infarct volumes were slightly smaller than those of the animals who had early craniectomy at 4 hours. Craniectomy 12 hours or less is associated with lesser infarctions compared to no craniectomy. Infarctions occur due to the lenticulostriate arteries seen in all animals irrespective of treatment. Patients that were treated in the control unit and in the later stage of the disease had more cortically localized, rather than larger infarctions (Groups C-E).

Table 2. The estimated infarction volumes for various treatment classes

Group	Infarction volume (mm <sup>3</sup> )	p value
A (20 rats)	185 ± 17.1	<0.002 vs. B Group
		<0.11 vs. C Group
		<0.7 vs. D Group
		<0.6 vs. E Group
		<0.00 vs. C Group
B (15 rats)	110 ± 10.90	<0.003 vs. D Group
		<0.006 vs. E Group
		<0.24 vs. D Group
C (15 rats)	148 ± 9.90	<0.26 vs. E Group
		<0.78 vs. E Group
D (15 rats)	170 ± 12.50	
E (15 rats)	171 ± 19.80	NA

When the body weights and neurologic scores of the animals in the experimental groups were analyzed, it was found that the neurologic scores of the groups that underwent decompressive craniectomy in the early period (Groups B, C, D and E) were significantly lower than the control group (Group A). While the mean neurologic score was 3.8 in the control group (Group A), this score was 1.8 in Group B, which underwent craniectomy after 4 hours. After 12 hours, the mean neurologic score was 2.4 in Group C, 2.6 in Group D after 24 hours and 2.8 in Group E after 36 hours. In addition, while the mean body weight of the control group was 270±15.2 g, these values were slightly higher in the treatment groups. These data suggest that early decompressive craniectomy contributes significantly to neurologic recovery (Table 3).

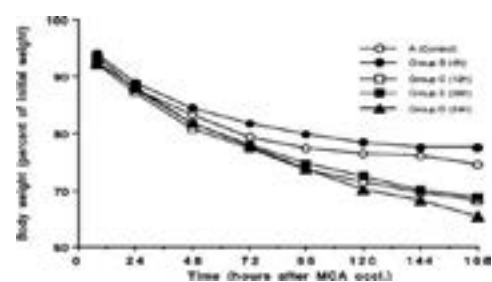


Figure 4. Changes noticed in the weight of treatment versus control group after occlusion of MCA in rats during the 168 hours

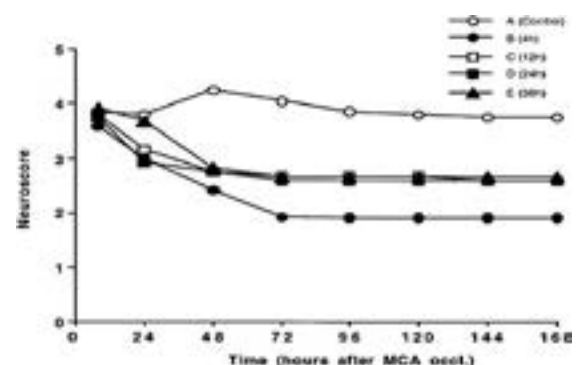


Figure 5. Changes noticed in the neurological score of treatment versus control group after occlusion of MCA in rats during the 168 hours



Table 3. Body weight and neurological scores of experimental animals

Group	Mean body weight (g)	Standard deviation (g)	Mean neurological score	Standard deviation	Statistical significance (p value)
A (Control)	270 ± 15.2	15.2	3.8	0.5	Reference Group
B (4 hours)	290 ± 14.8	14.8	1.8	0.3	<0.001 (vs. Group A)
C (12 hours)	280 ± 13.5	13.5	2.4	0.4	<0.001 (vs. Group A)
D (24 hours)	275 ± 16.0	16.0	2.6	0.4	<0.001 (vs. Group A)
E (36 hours)	272 ± 17.1	17.1	2.8	0.5	<0.001 (vs. Group A)

