The effect of about one third craniectomy on the cerebrospinal fluid flow rate as estimated by radionuclide cisternography in normal rabbits

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Abstract

Since, the effect of a large cranial defect on the cerebrospinal fluid (CSF) flow rate is still not clear, this study was designed to evaluate the effect of craniectomy in rabbits by using a radionuclide technique, under in vivo physiologic conditions. *Eleven male* New Zealand white rabbits were examined. After the injection of technetium-99m-diethylene-triaminepenta-acetic acid into the fourth ventricle of each rabbit, dynamic acquisition for 60min (1min per frame) was performed pre-op followed by about one third craniectomy to each animal. Injection of the radiopharmaceutical and the imaging steps were repeated at 24h (post-op 24h) and at 7 days (post-op 7d) after craniectomy. The region of interest (ROI) was drawn around the injection site and a time activity curve was generated. Slopes of each curve were calculated to detect the flow rate of the radiopharmaceutical from the injection site during 60min. Besides, the count decreased ratio (ROIcounts of the last frame ROI counts of the first frame X100) was calculated. *Our results showed* that the pre-op values of the slope of the time-activity curve and the count decreased ratio were decreased 24h and 7d post-op but statistically significant was only the difference between the above values pre-op and 7d post-op (P=0.04, P=0.01 respectively). *In conclusion,* the data of the present study indicate that the CSF flow rate in rabbits decreased 7d after one third craniectomy.

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Introduction

The normal cerebrospinal fluid (CSF) is mainly produced by the choroid plexus, with some arising from the ependyma and brain [1]. Circulating through the interventricular foramina into the third ventricle and then via the mesencephalic duct into the fourth ventricle ends into the subarachnoid space through two lateral and one median apertures. It is then considered to be absorbed mainly from the subarachnoid space into the venous system by the arachnoid villihttp://en.wikipedia.org/wiki/Venous_system [2]. The total amount of CSF is about 150mL, and about 500mL are produced per day, indicating a very active circulation [3-4]. The CSF has many putative roles including mechanical protection of the brain, distribution of neuroendocrine factors, and facilitation of pulsatile cerebral blood flow. Since it is replaced several times a day, CSF flushes the central nervous system and helps to provide the nervous system with a steady supply of nutrients.

In clinical practice, decompressive craniectomy is often performed to reduce the increased intracranial pressure. This surgical procedure causing a skull bone defect may sometimes lead to neurological deficits and clinical findings known as 'the syndrome of the sinking skin flap' or 'the symptom of the trephined' [5, 6]. Clinical and cognitive findings of this syndrome may improve after cranioplasty [6-9]. The physiopathology of this syndrome is not yet clarified, although changes in CSF hydrodynamics may be due to the pressure gradient between the atmospheric pressure and the intracranial pressure [10, 11].

The aim of this study was to evaluate the effect of 1/3 craniectomy in rabbits on CSF flow by using a radionuclide technique under in vivo normal conditions.

Animals and methods

Animals

Eleven male New Zealand white rabbits weighing between 1500gr and 1800gr (mean: 1680gr) were included in the study. Rabbits were anesthetized by a mixture of 30mg/kg

ketamine hydrochloride (Parke Davis-England) and 10mg/kg xylazine (Rompun Bayer-Germany), solution injected intramuscularly before each intraventricular injection and before craniectomy. Our hospital Ethics Committee for animal studies approved our study protocol.

Surgery

The scalp of the anaesthetized rabbits was shaved, rubbed with povidone iodine, and a midline scalp incision was made. Approximately one third of the cranial bone was removed under microscopic magnification and then the scalp was sutured and closed (Fig. 1).

