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Mathematical model by using gamma distribution to estimate the gallbladder ejection fraction comparison results

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Abstract
Gallbladder ejection fraction measured with a fatty meal was compared with that measured with two equal sequential intravenous infusions of cholecystokinin (CCK-8) in a paired study of healthy subjects. A hyperbolic Brownian motion and other random motion on hyperbolic spaces were used to estimate the effect of gallbladder ejection fraction comparison results with the help of gamma distribution.

Keywords: Gallbladder Ejection Fraction, Gamma Distribution, Hyperbolic Spaces, Hyperbolic Brownian Motion.

1. Introduction

Quantification of function is an essential part of hepatobiliary imaging in general and biliary dyskinesia in particular [4]. Measurement of gallbladder ejection fraction (GBEF) with intravenous infusion of exogenous cholecystokinin (CCK) is a well-established technique for the diagnosis of biliary dyskinesia, which includes both chronic acalculous cholecystitis (CAC) and sphincter of oddi spasm (SOS). Biliary dyskinesia is characterized primarily by functional alterations without accompaniment of morphologic changes [4]. A low GBEF is the characteristic feature of CAC. Reflux into the intrahepatic ducts of bile emptied from the gallbladder during CCK infusion, and subsequent paradoxic filling of the gallbladder immediately after cessation of octapeptide of CCK (CCK-8) infusion are the main features of SOS. These are well established parameters using an intravenous infusion of CCK-8 as the stimulus.

A total of 30 min of data collection with CCK-8 is usually sufficient to generate all the necessary parameters required for diagnosis [2]. A fatty meal, which releases endogenous CCK, also has been used as a stimulant to empty the gallbladder [1, 3]. A direct comparison between CCK-8 and fatty meal, however, has not been made in a sufficient number of healthy individuals to contrast and compare these 2 stimuli. With the current shortage and impending non availability of CCK-8, such a comparison has become more of a necessity than ever before [2]. This project was undertaken to assess in a paired study the effects of dose and duration of infusion of CCK-8 or of fatty meal contents on the magnitude of gallbladder emptying in healthy subjects.

The hyperbolic Brownian motion hardly reflects the underlying structure of the hyperbolic space where it develops. Motions at finite velocity on geodesic lines have been introduced and analyzed in [6-8].

In particular, a motion on half circle geodesics at hyperbolic constant velocity c is studied when deviations on orthogonal lines are assumed to occur at Poisson times. The explicit form of the mean distance of the randomly moving point is obtained and reads

$$E \cosh \alpha(t) = e^{-\frac{\lambda t}{2}} \left\{ \cosh \frac{tA}{2} + \frac{\lambda}{A} \sinh \frac{tA}{2} \right\}$$

Where, λ is the rate of the Poisson process. The above equation used to estimate the effect of gallbladder ejection fraction comparison results with the help of gamma distribution.

2. Mathematical Model

The best known hyperbolic space is the Poincare half plane consisting of the set of points endowed with the metric $D^* = \{(x,y): y > 0\}$ endowed with the metric

$$ds^2 = \frac{dx^2 + dy^2}{y^2}$$

In $D^* = \{(x,y): y > 0\}$ the position of points can be defined by means of Cartesian coordinates (x,y) or by hyperbolic coordinates (α, β) which are connected by means of the formulas

$$\begin{cases} x = \dfrac{sinh\,\alpha \cos\beta}{cosh\,\alpha - sinh\,\alpha \sin\beta} & \alpha > 0 \\ y = \dfrac{1}{cosh\,\alpha - sinh\,\alpha \sin\beta} & -\dfrac{\pi}{2} < \beta < \dfrac{\pi}{2} \end{cases}$$

The geodesic lines in $D^* = \{(x,y): y > 0\}$ are represented by half circles with center on $y = 0$ or vertical half lines, the hyperbolic distance between two arbitrary points (x_1, y_1) and $(x_2, y_2)$of $D^* = \{(x,y): y > 0\}$ is given by

$$\cosh\alpha = \frac{(x_1 - x_2)^2 + y_1^2 + y_2^2}{2y_1 y_2}$$

For a right hyperbolic triangle the following Pythagorean Theorem holds

$$\cosh\alpha = \cosh\alpha_1 \cosh\alpha_2$$

Another important hyperbolic space is the Poincare disk $S = \{(u,v): u^2 + v^2 < 1\}$ and points $(x,y) \in D^* = \{(x,y): y > 0\}$ are mapped onto S by means of the conformal transformation

$$w = \frac{iz+1}{z+i} \qquad (1)$$

Hyperbolic Brownian motion in is a diffusion with generator D^* is a diffusion with generator

$$\frac{1}{2} y^2 \left\{ \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right\}$$

