

Evaluation of Automatic Monitoring of Instillation Adherence Using Eye Dropper Bottle Sensor and Deep Learning in Patients With Glaucoma

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Purpose: We developed and evaluated an eye dropper bottle sensor system comprising motion sensor with automatic motion waveform analysis using deep learning (DL) to accurately measure adherence of patients with antiglaucoma ophthalmic solution therapy.

Methods: We enrolled 20 patients with open-angle glaucoma who were treated with either latanoprost ophthalmic solution 0.005% or latanoprost-timolol maleate fixed combination ophthalmic solution in both eyes. An eye dropper bottle sensor was installed at patients' homes, and they were asked to instill the medication and manually record each instillation time for 3 days. Waveform data were automatically collected from the eye dropper bottle sensor and judged as a complete instillation by the DL instillation assessment model. We compared the instillation times captured on the waveform data with those on each patient's record form. In addition, we also calculated instillation movement duration from Waveform data.

Results: The developed eye bottle sensor detected all 60 instillation events (100%). Mean difference between patient and eye bottle sensor recorded time was 1 ± 1.22 (range, 0–3) minutes. Additionally, mean instillation movement duration was 16.1 ± 14.4 (range, 4–43) seconds. Two-way ANOVA revealed a significant difference in instillation movement duration among patients ($P < 0.001$) and across days ($P < 0.001$).

Conclusion: The eye dropper bottle sensor system developed by us can be used for automatic monitoring of instillation adherence in patients with glaucoma.

Translational Relevance: We believe that our eye dropper bottle sensor system will accurately measure adherence of all glaucoma patients as well as help glaucoma treatment.

Introduction

An estimated 80 million people worldwide are affected by glaucoma, and the numbers are rising annually.¹ Glaucoma is one of the leading causes of blindness worldwide.² Patient adherence plays a significant role in the outcomes of glaucoma treatment with ophthalmic solutions. Approximately 30% of the patients who newly begin glaucoma treatment

with prostaglandin eye drops discontinue the treatment within 3 months.³ Unfortunately, recent studies have concluded that persistence with initial glaucoma medication is as low as 33% to 39% at 1 year.^{4–7} Such poor adherence renders the treatment ineffective and causes a 6-fold or more increase in the risk for further development of visual field disorders.⁸ From a clinical perspective, various methods to measure patient adherence to antiglaucoma medications have been

devised, including self-reporting,⁹ eye dropper bottle weight changes,¹⁰ and motion of eye dropper bottle case.¹¹ Each methodology associated with problems such as low reliability, low precision, and complexity, and to our knowledge, no widely established methodology exists in the actual clinical practice.

Recently, efforts for improving medication adherence using mobile health have been reported.¹² Mobile health is a part of the concept of the Internet of Things, which collects individual information through network connections via smartphones or tablet devices. As it enables thorough automatic collection of enormous data and does not require manpower, it has excellent cost effectiveness.¹³ A system that monitors patients' adherence to medication regimens by attaching a sensor to ingestible tablets for chronic hypertension has been reported.¹⁴ Furthermore, medical applications of deep learning (DL) are becoming popular.¹⁵ DL has a highly accurate discrimination ability that is much better than preceding machine learning methodologies. Many studies on DL have been published in the ophthalmologic field, especially in the area of image identification.^{16–20} However, no studies have examined the applications of this new technology in improving patient adherence to antiglaucoma medications.

We developed an eye dropper bottle sensor that automatically detects the motion of an eye dropper.²¹ Furthermore, we designed an automatic instillation motion waveform discrimination model using DL and used it with the eye dropper bottle sensor (hereinafter referred to as the eye dropper bottle sensor system). In this study, we provided eye dropper bottle sensors to patients to evaluate the automatic monitoring of patient adherence to antiglaucoma ophthalmic solutions by this system.

Methods

Patients

In total, 20 patients (9 females and 11 males) with open-angle glaucoma who were treated with either latanoprost ophthalmic solution 0.005% or latanoprost-timolol maleate fixed-combination ophthalmic solution in both eyes were enrolled between May 1, 2016, and August 30, 2017. The mean patient age was 64.1 ± 12.0 years. The research protocols and implementation were approved by the Ethics Committee of the Tsukazaki Hospital.

