Mathematical Biosciences and Engineering

MBE, 18(6): 8758–8782.
DOI: 10.3934/mbe.2021432
Received: 05 April 2021
Accepted: 23 September 2021
Published: 13 October 2021

http://www.aimspress.com/journal/MBE

Research article

Mathematical model for treatment of neonatal hyperbilirubinemia

DongMei Li[1,*], Rui-xue Zhang[1], Qian Xie[2] and Qi Wang[2]

[1] College of Science, Harbin University of Science Technology, Harbin 150080, China
[2] Heilongjiang Hospital, Harbin 150036, China

* **Correspondence:** Email: dmli_2013@126.com; Tel: +8615004650372.

Abstract: Based on the mechanism of neonatal hyperbilirubinemia treatment methods (light, exchange blood and drugs), three types of neonatal hyperbilirubinemia treatment mathematical models are established, and the expressions of the model solutions are given in this paper. By applying clinical test data and numerical approximation algorithm, the relevant parameters in the model can be estimated. According to the standards of "Expert Consensus", two treatment plans are designed, which are 1) the combined transfusion and phototherapy treatment plan and 2) the combined treatment plan of drugs, transfusion and phototherapy. The results of the program operation are numerically simulated and compared with the treatment data of clinical cases. It is found that the coincidence effect is important, which verified the rationality of the model. The model results can track and predict the changes of bilirubin levels in real-time, which provides a theoretical basis for the clinical design of treatment plans.

Keywords: neonatal hyperbilirubinemia; mathematical model; combination treatment plan design; numerical simulation

1. Introduction

Neonatal hyperbilirubinemia is one of the most common diseases in the neonatal period [1]. According to statistics, at least 481,000 full-term and near-term infants in the world suffer from severe hyperbilirubinemia each year. Of which 114,000 have died and 63,000 surviving children have permanent sequelae of varying degrees [2,3]. Due to the imperfect development of newborns, they cannot metabolize the excess indirect bilirubin that continues to increase. Clinically, light therapy, exchange blood therapy and drug therapy are usually used to reduce total bilirubin levels [4,5]. Phototherapy is a treatment that irradiates blue light on the newborn's skin to decompose and reduce the

level of bilirubin in the skin. Transfusion is the simultaneous two-way exchange of blood volume for newborns, the input of blood with a lower bilirubin level, and the replacement of blood with a higher bilirubin level. It is a therapy that effectively reduces the bilirubin level in a short time. The main role of drugs is to promote the conversion of indirect bilirubin into combined bilirubin, accelerate the metabolism and discharge of bilirubin, so as to achieve a treatment to reduce the level of bilirubin.

When the newborn disease is mild, the use of phototherapy can effectively control the disease. An analysis of light therapy statistics found that, the effect of phototherapy is related to factors such as light intensity, age of newborns, the conversion rate between total bilirubin in the body and bilirubin on the skin surface [6]. By comparing the curative effect of intermittent and continuous irradiation, it is found that there is no significant difference, so intermittent treatment with less toxic side effects is adopted [7,8].

When the newborn disease is more serious, the need for blood exchange therapy. Blood exchange therapy for newborns, single or double circulation is usually used for blood exchange. The single-time exchange blood volume is about 80~90 ml/kg for ml/kg its blood volume, and the double-circulation exchange blood volume is about 150~180 ml/kg. The time for exchange blood is generally within 1.5–2 hours [9,10]. Data testing found that a single use of double circulatory exchange can reduce about 45 to 70% of total bilirubin and antibodies in the blood system. The decrease in bilirubin level is positively correlated with the volume of blood exchange per unit weight and the bilirubin level before exchange blood [11,12]. When total bilirubin level is reduced to 50% of the initial state, the time required for exchange blood is much shorter than phototherapy. However, the cost of exchange blood treatment and possible serious adverse reactions are often better for children with severe hyperbilirubinemia [13].

According to the treatment requirements of the condition, drug combined blood exchange and light therapy are often used clinically. Combined treatment can effectively reduce the number of blood exchange or the time of light therapy [14,15]. In order to get a better treatment effect, medication is implemented before exchange blood, which converts part of the indirect bilirubin, which is excluded from the body during exchange blood. The result is better than simple exchange blood [16]. The amount of blood exchange directly affects the replacement rate of the total bilirubin levels, which in turn affects the efficiency of exchange blood [17].

In the second part of this article, based on the analysis of clinical treatment statistics, the relevant factors and treatment mechanisms of the three therapies are selected, and the mathematical models of phototherapy, exchange transfusion and drug treatment of neonatal hyperbilirubinemia are established respectively, and the properties of the models are studied. The trend of bilirubin level changes over time. The third part combines clinical data to identify the parameters in the model. The fourth part is aimed at newborns whose average age of the actual clinical treatment object is over 96 h ,and designs synergistic and combined treatment plans based on clinical treatment principles. The fifth part is to simulate the treatment effect of the design plan, and provide a theoretical basis for the clinical selection of a reasonable exchange blood synergistic phototherapy plan and a combined treatment plan. The sixth part verifies the rationality of the model based on actual clinical treatment cases.

