Xenon Enhanced CT for Analysis of Cerebral Integrity, Perfusion, and Blood Flow

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SUMMARY  Enhancement of the brain substance for CT evaluation using inhaled Xenon is confirmed. This technique was applied to the study of the normal and the embolized adolescent baboon. Healthy cerebral tissue enhances symmetrically, while abnormal areas show significantly diminished enhancement. At maximal enhancement, an indication of gross comparative cerebral perfusion is obtained. By obtaining serial CT scans over a 10 minute time interval, the clearance rate of Xenon (cerebral blood flow) may be evaluated. Xenon-enhanced CT enables a visual and numerical analysis of both brain morphology and physiology.

 SINCE THE INITIAL application by Kety and Schmidt, various techniques to measure cerebral blood flow have been utilized with varying success. Although intra-arterial methods appear reasonably reproducible, they may be difficult, time-consuming and morbid. Inhalation techniques, though far less invasive, present difficulties in data analysis due to recirculation and extracranial activity. All radionuclide methods, whether done by intra-arterial injection or inhalation, are limited by the non-morphologic nature of isotope studies. This makes it difficult to distinguish precisely which brain locality has produced the externally detected activity.

The introduction of cranial computed tomography (CT) has enabled accurate morphologic definition of the brain and its surroundings. As the iodinated contrast agents routinely used for intravenous CT enhancement do not diffuse into the brain substance, they are not ideal for the measurement of cerebral blood flow. CT enhancement may also be obtained using diffusible Xenon administered by inhalation. Thus, problems generated by the third component of circulation are readily overcome by CT imaging. This preliminary study will describe a CT technique to define cerebral perfusion and cerebral blood flow in the nonhuman primate as monitored by Xenon-enhanced CT.

Methods

Experimental Subjects

Cerebral blood flow measurements were obtained on 2 adolescent baboons (Papio anubis/cynocephalus) weighing 7.8 and 8.6 kg. One animal was a healthy control with no evidence of neurologic dysfunction. The second baboon was studied 103 days following successful embolization of the left middle cerebral artery via injection of a silastic-tantalum embolus (205PE) through the left internal carotid artery. The position of the embolus was monitored by CT (fig. 1) as well as by cerebral angiography. The baboon was clinically evaluated daily after the embolization.

Anesthesia

General anesthesia was used for all CT (including cerebral blood flow) studies. Following sedation with 8 mg of phenytoin (Seralyn*), endotracheal intubation with auffed tube was carried out. Anesthesia was induced with a halothane (4%)-Oxygen (100%) mixture by face mask. Halothane (1%) was given throughout the scanning procedures to keep the animal immobile. Continuous cardiac and respiratory monitoring was routine.

Serial CT

Serial CT scans were performed 4, 7, 10, and 45 days following embolization of the left middle cerebral artery both with and without intravenous contrast enhancement. Another CT scan (with no intravenous contrast) was done just prior to the cerebral blood flow study (day 103). CT was performed just before the cerebral blood flow study in the healthy control baboon.

An EMI 5005 head-body scanner with a 320 X 320 matrix and 13 mm collimation was used. Scanning time for each slice was 40 seconds and the scans were done at 32 ma and 120 Kvp. A scan angle of 0 to 5% above the orbitomeatal baseline was routine. Head movement was not a problem with adequate anesthesia. Careful packing of the head was done with bolus bags.

Xenon CT Cerebral Blood Flow

Anesthesia with halothane was carried out as described above using a Harvard respirator on a closed rebreathing ventilation circuit. A baseline CT scan was performed choosing a section where the frontal horns of the lateral ventricle were seen to advantage. A multi-channel analyzer (Corning) was used to measure PaO₂, PacO₂, and pH drawn from an arterial line and the O₂ content of the expired air at baseline and during serial scanning.

A 100% Oxygen-1% halothane mixture (5 liter flow rate) was inhaled by the baboon until the nitrogen was almost entirely washed out of the respiratory system as determined by an oxygen concentration in the expired air of greater than

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*Corning Medical Diagnostics, Medfield, MA.
FIGURE 1. Embolus, Left Middle Cerebral Artery. A silastic-tantulum embolus (arrow) is seen by CT in the location of the horizontal portion of the left middle cerebral artery. Angiography confirmed the presence of the embolus completely occluding the horizontal middle cerebral artery.

95%. Commercial (non-radioactive) Xenon was then added to the system. A concentration of approximately 80% Xenon was attained as estimated from the decrease in the measured oxygen concentration.