Injection technique, acquisition protocol and instrumentation

A dose of 11.1±1.8MBq/0.1mL of ^{99m}Tc-diethylene-triaminepenta-acetic acid (^{99m}Tc-DTPA, Monrol, ́stanbul, Turkey) was injected into the 4th ventricle of each rabbit with an insulin injector (0.45X12mm*)* in order to evaluate the CSF flow of each animal. Animals were positioned laterally on the imaging table of a gamma camera (GE, Millennium, Milwaukee, WI, USA) equipped with low energy high-resolution collimator and dynamic acquisition for 60min (1min per frame) was initiated immediately, using a 15% window centered over the 140keV photopeak (Fig. 2). Injection of the radiopharmaceutical and an imaging study were performed before craniectomy (pre-op) as a baseline study and repeated after 24h and after 7 days post-operatively (post-op) to evaluate the effect of craniectomy on the CSF flow rate.

Image evaluation

A circular and an identical to that size regions of interest ROI were drawn around the injection site of the radiopharmaceutical for the dynamic image set. The time activity curve was generated for each study and the slope of each curve was calculated to detect the flow rate of the radiopharmaceutical from the injection site during 60min (Fig. 3). Furthermore,

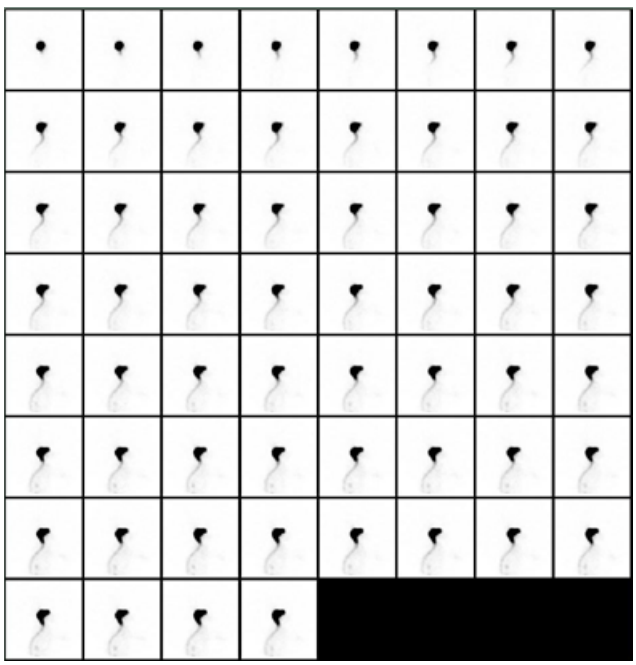

Figure 2. Shows the all dynamic image set of a baseline study of a rabbit.

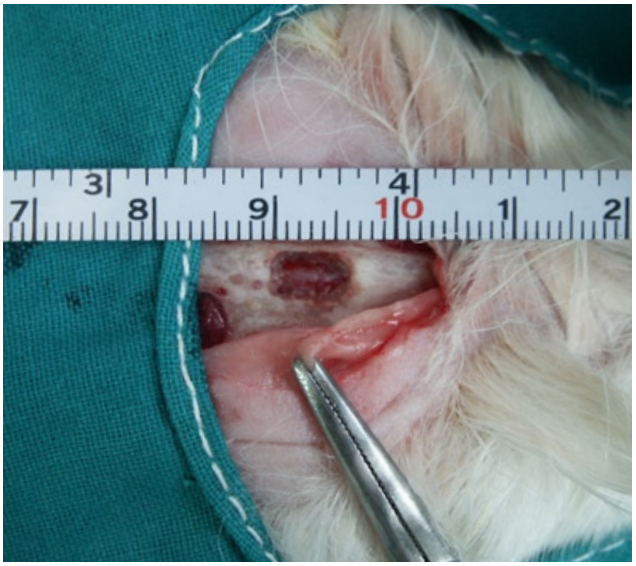

Figure 1. Shows the craniectomy area on the calvarium of a rabbit.

counts from the ROI of the same size and location, as above were measured on the first frame and on the last frame of the dynamic images in order to calculate the count decreased ratio. So, ROI counts from the last frame/ROI counts from the first frame X100 were calculated. This ratio signified the CSF flow rate of the radiopharmaceutical from the injection site.