Structure of the Eye Dropper Bottle Sensor

The eye dropper bottle sensor comprises an eye dropper bottle, a TWE-Lite2525A (hereinafter referred to as sensor), an eye dropper assistance holder, a processing terminal, and a power cord (Fig. 1). The eye dropper assistance holder consists of a base for the eye dropper, a cap, and a bottom lid that stabilizes the eye dropper. The base is hollow, and the sensor is placed inside it. The sensor uses a CR1632 lithium battery. A data logger shield (ADSLD) was used to record the data of the processing terminal. The data logger shield is equipped with various functions, such as a real time clock (RTC) function, CR1220 lithium battery to run RTC, secure digital (SD) socket, external data interface, and reset button for resetting the program in case of malfunction. It also has a power cord plug and universal serial bus plug. In addition, the system has a TWE-Lite radio microcomputer, dual bidirectional I2C bus voltage-level translator (PCA9306), built-in antenna in the case (MW-A-P4208), and light-emitting diode (LED) indicator and a buzzer to indicate data reception.

Mechanism of the Eye Dropper Bottle Sensor

The sensor is an XYZ 3-axis acceleration sensor, that detects the gravitational acceleration value approximately every 0.08 seconds. Once the sensor detects the motion of the eye dropper bottle, the data are dispatched to the processing terminal via the IEEE802.15.4 wireless network. Even when the sensor itself is in a stationary state, it always detects the acceleration in its own memory and accumulates data. Therefore, data from approximately 5 seconds prior to the detection of the motion to that after 5 seconds of the motion were accumulated. The transmitted data are received at the built-in antenna in the case (MW-AP4208) and sent to the TWE-Lite radio microcomputer. The radio microcomputer processes the data, which are then transmitted to the outside data interface via a cable. Eventually, the data are recorded in an SD memory card present in the SD socket. We used a dual bidirectional I2C bus voltage-level translator (PCA9306) because the power supply voltage of the TWE-Lite radio microcomputer was 5 V and that of the SD socket was 3.3 V. Furthermore, we added a buzzer and an LED light indicator to indicate that the data are being received via a wireless network. With RTC function of the data logger shield, graphed data with gravitational acceleration, and time on longitudinal and horizontal axes,