When the Xenon concentration equilibrated at 80%, an immediate CT scan (maximum Xenon) was performed at the same section level as the baseline. The inhalation of Xenon was then abruptly discontinued and replaced by the inhalation of 100% oxygen (5 liter flow rate). As the Xenon was washing out, serial CT scans (at the same cut level) were performed at 0.3, 2.0, 3.7, 5.4, 7.1, 8.8, and 10.5 minutes following discontinuing Xenon inhalation, i.e., 2.0 minutes means a scan was begun at 1 minute and 40 seconds and completed at 2 minutes and 20 seconds.

A matching image region in the anterior left and right hemispheres, including gray and white matter, was then compared both by visual (various window settings) and numerical (print-out averaging) methods to evaluate brain enhancement with Xenon. The mean and histogram were obtained from comparable 95 to 100 voxel regions in each hemisphere. These same regions were studied on each of the successive serial CT scans to produce a Xenon clearance profile. Cerebral blood flow (ml/100 gm per minute) was then analyzed by two methods:

1. \[
    \text{CBF} = \frac{(\Delta H)}{(\Delta A)} \times \frac{(0.693 \times 100)(\lambda)}{(T_n)}
\]

The partition coefficient of Xenon (\(\lambda\)) was based on the hemoglobin level. No correction was made for recirculation, \(\text{Paco}_2\), phencyclidine HCl sedation, or halothane (1%) anesthesia.

Results
Baseline CT and Neurologic Condition
The baseline CT scan and neurologic status of the healthy, control baboon were normal. The successfully embolized baboon (embolus in horizontal portion of left middle cerebral artery) never showed any abnormality in his neurologic examination. The serial CT scans at 4, 7, 10, 45, and 103 days were repeatedly normal (fig. 2).

Xenon Brain Enhancement
In the control animal, the maximum CT enhancement at approximately 80% Xenon concentration was symmetric in the two cerebral hemispheres (table 1). Both deep and superficial brain substance seemed to enhance to the same degree at this level of Xenon inhalation. In the embolized baboon, there was definite asymmetrical enhancement of the two cerebral hemispheres at 80% Xenon concentration. The non-embolized right hemisphere had a maximal enhancement of 11.0 EMI units above baseline. The left hemisphere in the distribution of the left middle cerebral artery, both superficial and deep, showed diminished maximal enhancement (9.4 EMI units) as compared to the right. A small area in the left opercula region had an enhancement of only 7.8 EMI units. This poorly enhanced region was accentuated on the delayed (3.7, 5.4, 7.1, and 8.8 minute) serial washout scans (figs. 3, 4).

Cerebral Xenon Clearance
The cerebral clearance curves for Xenon were similar in both animals as calculated by both compartmental (TV4) and stochastic (H/A) methods (table 1). Due to scanner speed and processing limitations, only 3 early scans (Maximum, 0.3 and 2.0 minute) were available for the evaluation of the fast component of Xenon clearance (washout). Nevertheless, a distinct fast and slow component of cerebral blood flow was readily demonstrated (table 2). In addition, stochastic analysis defined the combined gray and white flow as similar in both hemispheres of both baboons. Using measure mode (WW 0, WL 27) reproductions, a visual assessment of the Xenon washout was also readily obtained (fig. 4).

Gas Analysis
The Paco2 and expired air O2 were never lower than 78 torr when breathing pure Xenon thus reflecting some leakage in the inhalation system. This was not of consequence as an approximately 80% Xenon concentration was more than adequate for CT enhancement and washout observations. In both baboons, the serial blood gas measurement made at the time of each washout CT scan showed a progressive increase in Paco2 and expired O2 concentrations (table 1). This increase in O2 reflects the decrease in Xenon concentration and coincided with the diminishing attenuation coefficient noted by CT scan. The Paco2 remained fairly constant in an essentially physiologic range (table 1).

Discussion
One of the early limitations of CT scanning was its primarily anatomic orientation. However, with the use of intravenous contrast enhancement, physiologic information can be derived. It has also been suggested that cerebral
TABLE 1A  WNL Objective Findings with Xenon CT Studies