Statistical analysis

Wilcoxon ranks test was used to evaluate the difference between the consecutive calculated slopes and ratios. Statistical analysis was performed by using the SPSS 10.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA). Differences were considered significant at $P<0.05$.

Results

Leakage of CSF through the puncture site was not detected by physical examination in any of the animals and, scintigraphic images did not show any ^{99m}Tc-DTPA leakage on the skin of the injection site.

The slopes of time-activity curves and count decrease ratios and their descriptive statistics are presented in the Table. Time-activity curves exponentially decreased in all studies. A time activity curve derived from the ROI of a case showing a typical change is shown in Figure 3.

Pre-op values of the slope of the time-activity curves and count decreased ratio were decreased at 24h and at 7d post-op, but statistically significant difference was detected only between the pre-op values and those obtained on the 7th post-op day (Fig. 4 and 5).

Discussion

The size of 1/3 craniectomy was chosen empirically to correspond to a large craniectomy in humans. Defects larger than 6cm^2 in humans are considered appropriate for cranioplasty [12], because the removal of a large bone segment will leave the cranium with a flaccid area of scalp and the gradient between atmospheric and intracranial pressure will press

Table. *Results and descriptive statistics of the study*

	Slopes of the time-activity			Count decrease ratios*		
Rabbits	Pre-op	Pos-top 24h	Post-op 7 days	Pre-op	Post-op 24h	Post-op 7 days
1	-0.23	-0.21	-0.20	26.49	20.91	35.37
2	-0.17	-0.18	-0.20	31.07	59.68	56.2
3	-0.19	-0.22	-0.20	61.37	54.63	57.55
4	-0.20	-0.14	-0.18	44.63	66.44	55.2
5	-0.22	-0.25	-0.15	39.18	29.83	65.26
6	-0.25	-0.18	-0.19	42.81	71.45	59.64
7	-0.24	-0.24	-0.20	25.09	41.21	49.32
8	-0.27	-0.24	-0.23	37.14	46.22	41.44
9	-0.34	-0.26	-0.21	26.11	31.77	49.9
10	-0.16	-0.20	-0.19	58.24	42.41	50.74
11	-0.23	-0.20	-0.21	43.98	46.09	45.14
Median	-0.23	-0.21	-0.20	39.18	46.09	50.74
(%25, %75)	(-0.25, -0.19)	(-0.24, -0.18)	(-0.21, -0.18)	(26.49, 44.63)	(31.77, 59.68)	(45.14,5 7.55)

*:ROI Counts from the last frame/ROI counts from the first frame X100

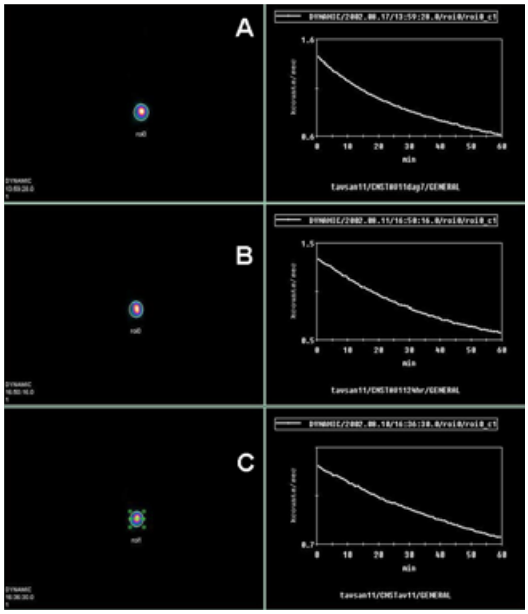

Figure 3. Shows on the left, the site of the ^{99m}Tc-DTPA injected into the 4th ventricle of rabbit No: 11 and the ROI drawn around the injection sites. On the right are the corresponding time–activity curves pre-operatively and 24h and 7d post-operatively in lower, middle and upper rows, respectively.

over the cortex [13] and may cause the "syndrome of the trephined" or the "sinking skin flap syndrome" which may induce neurological symptoms [13].