2. Mathematical model for the treatment of neonatal hyperbilirubinemia

The daily production of bilirubin by newborns is significantly higher than that of adults. Due to

the insufficient uptake, binding, and excretion of bilirubin by their liver cells (the excretion rate of newborns is about $0.001\ /h$), the accumulation of the total bilirubin makes the intestines, The particularity of hepatic circulation cannot exclude excess bilirubin. With the increase of age, the production and elimination of bilirubin appear unbalanced, and total bilirubin rises rapidly [18]. When bilirubin increases to saturation, it cannot be metabolized naturally, and the total bilirubin level in neonates can only be reduced by manual intervention.The following combination of clinical treatment data selects relevant factors and the treatment mechanism of various therapies, and establishes related mathematical models.

2.1. Mathematical model of light therapy for neonatal hyperbilirubinemia

Under blue light irradiation, the internal configuration of the indirect bilirubin molecule under the skin of newborns changes, which can be converted into photochemical products and eliminated from the body. Some of the photochemical products 4Z, 15E isomers will be reversed and participate in the circulation of bilirubin in the skin and body again [19]. Clinically, the standard light intensity is usually used for irradiation, with an intensity of $8\sim12\mu w/(cm^2\cdot nm)$, but sometimes strong light with an intensity of $35\sim45\mu w/(cm^2\cdot nm)$ is also used. The paper [20] gives the statistical data of the bilirubin level of newborns under standard light intensity L_1 and strong light intensity L_2 as shown in Table 1.

Table 1. Transcutaneous bilirubin levels before and after treatment of neonates with different light intensity.

Group	Before treatment bilirubin level ($\mu mol/L$)	Treatment for 12 hours bilirubin level ($\mu mol/L$)	Treatment for 24 hours bilirubin level ($\mu mol/L$)
Standard intensity L_1	307.25 ± 48.73	252.65 ± 45.24	206.49 ± 40.83
Strong light L_2	311.36 ± 49.52	235.81 ± 41.69	172.60 ± 38.95

According to the statistical analysis of the data in Table 1, it is found that under blue light irradiation, there is a linear correlation between the reduction of bilirubin and the light intensity. Use $I(L)$ to represent the light decomposition rate, let us assume $I(L)=kL$ (L is the light intensity, and k is the decomposition coefficient). Due to the reversal nature, the light decomposition rate is $(1-\sigma)I(L)$. When the light is stopped, $I(L)=0$. Through blood circulation, the body's total bilirubin and transcutaneous bilirubin are continuously exchanged at speeds k_{12} and k_{21}, respectively, thereby gradually reducing the total bilirubin level. The Natural growth rate of neonatal total bilirubin is $r(t)$, if the exchange process of total bilirubin level $x(t)$ and transcutaneous bilirubin level $y(t)$ is regarded as a two-compartment model. The conversion relationship between the two under illumination is shown in Figure 1, and the corresponding parameters are shown in Table 2. For the convenience of research, it is better to use the standard light intensity as the reference (standardized) light intensity and take it as dimensionless 1.

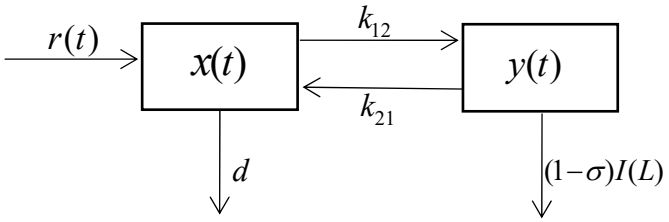

Figure 1. Transformation diagram of percutaneous bilirubin and total bilirubin.

Table 2. The relevant parameters in Figure 1.

Parameter representation	Parameter meaning	Unit
$x(t)$	Total bilirubin level of newborns at time t	$\mu mol / L$
$y(t)$	Transcutaneous bilirubin level of newborns at time t	$\mu mol / L$
$r(t)$	The natural growth rate of neonatal total bilirubin at time t	$\mu mol \cdot L^{-1} \cdot h^{-1}$
k_{12}	The rate at which the skin converts bilirubin into the body	h^{-1}
k_{21}	The rate at which the body converts bilirubin to the skin	h^{-1}
d	Neonatal total bilirubin excretion rate	h^{-1}
k	Illumination decomposition coefficient	h^{-1}
L	Light intensity	——
σ	Reversal rate of bilirubin decomposition products	——