<table>
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<tr>
<th>Baboon #1</th>
<th>WNL Serial CT, WNL Clinical, No embolus</th>
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<tr>
<td></td>
<td>Left¹</td>
<td>Right¹</td>
<td>PaCO₂</td>
<td>PaO₂</td>
<td>pH</td>
<td>Expired O₂</td>
<td>HB</td>
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<td>Baseline</td>
<td>17.8</td>
<td>18.0</td>
<td>37.2</td>
<td>451</td>
<td>7.38</td>
<td>632</td>
<td>13.2</td>
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<td>Maximum (75-80% Xenon)</td>
<td>28.1</td>
<td>25.3</td>
<td>36.0</td>
<td>108</td>
<td>7.45</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>0.3 Minutes</td>
<td>27.5</td>
<td>27.3</td>
<td>37.3</td>
<td>326</td>
<td>7.44</td>
<td>521</td>
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<tr>
<td>2.0</td>
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<td>32.9</td>
<td>395</td>
<td>7.45</td>
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<td>33.8</td>
<td>416</td>
<td>7.41</td>
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<td>5.4</td>
<td>20.6</td>
<td>20.7</td>
<td>35.6</td>
<td>432</td>
<td>7.49</td>
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<td>418</td>
<td>7.38</td>
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<td>10.5</td>
<td>19.4</td>
<td>18.8</td>
<td>41.8</td>
<td>494</td>
<td>7.38</td>
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<tr>
<td>rCBF¹ Brain (H/A)</td>
<td>30.9</td>
<td>33.5</td>
<td></td>
<td></td>
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<tr>
<td>rCBF¹ Slow (T³/₂)</td>
<td>21.3</td>
<td>27.7</td>
<td></td>
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<tr>
<td>rCBF¹ Fast (T³/₂)</td>
<td>49.1</td>
<td>53.6</td>
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1. Expressed in EMI units (mean of specified voxel region).
2. ml/100g/min.

TABLE 1B  Objective Findings with Xenon CT Studies

<table>
<thead>
<tr>
<th>Baboon #2</th>
<th>WNL Serial CT, WNL Clinical, Embolus left MCA</th>
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<td>Right¹</td>
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<td>PaO₂</td>
<td>pH</td>
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<td>HB</td>
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<td>32.6</td>
<td>481</td>
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<td>653</td>
<td>12.7</td>
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<tr>
<td>Maximum (80-85% Xenon)</td>
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<td>27.4</td>
<td>29.3</td>
<td>78</td>
<td>7.45</td>
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<td>0.3 Minutes</td>
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<td>3.7</td>
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<td>5.4</td>
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<td>20.6</td>
<td>35.1</td>
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<td>7.1</td>
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<td>656</td>
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<tr>
<td>rCBF¹ Brain (H/A)</td>
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<tr>
<td>rCBF¹ Slow (T³/₂)</td>
<td>27.7</td>
<td>26.4</td>
<td></td>
<td></td>
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<tr>
<td>rCBF¹ Fast (T³/₂)</td>
<td>62.0</td>
<td>51.5</td>
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</tbody>
</table>

1. Expressed as EMI units (mean of specified voxel region).
2. ml/100g/min.

Blood volumes may be measured using intravenous enhancement. However, intravenous water-soluble contrast agents are not freely diffusible into the brain substance and are thereby inadequate for the evaluation of cerebral blood flow. Intrathecal contrast enhancement with metrizamide (Amipaque, Sterling-Winthrop Research

TABLE 2. Xenon Enhanced CT Analysis of Cerebral Blood Flow (Compartmental Analysis)

A comparison of the blood flow curves in the right (no embolus) versus the left (embolus horizontal MCA) hemisphere using semilogarithmic analysis of the information in Table 1B and Figure 4. Although maximal perfusion of the right side is greater than the left, calculated cerebral blood flow (fast and slow component) was very similar.
FIGURE 3. Baseline CT (Before Xenon Enhancement) A. A CT section of the level of the lateral ventricles photographed at WW75 and WL28. B. A specimen radiograph of a baboon at a similar level to CT section plane showing the normal anatomic structures. C. The same CT section as in A now photographed using measure mode and WL27. D. A reversal photograph (measure mode, WL27) of Figure 3C (Baseline for Figure 4).

FIGURE 4. Cerebral Perfusion and Flow by Xenon CT Serial CT scans (measure mode, WL27, reversal photograph) of the anterior half of each cerebral hemisphere at precisely the same section level as the baseline (fig. 3) were performed at measured time intervals during Xenon washout with oxygen. The described window settings will show volume elements containing material of 27 EMI units or greater as black.

The diminished Xenon enhancement in the left middle cerebral artery distribution (embolus horizontal left MCA, fig. 1) as compared to the right is evident on all scans indicating diminished perfusion. The progressive diminution of Xenon enhancement in both hemispheres over a 10 minute clearance (washout) interval is readily demonstrated even by visual analysis of the scans. The complimentary numerical data (table 1) permits the calculation of cerebral blood flow.

