

## Circadian Rhythm of Urinary Free Cortisol in Brain Injured Patients\*\*

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- 국문요약 -

Key words : Brain injury, Urinary free cortisol, Circadian rhythm, Stress

### 뇌손상 환자의 요중 Free Cortisol의 Circadian Rhythm

민순

뇌손상이라고 하는 과도한 stress를 받았을 때 free cortisol의 분비되는 양과 urinary free cortisol의 circadian 리듬에 어떻게 영향을 주는지 확인하기 위하여 시도하였다. 연구대상은 대조군은 건강한 젊은 여성 6명과 실험군은 CT상 뇌에 손상을 받은 4명의 여성으로 30대 환자이었다. 담당의사와 중환자실 관리책임자의 동의하에서 시도되었으며, 실험기간은 2000년 7월 1일에서 7월 10일까지였다. 대조군과 실험군의 뇨를 채취하여 뇨중 free cortisol 농도의 circadian rhythm을 알아보기 위해 채뇨 후 분석하였다. 채뇨는 뇌손상을 받고 응급실을 통해 신경외과 중환자실에 입원한 지 5시간 이내에 해당된 환자로 24시간 유지되는 foley catheterization 상태에서 12:00부터 3일 동안 72시간을 2시간 간격으로 채뇨하였고, 대조군은 오전 12시부터 24시간 동안 2시간 간격으로 채뇨하였다. 측정방법으로는 cortisol의 정량은 solid-phase radioimmunoassay 방법을 이용하였으며, 분석재료는 Coat-A-Count® Cortisol kit(DPC, U.S.A.)을 사용하여 DPC사의 측정방법을 따랐다.

연구대상자의 free cortisol의 총량은 대조군에서는  $42.8\mu\text{g}$ 이었고, 실험군은 1일에  $991.2\mu\text{g}$ , 2일에  $809\mu\text{g}$ , 3일에  $544.2\mu\text{g}$ 으로 대조군과 통계적으로 유의한 차이를 나타내( $p < .05$ ), 실험군에서 현저하게 증가된 양상을 보였고, 시간이 지나면서 점점 감소하는 경향을 나타냈다.

시간별로 t-검정으로 분석한 결과로는 모든 시간대에서 대조군과 실험군의 평균치는 통계적으로 유의한 차이를 나타냈다. Free cortisol의 circadian에서는 대조군에서는 정상인의 cortisol의 circadian의 경우와 같은 리듬을 보였으나, 손상을 받은 실험군의 경우 분비량은 현저하게 증가했음을 보여주었다. 최고치가 제1일에 18:00과 다음날 10:00에 나타나 최고치가 2회 나타났으

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며, 제2일에도 제1일과 마찬가지로 18:00에 나타났고, 제3일에는 24:00에 나타나 제1일보다 제2일에는 최고치가 한 번 나타난 리듬을 보여주었고, 분비량은 2일에 감소하였다. 제3일에는 최고치가 8시간 지연된 나타난 리듬의 변화를 보여주었다. 최저치는 제1일, 제2일, 제3일 모두 24:00에 나타난 리듬을 보여주었다.

이상의 결과에서 실험군인 뇌손상 환자군에서는 뇌손상이 과도한 stress로 작용하여 환자의 free cortisol 분비량과 circadian 리듬에도 영향을 주는 것으로 나타났다. 그러므로 뇌손상환자를 간호하는 간호사는 스트레스상태인 것을 인지하여 환자 개개인에 필요한 간호를 해야 할 것으로 사료된다.

## Introduction

Man's biological rhythm is as important an elementary character of the important body as the homeostasis. It is, according to its cycle, classified as infradian(cycle : beyond 29hrs), circadian(cycle : 20-28hrs), ultradian(cycle : below 19hrs), of which the most important and general cycle is circadian.

The physiology of the human body is regulated by the nervous and the endocrine system, of which one of the stress hormones is cortisol.