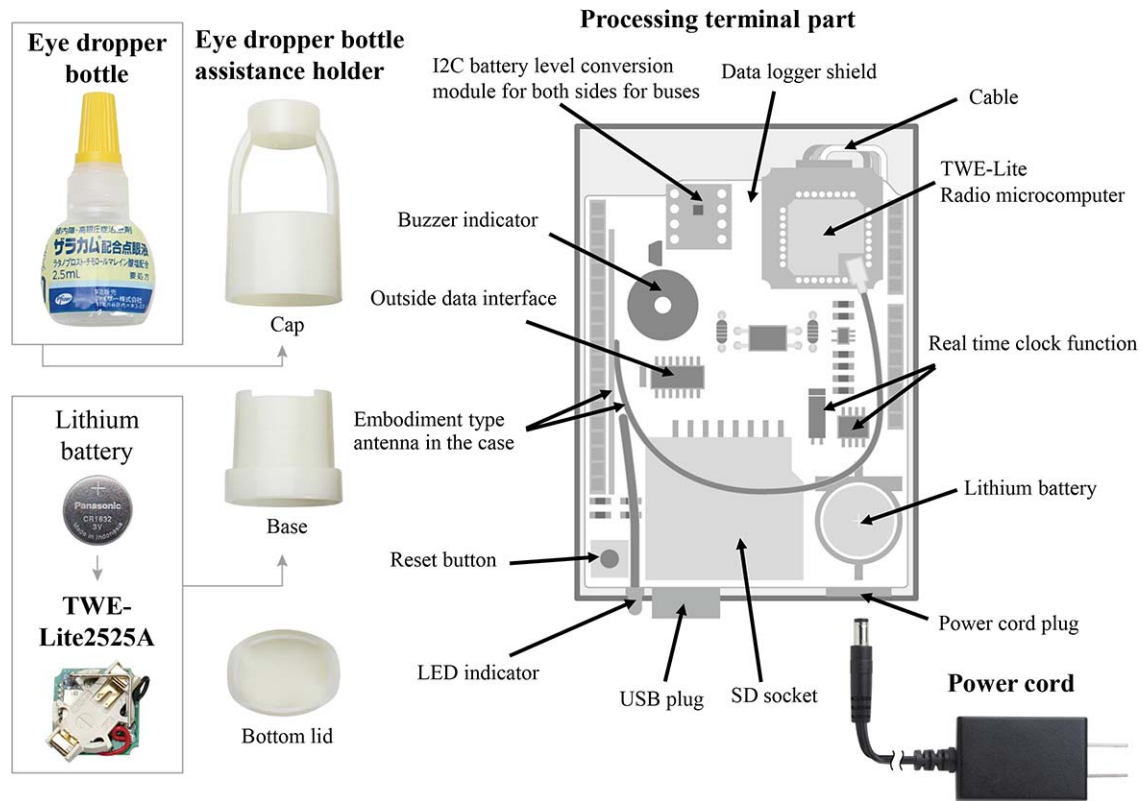


Figure 1. Structure of the eye dropper bottle sensor.

respectively, are recorded to the SD card. Representative data collected from the patients during the instillations are depicted in Figure 2. Because the acceleration sensor detects the gravitational acceleration, it is possible to measure the inclination of the sensor with the vector and quantity of the gravitational acceleration. We defined the X, Y, and Z axes of the three-axis acceleration sensor as shown in Figure 2. In this study, we focused on detecting the gravitational acceleration for the Z axis. First, the state when the gravitational acceleration is +1 G (Fig. 2, part 1) is examined. At this time, the gravitational acceleration G is in a downward direction on the Z axis (downward being positive); thus, the output is +1 G. Next, the state when the gravitational acceleration is 0 G (Fig. 2, part 2) is examined. When the tip of the eye dropper bottle is tilted by 90° from the state (Fig. 2, part 1), the Z axis becomes vertical to the gravitational acceleration. Thus, at this point, the output is 0 G. In this state, the eye dropper is brought close to the eyes. Next, the state when the gravitational acceleration is -1 G (Fig. 2, part 3) is examined. When the tip of the eye dropper bottle is tilted further by another 90° from the state (Fig. 2, part 2), the gravitational acceleration G is in a

downward direction on the Z axis (upward being positive); thus, the output is -1 G. In this state, both the eyes were instilled. Last, the state when the gravitational acceleration was 1 G (Fig. 2, part 4) was examined. When the tip of the eye dropper bottle was further tilted by another 180° from the state (Fig. 2, part 3), the gravitational acceleration G was in a downward direction on the Z axis (downward being positive); thus, the output was +1 G. In this state, the instillation was over and the eye dropper had returned to its original position. Hence, the time with the smallest gravitational acceleration on the graph indicates the point at which the patient is instilling the medication.

We defined the time when the gravitational acceleration diminishes from +1 G as A, the time when it returns to +1 G as B, the instillation time (in seconds) on the instillation waveform data as $(A + B)/2$, and the instillation duration as $(B - A)$. For analysis, the operation record of the eyedropper stored in a compact recording device was connected to the terminal and only the waveform, including the constant amplitude, was extracted from the operation record by the macro function of the spreadsheet software on the terminal.