Institute may enable the dynamic evaluation of the cerebrospinal fluid (CSF) circulation and the CSF-brain barrier. 11-13 Xenon, an inert gas with an atomic number of 54, is freely diffusible into the gray and white matter of the brain. Xenon is readily exchanged between blood and tissue and highly soluble in fat. Commercially available, non-radioactive Xenon is faintly visualized by conventional radiographic techniques and prominently seen using CT scanning. 6 This gas also has a definite anesthetic effect if given in sufficient concentrations. 14-15

Xenon has proven to be an important radionuclide for the evaluation of cerebral blood flow. The most consistent data are derived from the intracarotid injection of the radioisotope with interpretation of serial washout information using a modification of the Kety-Schmidt formula. 1 Inhalation techniques, 4-16 although requiring far more complex manipulation of information, appear to supply similar results with lower morbidity. Compartmental analysis enables the separation of the brain washout curve into 3 basic compartments using inhalation methodology; fast (predominantly gray matter washout), slow (predominantly white matter washout), and slower (predominantly extracerebral sources).

Actual brain imaging using radionuclides requires cyclotron-produced radionuclides introduced by intracarotid injection. 17, 18 Even with adequate collimation, the morphologic resolution of radionuclide techniques seems extremely limited when compared to CT scanning. Since non-labelled Xenon readily enhances the brain substance by freely diffusing across the blood-brain barrier, CT scanning provides a simple and reliable method for monitoring this enhancement. The presence and rate of clearance of Xenon from small regions of gray and white matter may be monitored by knowing the anatomy of the brain as defined by the CT scan. Even prior to the utilization of the numerical CT data, a visual analysis can separate the faster gray matter washout from the slower white (fig. 4) as well as compare the Xenon enhancement of the right versus the left hemisphere.

Xenon-enhanced CT scanning appears to have 3 basic
applications: (1) evaluation of capillary-brain tissue integrity, (2) evaluation of gross comparative cerebral perfusion, and (3) evaluation of cerebral blood flow.

1. A baboon with a cerebral embolus had repeatedly normal CT scans and clinical examinations. However, a Xenon enhanced CT scan revealed a small area of minimally perfused brain in the opercular region. The location of the abnormality was consistent with the characteristic location of infarction in the baboon following occlusion of the middle cerebral artery as documented by previous CT scan and pathologic studies. Therefore, Xenon-enhanced CT scanning appears to be an important adjunct to routine and enhanced CT scanning, especially when subtle tissue abnormalities of either gray or white matter are sought.

2. A symmetrical, bilateral, total regional brain perfusion should occur in a normal primate. The deep and superficial diminished enhancement in the distribution of the embolized left middle cerebral artery is expected even though the leptomeningeal anastomosis aids in the perfusion of a non-human primate hemisphere with vascular compromise. Thus, a simple technique is now available to evaluate the gross perfusion of comparable areas of the same brain. Potential applications include the evaluation of transient ischemic attacks, surgical vascular procedures, cerebral autoregulation, and cerebral edema.

3. The cerebral blood flow estimations as calculated using serial Xenon-enhanced CT scans correlated closely with those reported for baboons using the hydrogen clearance method. The findings of normal cerebral blood flow with chronic infarction in the baboon has been previously reported. The analysis obtained more accurately (i.e. consistent with previous nonhuman primate studies of cerebral blood flow) reflects the slow component of flow. This, however, is merely a limitation of scanner speed and the smallest size of a region of brain from which an accurate mean of attenuation coefficients may be obtained. Scans will be performed in from 2 to 10 seconds with newer CT scanners. This should enable the acquisition of multiple attenuation values during the initial 2 to 3 minutes permitting a more significant fast component analysis. The extracranial Xenon flow is obviously not a problem as CT presents a cross sectional image of the brain. In this study, recirculation was not an important element as it has little effect on the slow compartment washout curve. Our blood flow values may need minor correction due to the use of halothane anesthesia and the mildly lowered arterial CO2 values. Nonetheless, these are experimental variables and do not detract from the concept of using serial Xenon-enhanced CT scans to evaluate accurately regional cerebral blood flow.