According to serum cortisol levels, urinary cortisol levels are changed(Ney et al., 1963), and they increase at the time of excessive stress, work and exercise(Hartley, 1972 ; Farrel et al., 1983). The homeostasis maintenance of the human body is completely changed when stressed(Kang, 1983 ; Ramsey, 1982) and the glucocorticoid that is secreted at the adrenal cortex is activated by almost every stress (Ganong, 1983). In the normal physiological condition, cortisol secretion shows circadian rhythm and it corresponds with circadian rhythm of adrenal cortex stimulative hormone so that it is secreted in the evening very low(the minimum)slowly, and begins to increase

radically and reach as the maximum early in the morning.

It takes 2-5 minutes to increase steroid hormone secretion, and it takes more time till the maximum(Choi et al., 1994). When stressed excessively, and when one has a major operation, cortisol is radically increased and then returns to normal within 24 hrs(Gordon et al., 1973 ; Hamanaka et al., 1970 ; Ichikawa et al., 1971).

Tracy(1981), in a study that makes object of 10 persons that have had surgical operations, reported that there is positive correlation with the rise of plasma cortisol in proportion to the degree of surgery severity both in the low trauma group and high trauma group. Min et al.(1997) and Min(1998), in a study that makes object that have had a shift duty, reported that : shift workers prove to have higher urinary free cortisol than shift workers.

17-OHCS(hydrocorticosteroid) is a metabolism product of adrenal cortex steroid hormone and is excreted as cortisol(Oh & Min, 1994).

Excessive stress and excessive exercise incite an unbalance of hormone and electrolyte, and when unbalance of the body fluids and the electrolyte is caused, it can influence all the functions of the body(Cho, 1982).

This study examined the influence of an excessive stress, that is the brain injury, on the secretion amount and the circadian rhythm of urinary free cortisol, which can be used to inform nursing practice. Till now the study of the 'brain injured patient' has been unexhausted. And I think that it is necessary to take appropriate cares of them at the base of the physiological data. Therefore, this study is to try out to present data for the nursing of the patient.

## Methodology

### A. Object of study

Control group consist of six healthy young women whose menstrual cycle was distributed on the 20th day, and the school they're attending is within one hour's distance, and who can avoid coffee and tea during the time the urine was obtained, and who don't do over activities and part time jobs after school, and who can sleep between 22:00 and 23:00 hours, and who don't take drugs enough to influence on the result of the experience.

Test group made object of 4 patients of brain injury, to whom no steroid agents were given during urine sampling, They received antihypertention drugs, antibiotics and 5% D/S 1000ml/day and they were within 5 hours after brain injury. The brain injured patient are composed of the female who are in their thirties and who are fallen into a semicoma, diagnosed as brain injury by the medical diagnosis computer photographically.

This study was practiced under the agreement of medical personnel and the administrator of intensive care unit, and the

period of test was from 2000 July 1 to 10.

### B. Method of the study

We analyzed after urine sampling to examine the amount and circadian rhythm of urinary free cortisol.

#### 1. Urine sampling

From the test group, we obtained urine specimen under foley catheterization for 3 days with two hour interval for three days ; from the control group, with two hour intervals from 12:00 for 1 day.

At each urine sampling, we measured 10cc of midstream by freeze-keeping in a test tube after 24 hours or so.

#### 2. Analytical procedures

Cortisol was measured by solid-phase radioimmunoassay which was recommended by the DPC Co.(Coat-A-Count<sup>®</sup> Cortisol, U.S.A.). To estimate urinary unconjugated cortisol, urine specimens were extracted with dichloromethane. The extracts were dried directly in the Ab-Coated Tube(DPC, U.S.A.). The free cortisol in urine specimens was competed with <sup>125</sup>I-labeled cortisol, then counted in a gamma counter.

## Result

The total amount of urinary free cortisol obtained with two hour interval from the person of object is as follows : (Fig. 1).