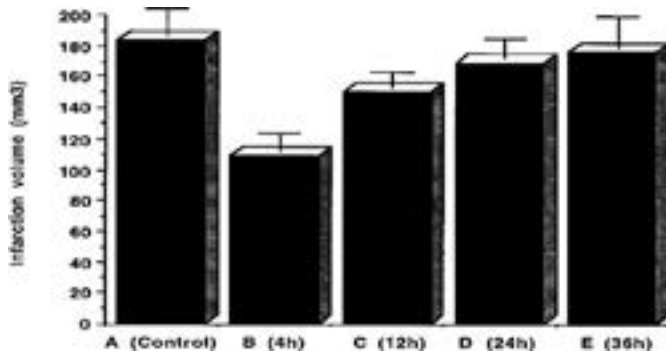


Figure 6. Changes noticed in the infarction size of treatment versus control group after occlusion of MCA in rats during the 168 hours

## DISCUSSION

In 10-15 percent of supratentorial infarctions, large hemispheric infarctions affecting the whole area of the MCA may be associated with extreme brain swelling and death as a result of brain edema. This malignant hemispheric infarction is caused by embolic ICA or proximal (M1) occlusion with inadequate collateral flow and early-brain edema around the entire MCA region or a larger area (ACA and PCA regions, in severe cases). Hacke et al<sup>8-9</sup> indicated that the death rates ranged between 30% and 66% in unselected groups of MCA patients and their locations; patients who had developed a malignancy of the hemisphere were 80% mortal. The malignancy of an ischemic lesions must be identified within the first hours of symptoms in order to provide a prompt and likely successful treatment. The prediction of patients with malignant hemangioma comes as a surprise to researchers and healthcare practitioners alike. Where a person has had a subarachnoid, he or she is more likely to be in a coma. However, the characteristics of computerized tomography (CT) may well be closer to perfection. In a prospective research by Kummer et al.<sup>9,10</sup>, that finds that “neoplastic” hypo-sign on CT-scan is 85 % certain if the rest of the parenchyma lodges in the MCA territory, find it is (European Cooperative Clinical Study) hematoma was the leading cause of death for those who had undergone the interventional treatment, occurring in 7.3% of the right group of the patients and 4.9 % of the control group within the first seven days. The prognostic of the initial nerve deficiency is directly proportional to hemiplegia and reduced awareness indicate a bad result. Altered sense is the same prognosis factor as younger, less atrophic brains that have generalized atrophy are less likely to resist swelling than brains.<sup>11,12</sup> Intubation treatment, artificial ventilation and antimicrobial drugs are normally ineffective in preventing fatal hernia. Decompressive craniectomy as an alternative for such cases has been suggested and may save lives.<sup>13,14</sup> The numbers can all be used to make various combinations. One of the oldest neurosurgical principles is the removal of a portion of the cranial vault to alleviate intracranial pressure.<sup>15</sup> The palliation of high ICT

caused by tumors that cannot be traced by available neurodiagnostic techniques was one of the first signs of the treatment.<sup>14</sup> Harvey Cushing used a sub temporary technique to describe cranial decompression in a landmark article published in 1905. However the beneficial effects of decompressive craniectomy in patients with massively supratentorial edemas caused by head trauma remain debatable since decompression may lead to progression of edemas.<sup>15-16</sup> Kondziolka and Fazl found that craniectomy was a life-saving treatment in a small group of 5 stroke patients.<sup>17</sup> 3 patients with large hemispheric infarctions recovered after craniectomy, according to Rengachary and colleagues but 2 of them had significant focal neurological deficits. 4 patients received decompressive craniectomy and unsustainable brain resection by Kalia and Yonas with good clinical outcomes for all 4 patients. Earlier research was purely retrospective and anecdotal. Latest prospective studies in 53 patients with malignant hemispheric infarction have shown that decompressive hemicraniectomy decreased mortality and morbidity and suggested the immediate start of intensive surgical therapy.<sup>18</sup> On the other side, there is also a debate about the best time for decompressive surgery. To date the effectiveness of decompressive craniectomy in acute stroking has only been observed for some time now. Experimental focal cerebral ischemia may require a craniectomy to explain Tamura et a first's model of focal ischemia. We are unable to determine whether the findings of the study apply to a control group because of the craniectomy. Conversely, on the other hand, embolic models do not involve a brain operation, but the sizes of the infarcts do differ widely, making it difficult to measure the outcomes of the surgery.<sup>19,20</sup> An endovascular occlusion, which was discovered by Koizumi et al<sup>21</sup> and refined by many others in the next decades, was almost entirely effective in human beings as well when correctly placed, the intralaminar should follow the ACA. As a result, a major ischemic lesion has developed from the ICAs, ACAs and PCAs, there has been significant hemispheric ischemia. In our sample, mortality rates were 0 % for each animal treated with decompressive craniectomy compared with 40 % for the control group. In the control community, several animals died within 24-48 hours of the occlusion. We were perplexed by the absence of deaths during the 36 hours cohort but as shown by the reduction in TIA complications after 72 hours occlusion, we conclude that it was due to the life-saving efficacy of a safe craniectomy after MCA or TAC. None of the 80 animals was randomly placed in one of the 5 treatment groups (Groups A-E). The conversion, which prevents uncalled herniation, of the cranium from a “closed” cavity is most likely to be responsible for the decrease in mortality.<sup>22</sup> A decline in infarction in animals treated early on and better neurologic results were the most striking results for our current study (Group B). There was a differential difference in Group C relative to Group D, (Fig. 3). While the medication was successful, it did not save the patient's life. All the animals