Xenon enhanced CT scanning has definite shortcomings as a cerebral blood flow technique. However, these all appear readily surmountable with advancing CT technology. Rapid scanning times are needed for more significant gray and white matter washout curves; newer scanners need only 2 to 10 seconds per section. With repeated scans at a similar level, the radiation dosage is quite high; future generation scanners may possibly lower the dose. Artifacts may alter the enhanced scan appearance and especially affect the maximal enhancement values; faster scan times, careful subject positioning, and prevention of movement make artifact a minor problem. The cerebral blood flow for only a single section of brain has been demonstrated. Newer scan designs may permit the scanning of multiple brain levels simultaneously, providing information for constructing both horizontal and coronal cerebral blood flow analysis. Since absolute CT values are dependent on the effective energy of the X-ray beam, which varies with the kilovoltage and type and amount of attenuating material, small variations may occur in these CT values on presently used scanners; these variations are quite small when studying the cranial contents and newer scanners should almost completely correct for even these minor shifts. Finally, a common scale and unit for CT attenuation coefficient (u) has not yet been established and varies with each manufacturer's scanner; however, values may be established for each specific scanner and reasonable reproducibility assured for any individual scanner by using phantom calibrations.

Xenon-enhanced CT scanning now permits the evaluation of cerebral blood flow and comparative brain perfusion in both anatomic and physiologic terms. We are presently establishing cerebral washout curves in various physiologic and pathologic states in the baboon using numerically averaged CT attenuation coefficients and comparing these to flows obtained using Xenon inhalation. With further experience and newer developments in scanner technology, consistent and accurate cerebral blood flow and perfusion measurements should readily be obtained using Xenon-enhanced CT.

References
SUMMARY  In the absence of universally accepted criteria for the medical treatment of stroke, we made a rigorously randomized comparative study of different treatments in 300 patients. One group of patients received only a general supportive treatment designed to ensure adequate supplies of water, electrolytes and calories, plus whatever was needed to prevent infection and correct extant associated pathology. Three other groups of patients were treated in the same way but were also given, respectively, one of the following medications: Hydergine (Sandoz) (a mixture of three ergot alkaloids), dexamethasone, and mannitol.

No statistically significant difference emerged among any of the treatment groups and the reference group in terms of objective therapeutic results. The authors concluded that, at least with the dosage used in this study, none of the treatments proved more useful than conventional supportive therapy in the first 10 days after a stroke.

TREATING PATIENTS with stroke is often unrewarding. As in other fields of medicine, the lack of a basic reference treatment for stroke has generated a multitude of drug therapies, each being thought of as a cure, only to be soon abandoned. It is likely that some deaths in the first several days after a stroke are due to cerebral edema around the infarcted area rather than to the infarct itself. Edema reaches its peak about 3 to 4 days after the stroke, and can be responsible for transtentorial herniation of the brain, rostrocaudal deterioration, and impaired cerebral blood flow. Drugs thought to reduce edema reduce intracranial pressure which can indirectly improve brain circulation. Those used in recent years include mannitol, corticosteroids, and Hydergine, each with conflicting reports of clinical effectiveness. We have studied these 3 therapies using 1) a large number of patients; 2) random selection for treatment; 3) each drug alone; 4) results from reliable clinical parameters; 5) data evaluated by a correctly designed statistical program.

Materials and Methods

We studied 300 patients with a diagnosis of stroke, hospitalized in the Emergency Medicine Division of the Polyclinic Hospital in Milan, during 1974 and 1975. The mean age for the whole group was 71 years. There were 110 men (mean age 69) and 190 women (mean age 73). Of these 241 were diagnosed as having an ischemic stroke, 189 in the carotid artery territory, 40 in the vertebrobasilar territory. In 12 the classification was uncertain. At hospitalization, each patient was assigned randomly to one of the following 4 treatment groups:

Group A. These patients received adequate water and electrolyte replenishment by intravenous infusion for the first 48–72 hours, and then a suitable caloric intake, in the form of a special standard diet if necessary, administered by stomach tube. These patients also received suitable antibiotics and additional treatments, such as digitalis, diuretics, tracheal aspiration and instillation of mucolytic agents, and bedsores prevention.

Group B. These patients received the same treatment as those in group A, plus a proprietary mixture of dihydroergocornine, dihydroergocristine and dihydroergocryptine, 0.3 mg each (Hydergine) in a daily dosage of 6 ampoules representing 1.8 mg of each alkaloid in the mixture.

Group C. Patients in group C received the same treatment as group A plus dexamethasone 24 mg daily, given in divided doses.

Group D. Patients received the same treatment as group A plus a solution of 20% hypertonic mannitol given i.v. 0.8–0.9 g/kg daily.

In all groups treatment was instituted between 3 and 24 hours after onset of symptoms. The period of observation was 10 days for all 4 groups.
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