While the urinary free cortisol was 42.8μg in the control group, the free cortisol of the test group showed a rhythm remarkably increased and a tendency to decrease gradually as time

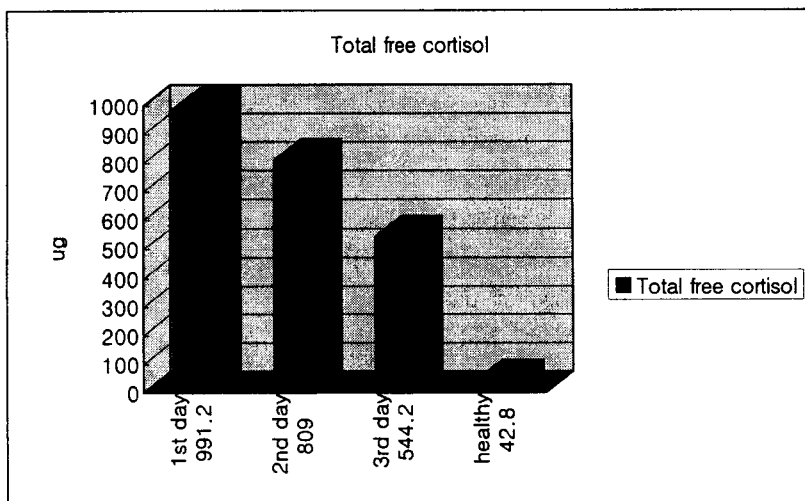


Fig. 1. Profiles of the sum of urinary free cortisol observed in 4 subjects for 3 days of brain injured patient and the sum urinary free cortisol of control group.

passed : 991.2 $\mu$ g first day, 809 $\mu$ g second day, 544.2 $\mu$ g third day.

The result of the analysis by t-test each hour is as follows : In all hours, the mean of the control group and test group is statistically significant.

In the control group, circadian rhythm showed the same rhythm as healthy person's cortisol circadian rhythm ; in the test group, it was showed that circadian rhythm was similar and that the amount of the secretion was remarkably increased at the first day and it decreased from 12:00(63.1) to 14:00(43.1), 16:00 (27.3). It showed the maximum at 18:00(223.6) and it decreased after 20:00(62.8) to reach the minimum at 24:00(18.4).

It increased slowly from 02:00 to 04:00 and decreased slowly from 06:00 to 08:00, and showed circadian rhythm that increased at 10:00(Fig. 2).

At the second day, the test group decreased from 12:00(139.7) to 14:00(25.7), 16:00(21.8) and showed the maximum at 18:00 as the first day.

It showed the minimum at 24:00(14.5), increased a little at the 02:00, decreased at 06:00, increased a little at 08:00 : it showed similar circadian rhythm to the first day(Fig. 3).

At the third day, the test group decreased slowly from 12:00(35.6) to 14:00(15.8) and 16:00 (12.6), and it increased at 18:00(83.9), to show a slightly different rhythm from the first and second days, showing the maximum at 02:00 and circadian rhythm that showed the minimum at 08:00(6.8)(Fig. 4).

The first day, the peak appeared two times at 18:00 and 10:00 the next day. The second day it appeared at 18:00(same as the first day). The third day, it appeared at 12MN, which showed the rhythm that the second day differently from the first day the peak appeared one time, and the second day cortisol amount diminished. The third day differently from the day before showed the change of the rhythm which appeared at 02:00, that the peak delayed for 8 hours. All the days (the first, second and third day) the minimum showed the rhythm