The transition function $p_D(x,y,t)$ is the solution to the Cauchy problem

$$\frac{\partial p_D}{\partial t} = \frac{1}{2} y^2 \left\{ \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right\} p_D$$
$$p_D(x,y,0) = \delta(x)\delta(y-1)$$

The previous problem in hyperbolic coordinates reads

$$\frac{\partial p_D}{\partial t} = \frac{1}{2} \left\{ \frac{1}{sinh\,\alpha} \frac{\partial}{\partial\alpha} \left(sinh\,\alpha \frac{\partial}{\partial\alpha} \right) + \frac{1}{sinh^2\alpha} \frac{\partial^2}{\partial\beta^2} \right\} p_D$$

from which we extract the Cauchy problem for the hyperbolic distance

$$\frac{\partial p_D}{\partial t} = \frac{1}{2} \frac{1}{sinh\,\alpha} \frac{\partial}{\partial\alpha} \left(sinh\,\alpha \frac{\partial}{\partial\alpha} \right) p_D \text{ For } \alpha, t > 0$$
$$p_D(\alpha, 0) = \delta(\alpha)$$

The solution to the previous problem (after the time change $t = t/2$) is

$$p_D(\alpha,t) = \frac{exp\left\{-\frac{t}{4}\right\}}{\sqrt{\pi}\left(\sqrt{2t}\right)^3} \int_\alpha^\infty \frac{\varphi exp\left\{-\frac{\varphi^2}{4t}\right\}}{\sqrt{cosh\,\alpha - cosh\,\varphi}} d\varphi$$

From the form of the generator $\frac{1}{2} y^2 \left\{ \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right\}$ we can see that the coordinates (X, Y) are solutions to the stochastic differential system

$$dX = Y dB_1, X(0) = 0$$
$$dY = Y dB_2, Y(0) = 1$$

The solution to the previous problem is given by

$$X(t) = \int_0^t e^{B_2(s) - \frac{s}{2}} dB_1(s)$$
$$Y(t) = e^{B_2(s) - \frac{t}{2}} \qquad (2)$$

Where B_1 and B_2 are independent Brownian motions.
The law of Brownian in the disk S is solution of

$$\frac{\partial p}{\partial t} = \frac{1}{2^2} (1 - x^2 - y^2)^2 \left\{ \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \right\} p$$

in Cartesian coordinates,

$$\frac{\partial p}{\partial t} = \frac{1}{2^2} (1 - r^2)^2 \left\{ \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial\theta^2} \right\} p$$

in Polar coordinates,

$$\frac{\partial p}{\partial t} = \frac{1}{2} \left\{ \frac{1}{sinh\,\alpha} \frac{\partial}{\partial\alpha} \left(sinh\,\alpha \frac{\partial}{\partial\alpha} \right) + \frac{1}{sinh^2\alpha} \frac{\partial^2}{\partial\beta^2} \right\} p$$

in hyperbolic coordinates. The initial conditions must be written accordingly.

A basic fact about the above equations is that

$$L^v(r,\theta;\varphi) = \left(\frac{1 - r^2}{1 + r^2 - 2r cos(\theta - \varphi)} \right)^v$$

is the Eigen function corresponding to the hyperbolic Laplacian, that is

$$\frac{1}{2^2} (1 - r^2)^2 \left\{ \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial\theta^2} \right\} L^v(r,\theta;\varphi) = v(v-1) L^v(r,\theta;\varphi)$$

The Poisson kernel $L^v(r,\theta;\varphi)$ can also be given in hyperbolic coordinates α, φ as

$$\left(\frac{1}{cosh\,\alpha + sinh\,\alpha \sin\varphi} \right)^v$$

and possesses the property that

$$\int_0^{2\pi} \left(\frac{1}{cosh\,\alpha + sinh\,\alpha \sin\varphi} \right)^v d\varphi = P_{-v}(cosh\,r) \quad (3)$$

The hyperbolic Brownian motion hardly reflects the underlying structure of the hyperbolic space where it develops. Motions at finite velocity on geodesic lines have been introduced and analyzed in [6-8].

In particular, a motion on half circle geodesics at hyperbolic constant velocity c is studied when deviations on orthogonal lines are assumed to occur at Poisson times. The explicit form of the mean distance of the randomly moving point is obtained and reads

$$E\,cosh\,\alpha(t) = e^{-\frac{\lambda t}{2}}\left\{cosh\frac{tA}{2}+\frac{\lambda}{A}sinh\frac{tA}{2}\right\} \quad (4)$$

Where, $A=\sqrt{\lambda^2+4c^2}$ and λ is the rate of the Poisson process. Many other properties of this finite velocity motion are derived and its version adapted on the sphere.