treated were much higher than untreated animals in terms of their neurological score and behavior (Group A), (Figure 2). Animals of groups C to E have lost 35 % of their body weight in the course of time, probably due to the stress of an aesthetic and surgery for the second time, while animals of groups A and B have lost just 25% of their body weight (Figure 1). Since TTC staining is ineffectual so long after death, untreated Group A animals that died of herniation before day seven could not calculate the infarction scale. It is much more likely that the difference in infarcts is what accounts for the significant disparity between treated and untreated animals in this population, rather than the actual infarct size. In the territory of the lentic arteries, all the findings are of ischemia. When the cerebral ischemic endovascular model is applied, this is the brain region is more impaired. Patients with a large leptomeningeal blood supply normally experience only human subcortical infarction near M1 occlusions.<sup>23,24</sup> The link between human blowing and our animal model supported the hypothesis that the most common reason for decompressive craniectomy is the better performed, leptomeningeal collateral vessels. Hemicraniectomy is a straight forward procedure that can be done with minimum auxiliary help in any community hospital, which is an important benefit because of the fact that the leading cause for death is cerebrovascular disease in the USA. One dilemma facing clinicians is how long conservative treatment should be given before decompressive craniectomy is taken into consideration.<sup>25</sup> Decompressive craniectomy should not be delayed long, as it can result in irreversible brain stroke improvement, such as dural hemorrhages, although it is unclear how well craniectomy is. Shaw and associates suggested in 1959 that vasogenic brain swelling in humans is responsible for the early mortality following a heart attack typically occurs within 2 to 5 days. In most patients, brain herniation is observed within 48 hours of the ischemia start. The edema peak is normally seen in rats during the first 24 to 48 hours, but not always in human times. As a result of this, our findings cannot provide a conclusive answer to the question as to when craniectomy is done in humans, along with other experimental studies. After the vessel was fully blocked off, we conducted four decompressive procedures 4 hours, 12 hours and then once again 24 hours later. Cranial infarction was found to be statistically important and those which received their treatment at the earlier or later stages showed greater signs of the disease than those left untreated (after 24 and 36 hours).<sup>26,27</sup> So the results from experiments with rats should not be applied to humans (as discussed above). Caution should always be used when applying results of animal experiments to humans. Studies of human patients with a controlled experimental design are needed in order to test the efficacy of decompressive craniectomy in humans. Most rat studies cannot definitively determine the extent of neurological disorders because of their high level of sensitivity to various environmental factors. The true significance of rodent mortality clearly exceeds that of human mortality.<sup>28</sup> The ultrasound results coupled with their

appearance on a computerized tomography (CT) scan are more sensitive in detecting these (inferior) is chemotherapy earlier on the road to the disease process of thrombosis.<sup>29</sup> Future randomized trials would need to examine the prognostic factors in order to determine criteria for craniectomy in patients.

## CONCLUSION

Cerebral vascular insufficiency decompressive craniectomy works well after the vessel is clamped eliminates the infarction. Craniectomy performed within 4 hours of surgery will restore lives, neurological results are not improved or infarction levels are minimized just as effectively as craniectomy immediately after vessel occlusion. A randomized pilot study of the clinical support is provided for the concept of providing an immediate and aggressive treatment for those who have mid-grade ICA and MCA occlusion neurosurgeons may play an important role in the treatment of patients with stroke by decompressive craniectomy.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was initiated with the approval of the Ankara University Medical Faculty Local Ethics Committee for Animal Experiments (Date: 05.09.2022, Decision No: 34).

### Informed Consent

Because the study was designed as an animal experiments, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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