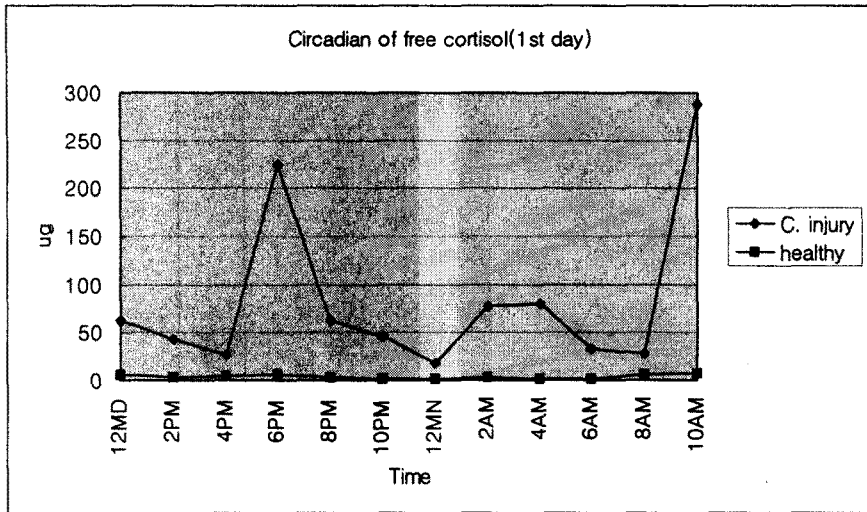


Fig. 2. Profiles of circadian rhythm of urinary free cortisol observed in 4 subjects during the first day of brain injured patient(○). The control urinary free cortisol levels curve is superimposed on each of the experimental days(□).

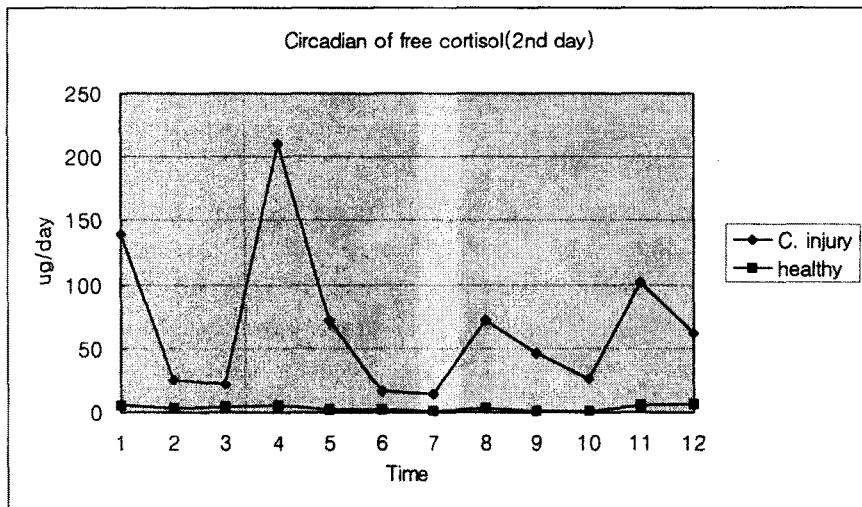


Fig. 3. Profiles of circadian rhythm of urinary free cortisol observed in 4 subjects during the second day of brain injured patient(○). The control urinary free cortisol levels curve is superimposed on each of the experimental days(□).

which appeared at 24:00.

## Discussion

The nervous and the endocrine system

regulate the physiology of the human body, and they play one of the most important roles in the maintenance of the homeostasis of inner environment, and they influence the kidney functions when stressed(Ramsey, 1982).

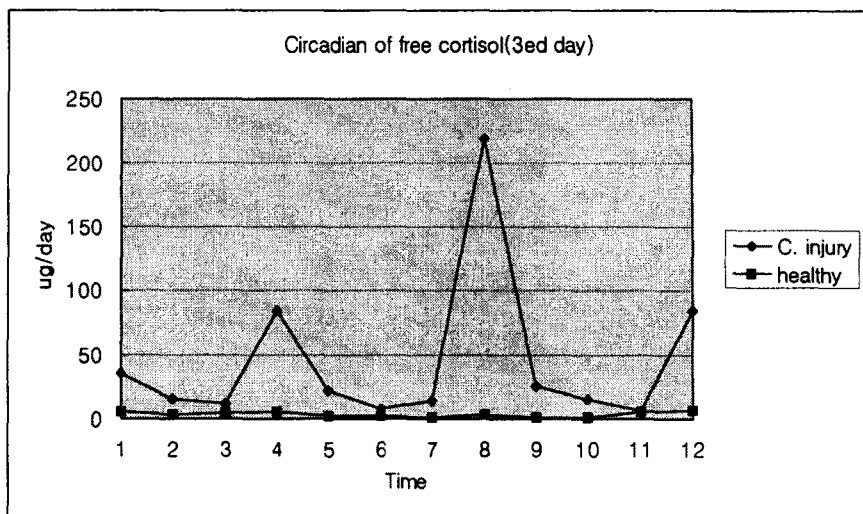


Fig. 4. Profiles of circadian rhythm of urinary free cortisol observed in 4 subjects during the third day of brain injured patient(○). The control urinary free cortisol levels curve is superimposed on each of the experimental days(□).