Analysis of our data indicated that cranial bone defect after one third craniectomy caused a decrease in the CSF flow as early as 24h after surgery which was statistically significant after a week. Slow adaptive changes seem to take place in the cerebral circulation. The underlying cause of this flow change may be a decrease in either the production or the absorption of CSF or in both.

The continued production of CSF in the lateral ventricles appears to be a major driving force for CSF flow [14]. Since the main pathway of CSF absorption is considered to be via the arachnoid villi and the rate of CSF absorption is pressure dependent and linear over a wide range of pressures, the craniectomy we applied could cause a decrease in the absorption rate of CSF [2].

The exact mechanism of our findings is not completely understood. Numerous factors influence CSF formation rate, but arterial blood flow plays an important role in the production of CSF, because a plasma ultrafiltrate derived from arterial blood flow is present at the choroidal epithelium under normal hydrostatic pressure. It has been reported that a relatively large bone defect itself may decrease cerebral blood flow and also disturb energy metabolism [8, 15, 16].

The main physiologic change after craniectomy is that the skull bone defect probably causes a pressure gradient between atmospheric pressure and intracranial pressure. Abnormal CSF hydrodynamics evaluated by lumbar CSF infusion test influence resting pressure, sagittal sinus pressure, balance between volume and pressure in the CSF and

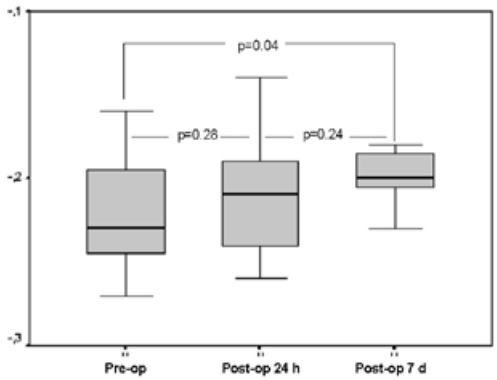

Figure 4. Shows the boxplot of slopes of the time activity curves. One week after craniectomy, statistically significant decrease in the slopes of the time activity curves can be noticed.

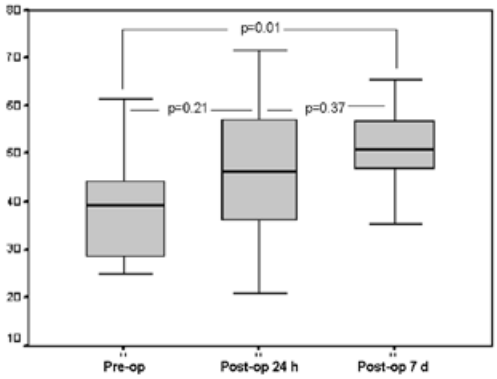

Figure 5. Shows the boxplot of count decrease ratios. Statistically significant decrease can be noticed in the values of the 7thd after surgery.

pulse variations of CSF at resting pressure which normalize after cranioplasty [11]. Our results as well as those of others suggest that calvarium plays an important role in the protection of equilibrium between the inside and outside pressure systems.

After intrathecal injection, ^{99m}Tc-DTPA as a CSF tracer having a high molecular weight does not pass through the ependyma, and remains in the CSF compartment [14]. This is the basis for performing cisternography for the differential diagnosis of hydrocephalus and CSF leakage [18]. Others have done similar cisternography studies [19-22]

As a limitations of the study, besides the small number of animals studied, we could not consider the long term follow-up of our animals due to their short survival time around 15 days after surgery. Performing cranioplasty we could have had more data referring to changes in arterial, venous, and CSF flow [23, 24].

In conclusion, according to our study, the CSF flow is decreased after 1/3 craniectomy in rabbits. This may be due either decreased production and/or to decreased absorption of CSF.

The authors have no conflicts of interest.

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