3. Example

Chosen subjects denied having any abdominal pain, had normal liver function, had normal liver and gallbladder on ultrasound examination, and were not taking medications that would affect gallbladder emptying. Each subject was studied twice, once with 2 equal sequential doses of CCK-8 and, on a separate occasion, with a half and half milk fatty meal (HHFM). Women in the reproductive age group were studied within 10 days after the onset of the last menstrual period. Because hormone replacement therapy (HRT) was controversial at the time, postmenopausal women on HRT were excluded. After 6 to 8 hours of fasting, each subject underwent cholescintigraphy, receiving 111 MBq (3 mCi) ^{99m}Tc-hepatic iminodiacetic acid (HIDA) intravenously while lying supine underneath a large field of view gamma camera fitted with a low energy, all purpose, parallel hole collimator. Hepatic phase images were obtained at 1 frame per minute for 60 min.

Gallbladder phase image data were collected separately at 1 frame per minute for another 60 min (61–120 minutes). Both studies were recorded on a 64×64×16 computer matrix. Two equal doses of CCK-8 (denoted as CCK1 and CCK2) were administered sequentially. Each CCK-8 dose consisted of 3 ng/kg/min administered intravenously for 10 minutes through an infusion pump. Infusion of the first dose (CCK1) was started at 65 minutes after ^{99m}Tc-HIDA injection and the second dose (CCK2) at 95 minutes after ^{99m}Tc-HIDA injection. The study with the fatty meal was performed on another day. The dose of half and half milk used as the HHFM was adjusted for body weight and ingested in the sitting position, just before gallbladder phase data collection in the supine position. Each HHFM included 24 gram fat, 8 gram carbohydrate, 8 gram protein and 320 calories. A count based GBEF was obtained as described previously with CCK-8 and fatty meal [2, 3]. The latent period (time from beginning of CCK-8 infusion or HHFM ingestion to beginning of gallbladder emptying), ejection period (EP, time from beginning to the end of gallbladder emptying) and ejection rate (ER, percentage ejection fraction [EF] divided by EP) were noted for each subject. Because the gallbladder was still emptying at 60 minutes after the meal in most subjects, GBEF was calculated at 60 minutes. Differences in EF, EP, and ER with CCK1, CCK2, and HHFM were subjected to repeated measures ANOVA with subsequent Newman Keuls analysis of pairs. $P<0.05$ was considered statistically significant [1].

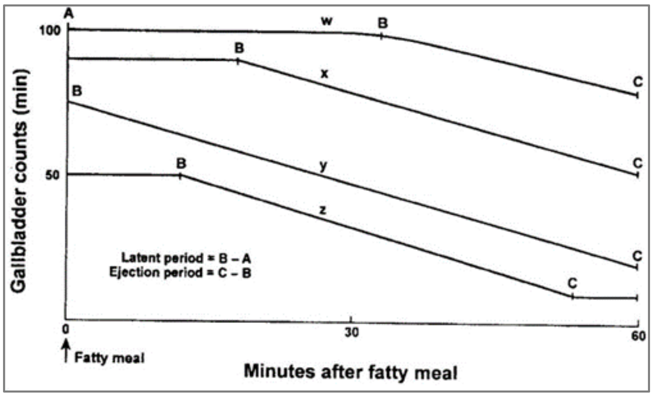

Fig 1: Types of Gallbladder Emptying Curves Seen with Fatty Meal

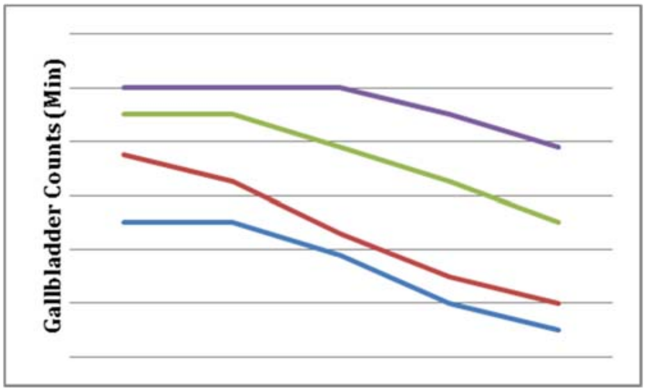

Fig 2: Types of Gallbladder Emptying Curves Seen with Fatty Meal (Using Gamma Distribution)

4. Conclusion

The medical report suggests GBEF with fatty meal can serve as an alternative method to intravenous injection of CCK-8 when the hormone is no longer available for clinical use. The measurement of GBEF with fatty meal requires careful attention to the details of the meal and the measurement time sequence. The medical reports {Figure (1)} are beautifully fitted with the mathematical model {Figure (2)}; $(i.e)$ the results coincide with the mathematical and medical report.

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