The steroids of the adrenal cortex are the compounds with the structure that consist of three cyclohexane rings and a cyclopentane ring, and are classified as C27, C19, C18 according to carbon-number(Carson et al., 1990).

Cortisol is secreted at the zona fasciculata and the retiform tissue. The amount of cortisol is controlled by stimulation intensity of ACTH (adrenocorticotrophic hormone) that is secreted at the pituitary gland(anterior lobe). In this study it shows circadian rhythm in normal healthy groups and coincides with the normal circadian rhythm, reaching the maximum early in the morning and minimum level in the evening(Choi et al., 1994).

The secretion of adrenal cortex stimulative hormone increases in response to the stress, and the sequential secretion of glucocorticoid increases. The function of glucocorticoid is not clear, but the possibility necessary for the maintenance of a blood vessel reaction to the catecholamine was presented(Onti et al., 1990).

Various hormone system in the body influences the amount of body fluids and secretion of the electrolyte, of which the blood plasma renin angiotensin is the most important hormone system. It was known that the activity of blood plasma renin is easily increased by the decrease of the amount of body fluids, the decrease of Na in the of body and the increase of stress(Vagnucci, 1969).

Operation and trauma cause the change of endocrine of hypothalamus-pituitary anterior lobe-adrenal axis and the change the hormone that is secreted by adrenal cortex. The urinary free cortisol of rapidly shift-worker group was more secreted than that of nonshift-worker(Min et al., 1997), and the level of free cortisol in shift-workers of counterclockwise direction showed higher than in shift-workers of clockwise direction(Min, 1998).

There are reports : blood plasma ACTH and cortisol levels are remarkably, rapidly and temporarily increased by the excessive stress

or great operation and they return to normal level within 24 hours(Gordon et al., 1973 ; Hamanaka et al., 1970 ; Ichikawa et al., 1971), but there is a case that they remain increased for 6 days(Frankson et al., 1954 ; Hume et al., 1962 ; Gill, 1975).

There are also other reports that they does not return to normal for a long period of time(King et al., 1970 ; Solopaev et al., 1976). The cortisol secretion is influenced by the excessive stress, irregular shift-worker, serious damage and the long period of exercise etc(Tracy et al., 1981 ; Werner, 1995).

In this study, the total secreted amount of urinary free cortisol remarkably increased in the test group: on the first day 991.2 $\mu$ g, on the second day 809 $\mu$ g, on third day 544.2 $\mu$ g and it showed a tendency to decrease gradually.

The increase of cortisol has a direct relation with the severity and the range of operation (Tracy et al., 1981). When the severity of damage increase, a large amount of adrenal cortex is secreted by the metabolism demand of the patient(Ingle, 1952). In this study, it is observed that brain injury had a relation with the rise of urinary free cortisol, and has a tendency to remain continuously increased for a long period.

In human blood plasma, cortisol levels increase at 24:00, which reach the maximum at 6-8hour, fall rapidly at 8-12hr, and decrease slowly till 12:00(Krieger et al., 1971 ; Weitzman et al., 1971 ; Weitzman, 1980).

The cortisol levels of the groups with that received high trauma showed the maximum early in the morning and have a tendency to rise rapidly(Tracy et al., 1981). The stress related to the head injury and brain injury causes various changes to the circadian rhythm

of corticosteroid(King et al., 1970 ; Solopaev et al., 1976).