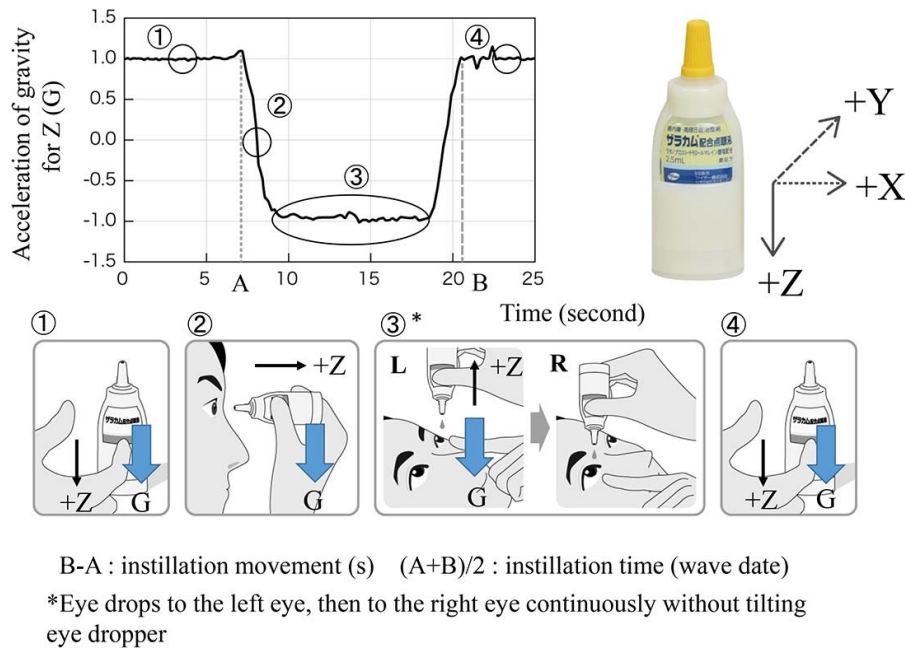


Figure 2. Representative instillation data obtained from the study patients.

Establishment of the DL Instillation Assessment Model

We used 400 pieces of data from healthy subjects who instilled eye drops to generate a learning model. An empty latanoprost ophthalmic solution 0.005% and an eye dropper bottle sensor were provided to all healthy subjects, with the instructions to simulate administration of eye drops in both the eyes (simulated instillation) in order to obtain 200-instillation waveform data. We instructed the healthy subjects to instill the drop simultaneously in both the eyes without tilting the eye dropper bottle. Furthermore, to obtain 200-waveform data by method other than instillation, we asked the healthy subjects 200 times to move the eyedropper horizontally. One representative waveform of noninstillation motions is given in [Figure 3](#). We thus used 200-instillation waveform data and 200-noninstillation waveform data to establish the DL instillation assessment model ([Fig. 4](#)).

With the sensor attached to the eye dropper bottle, an upright position was defined as 1 and an inverse downward position as -1 . One-dimensional waveform data collected approximately at every 0.08 seconds were converted into a colored line graph (216×216 pixel) and analyzed as input values.

In addition to the waveform data, partially extracted former waveform data, partially extracted latter waveform data, and smoothed waveform data

were newly generated and used as learning data to improve the learning precision.

Learning data were converted into images (64×64 pixel) irrespective of the length of the waveform data aligned on the X axis and used as input values. The images went through each convolution layer (conv2d 1 to conv2d 5), activation function (ReLU was used),²²⁾ pooling layer (max pooling2d 1 to max pooling2d 4), and flatten process before going through all the binding layers (dense 1, dense 2) with dropout process in between (at a rate set to 10%) in order to improve the generalization capability.

Moving the eye dropper bottle horizontally

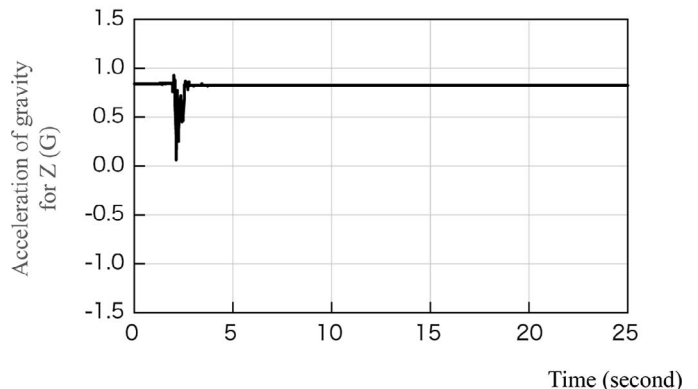


Figure 3. Representative noninstillation data obtained from the healthy subjects.