There was significant difference in circadian rhythm of cortisol in the young age group (Nakamura:1984). Also Alberti et al.(1975) have shown the significant difference in the young age group and the old age group. These studies have suggested that the rhythm could be changed by the difference of sex and age. The glucocorticoid secreted in adrenal cortex has been activated by all kinds of stress. The cortisol level of a person who has received excessive stress or great operation suddenly elevated and recovered normal condition before 24 hours had passed(Gordon et al., 1973, Hamanaka et al., 1970, Ichikawa et al., 1971). The ACTH level of night duty shift-worker lasted higher than that of day worker and the cortisol level of day worker was higher than that of night worker. These reports are consistent with our results. The reason in the old age groups of the high level of cortisol is that the activation of 18-hydroxylase in the adrenal cortex was damaged by aging(Touitou et al., 1982).

In this study, the circadian rhythm of urinary free cortisol was like this ; the control group showed the same rhythm as the case of cortisol circadian of healthy person ; in the test group with the damage, the rhythm of the circadian showed the maximum, which appeared two times on the first day and one time on the second day. On third day, the change of the maximum appeared at 02:00, which is the change of rhythm due to 8 hours delay. Therefore, it is considered that the secretion of cortisol is affected by the change of hypothalamus-pituitary, anteriorlobe-adrenal axis via brain injury(Ichikawa et al., 1971).

On the first day the level of cortisol decreased from 12:00(63.1) to 14:00(43.1) and 16:00(27.3) showing the maximum at 18:00 (223.6), and then decreased after 20:00(62.8), showing the minimum at 24:00(18.4). It showed the circadian rhythm that increased slowly from 02:00(77.1) to 04:00(80.5), and then decreased slowly from 06:00(33.4) to 08:00(27.7), and then increased at 10:00(288.4). The glucocorticoid secreted from the adrenal cortex is activated by almost all kinds of stress(Ganong, 1983) and it was showed : brain injured situation functions as an excessive stress and then the abundant secretion of adrenal cortex hormone by the metabolism demand of the patient is observed, and a lot of urinary free cortisol was excreted.

On the second day, the test group showed decreased amount from 12:00(139.7) to 14:00 (25.7), 16:00(21.8) and showed the maximum at 18:00(210.0), ad shown in the first day.

The level of cortisol showed the minimum at 24:00(14.5), and then increased a little at 02:00 (72.2), and started to decrease at 06:00(26.8), and then increased a little at 08:00(101.5) : it showed a similar circadian rhythm to that of the first day. And it is considered that the decrease of total amount of urinary free cortisol on the second day compared to that of the first day shows slow adjustment to the brain injury.

On the third day, the test group decreased slowly from 12:00(35.6) to 14:00(15.8) and 16:00 (12.6), and increased at 18:00(83.9), showing that the rhythm of the first day is slightly different from that of the second day. It showed a circadian rhythm reaching the maximum at 02:00(219.4) and the minimum at 08:00(6.8).

In the case of excessive stress, a lot of cortisol is secreted and its level takes over

24hr to return to normal. It is considered that on the third day the remarkable decrease of the total amount of the free cortisol is ascribed to an adjustment of metabolism to the physical demand in brain injury.

It is suggested that the nurses who take care of the brain injured patients, experiencing the change of the secretion of cortisol by the change of hypothalamus – pituitary, anteriorlobe – adrenal axis, must take a proper care of each patient by recognizing their situation of stress.

## Conclusion

All of the days, urinary free cortisol of the test group showed the rhythm remarkably increased and a tendency to decrease gradually.

In the control group, circadian rhythm showed the same rhythm as healthy person's cortisol circadian ; in the test group, it showed that circadian rhythm was similar and that the amount of the secretion was remarkably increased. The result is that a lot of cortisol is secreted, and it takes over 24hours to return to normal, when stressed excessively, on the third day, and total free cortisol increase remarkably.

As the result mentioned above : different from the control group of which healthy men were made object, in the brain injury group, the test group, the brain injury operates as excessive stress so that the secretion of adrenal cortex hormone becomes abundant according to the metabolism of the patient, and a lot of free cortisol is excreted by urine, but as time passes, total free cortisol decreases and the physical condition gets well gradually. In the nursing practice, nurses should serve an individualized care to stressful patients with brain injury.



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