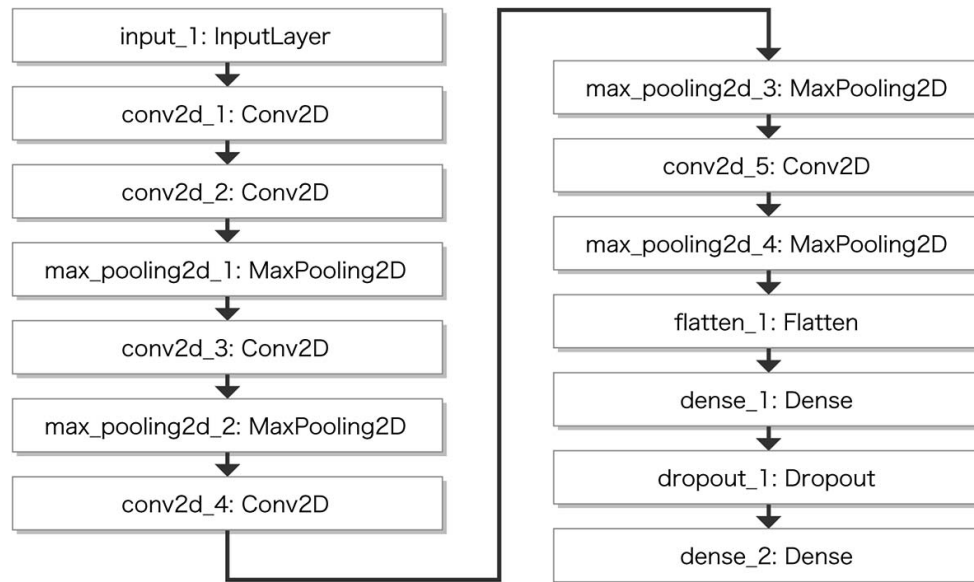


Figure 4. Establishment of the DL instillation assessment model.

Finally, we performed class classification using Softmax function at the output layer to verify whether the waveform showed the motion of instillation. An algorithm Adam was used to optimize the weight. The DL instillation assessment model with optimized internal parameters was established by repeating the above learning cycle 30 times.

Evaluation Methods

The patients were asked to install the eye dropper bottle sensor at home. They performed the instillations in the same room, within approximately 10 m from the processing terminal, for 3 days, and manually recorded the instillation events and their times (hours and minutes), as instructed by a pharmacist (KN). We instructed the patients to simultaneously instill in both eyes without tilting the eye dropper bottle. The information was later collected from the SD cards and the patients' record forms. We compared the instillation event data automatically obtained from the SD card with the written data on the patients' forms. However, it is 0 minutes if it is less than 30 seconds and 1 minute if it is over 30 seconds. In addition, we also calculated instillation movement duration.

Statistical Analysis

We examined the difference in the instillation movement duration among individuals and across days using nonrepeated two-way ANOVA. Additionally, multiple linear regression analysis was performed

to predict the instillation movement duration based on age, sex, and mean deviation (MD) value was evaluated using the 24-2 program by Humphrey field analyzer (Humphrey Company, Houston, TX) and the month from the start of their instillation. Statistical analysis was performed with JMP 10.0 (SAS Institute Inc., Cary, NC). The analysis time with the DL model was calculated using a MacBook Pro (Retina, 13-inch, Early 2015; Apple, Tokyo, Japan), an external device, eGFX Breakway Box (GPU-350W-TB3Z; eGPU Expansion System, Sonnet, Taipei, Taiwan), and NVIDIA GeForce (NVIDIA, Santa Clara, CA).

Results

The number of waveform data events judged as complete instillations by the DL instillation assessment model was 60. (20 patients \times binocular action as once \times 3 days). Details of 60 instillation data are depicted in Table 1. The mean difference between the instillation times on the instillation waveform data and that on the patients' record forms was 1 ± 1.22 (range, 0–3 minutes). Among them, the difference was 93% within 3 minutes and 100% within 5 minutes.

Regarding instillation movement duration in both eyes, the mean value was 16.1 ± 14.4 (range, 4–43) seconds. Two-way ANOVA revealed a significant difference in the instillation movement duration among patients ($P < 0.001$) and across days ($P < 0.001$).

Table 1. Details of 60 Instillation Data

Patient Number	Instillation Movement, s			Difference, m		
	1st Day	2nd Day	3rd Day	1st Day	2nd Day	3rd Day
1	52	36	41	3	1	1
2	41	24	28	1	0	1
3	4	4	4	0	1	0
4	5	5	5	3	5	2
5	11	13	14	2	1	1
6	9	5	6	1	0	0
7	10	7	6	4	2	2
8	35	14	12	0	0	2
9	64	31	11	1	0	1
10	11	15	12	1	0	3
11	11	13	12	1	0	2
12	14	15	10	1	1	0
13	25	13	16	0	0	1
14	5	6	6	3	1	2
15	12	13	10	0	3	0
16	12	11	11	1	2	1
17	10	12	13	1	2	1
18	73	36	17	4	1	2
19	17	8	7	0	1	2
20	6	5	6	3	1	4

The characteristics of 20 patients and their correlation with instillation movement duration are depicted in Table 2. Multiple linear regression revealed that there was no correlation between the instillation movement duration and age ($P=0.91$), sex ($P=0.93$), MD value (right: $P=0.24$ and left: $P=0.18$), the month from the start of their instillation ($P=0.58$).

Table 2. Patients' Characteristics and Correlation With the Duration of the Instillation Movement

Parameter ($n=20$)	Value	P Value
Age, yr, mean \pm SD	64.1 \pm 12.0	0.91
Sex (female), n	9	0.93
MD of the right eye, dB, mean \pm SD	-8.5 \pm 7.48	0.24
MD of the left eye, dB, mean \pm SD	-6.9 \pm 6.55	0.18
Time from first instillation, mo, mean \pm SD	14.0 \pm 8.87	0.58

P value was calculated by multiple linear regression analysis using JMP 10.0.

Discussion

First, within the idealized conditions of the present study, our eye dropper bottle sensor system successfully autoextracted the instillation data of 20 patients with glaucoma for 3 days with 100% accuracy. The analysis of the data was completed within 1 minute. A potential advantage of this system is that it allows for objective and accurate monitoring of patients' instillation adherence without depending on their self-reports. Measured adherence and patient reports often correlate poorly, as patients tend to exaggerate their performance.⁶ Another advantage of our system is that information can be automatically collected in a moment, suggesting easy implementation for actual clinical practice.

Second, we succeeded in measuring and recording the instillation movement duration, a new parameter that, to our knowledge, has not been reported so far. Our data showed a significant difference in the instillation movement duration among individuals; the longest mean instillation duration was 43 seconds in patient number 1, whereas the shortest was 4 seconds in patient number 3. This nearly 40 second difference seems to be due to differing instillation styles or dosages or difficulties instilling the drops accurately into the eyes. Recently, various devices have been developed to address different aspects of eyedrop placements, with which the patients struggle, and our developed system can contribute these efforts.²³ A report has indicated that difficulty in instillation procedure leads to poor adherence.²⁴ Our results of a multiple linear regression revealed no good predictive factor; however, we believe that this new parameter, the instillation movement duration, will provide useful information to improve patients' instillation procedures. It will be interesting to correlate instillation duration with other objective measures of adherence, such as prescription filling, eye drop bottle weight, intraocular pressure, and side-effect measurement.

One limitation of the present initial pilot study was a short duration; longer studies are required to examine the changes in behavior over longer periods of observation. Moreover, this study involved only one type of eye drop; therefore, a future study involving multiple eye drops is required. We did not perform a detailed examination of the cost of the eye dropper bottle sensor. However, for the sensor, we used low-cost, mass-produced parts often used in mobile phones and costing around 1000 JPY

(~US\$10). Furthermore, in the mechanical problem the Z axis waveform was model-learned because the features of the instillation motion majorly appeared in the Z-axis waveform. We will also learn the use of the waveforms of the X and Y axes, and we would like to construct a more precise model. Our system can only detect gravitational movement of the bottle in the Z axis but not the squeezing action of the bottle or the reduced weight or movement of the fluid through the tip. Therefore, even though we were able to detect the tipping movement of the bottle with great accuracy, we could not be sure whether a drop had actually been dispensed out of the bottle and whether the drop medication had correctly landed in the eye.

The learning model used in this study was generated from only 400 waveforms from the healthy subjects. However, it is necessary to generate models based on more learning data in preparation for long-term study. For learning data other than by instillation, we need to collect actions that can occur in everyday life such as being placed inside a handbag or being moved from various places across the house.

Wasting health care costs due to unused medications is not a trivial issue when most industrialized countries are facing the issue of increasing social security costs. In fact, the health care costs can be reduced by approximately 80% if pharmacists collect the unused medications from patients.²⁵ A practical application of the eye dropper bottle sensor system would lead to not only an improved patient adherence but also an efficient use of healthcare budgets.

Conclusion

In this study, we developed a system to objectively and accurately monitor instillation adherence by combining DL and an eye dropper bottle sensor. Further development and investigation are expected before its practical application.

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