In clinical practice, multiple courses of intermittent light therapy are usually used. Suppose the treatment period of $n(n=1,2\cdots,m)$ course of treatment is $[t_{n-1},t_n]$, and the irradiation time is τ_n. Establish the following mathematical model for neonatal hyperbilirubinemia in the nth course of light therapy

$$\begin{cases} X'(t) = AX(t) + R(t) \\ X(t_{n-1}) = X_{n-1} \\ X(0) = X_0 \end{cases} \qquad t_{n-1} \le t < t_n \tag{1}$$

where

$$X(t) = \begin{pmatrix} x(t) \\ y(t) \end{pmatrix}, \quad A = \begin{pmatrix} -k_{12} - d & k_{21} \\ k_{12} & -k_{21} - (1-\sigma)I(L) \end{pmatrix}$$

$$R(t) = \begin{pmatrix} r(t) \\ 0 \end{pmatrix}, \quad I(L) = \begin{cases} kL & t \in [t_{n-1}, t_{n-1} + \tau_n) \\ 0 & t \in [t_{n-1} + \tau_n, t_n) \end{cases}$$

The two characteristic roots of matrix A are λ_1, λ_2, satisfying

$$\begin{cases} \lambda_1\lambda_2 = (k_{12}+d)(1-\sigma)I(L)+dk_{21} \\ \lambda_1+\lambda_2 = -k_{12}-d-k_{21}-(1-\sigma)I(L) \end{cases}$$

The two characteristic roots of A are negative.

Within $[t_{n-1}, t_n]$, the solution of model (1) is as follows

$$X(t) = \Phi(t)X_{n-1} + \int_{t_{n-1}}^{t} e^{A(t-s)}R(s)\mathrm{d}s \tag{2}$$

where

$$\Phi(t) = \begin{bmatrix} e^{\lambda_1(t-t_{n-1})} & -\dfrac{\lambda_2+(1-\sigma)I(L)}{\lambda_2+d}e^{\lambda_2(t-t_{n-1})} \\ -\dfrac{\lambda_1+d}{\lambda_1+(1-\sigma)I(L)}e^{\lambda_1(t-t_{n-1})} & e^{\lambda_2(t-t_{n-1})} \end{bmatrix}$$

The initial value $X(0)$ of the first phototherapy is total bilirubin level measured, when the newborn is admitted to the hospital. The initial value $X(t_1)$ of the second course of treatment is the total bilirubin level after the end of the first course of treatment. By analogy, using an iterative method, the total bilirubin level and transcutaneous bilirubin level for each course of treatment can be calculated through Eq (2).

2.2. Mathematical model of exchange blood treatment for neonatal hyperbilirubinemia

Clinically, two infusion pumps are usually used for fully automatic peripheral arterial synchronous exchange of blood, inject blood containing trace bilirubin levels at a constant rate of v_1, and at the same time, replace the same amount of blood with high bilirubin levels in newborns at a rate of v_2. $x(t)$ is still used to represent the total bilirubin level of the newborn, and its natural growth rate is $r(t)$. The newborn is regarded as a chamber with a constant total blood volume, and the transfusion process can be regarded as an injection and drainage system. Because the transfusion time is short, the amount of self excretion is not considered. The exchange principle is shown in Figure 2 and the corresponding parameters are shown in Table 3.

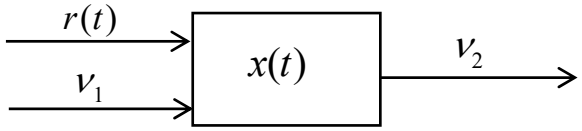

Figure 2. Relationship diagram of serum bilirubin.

Table 3. Figure 2 related parameters.

Parameter representation	Parameter meaning	Unit
$x(t)$	the total bilirubin level of newborns at time t	$\mu mol / L$
v_1	The input rate of the total bilirubin in healthy people	$\mu mol \cdot L^{-1} \cdot h^{-1}$
$r(t)$	The natural growth rate of neonatal total bilirubin at time t	$\mu mol \cdot L^{-1} \cdot h^{-1}$
v_2	Replacement rate of neonatal total bilirubin	h^{-1}

In a single exchange blood treatment course $[t_{n-1}, t_n]$, set the exchange blood time as T. A mathematical model for the treatment of neonatal hyperbilirubinemia by the $nth(n=1,2\cdots,m)$ exchange of blood

$$\begin{cases} x'(t) = v_1 + r(t) - v_2 x(t) \\ x(t_{n-1}) = x_{n-1} \qquad\qquad [t_{n-1}, t_{n-1} + T] \\ x(t_0) = x_0 \end{cases} \tag{3}$$

In time $[t_{n-1}, t_{n-1} + T]$, the solution of model (3) is as follows

$$x(t) = x_{n-1} e^{-v_2(t-t_{n-1})} + e^{-v_2(t-t_{n-1})} \int_{t_{n-1}}^{t} [v_1 + r(s)] e^{v_2(s-t_{n-1})} \mathrm{d}s \tag{4}$$

The initial value $x(t_0)$ of the exchange blood is the total bilirubin level measured, when the newborn is admitted to the hospital, and the change rule of the total bilirubin level of the child with multiple exchange blood is calculated through the formula (4).

2.3. Mathematical model of drug treatment of neonatal hyperbilirubinemia

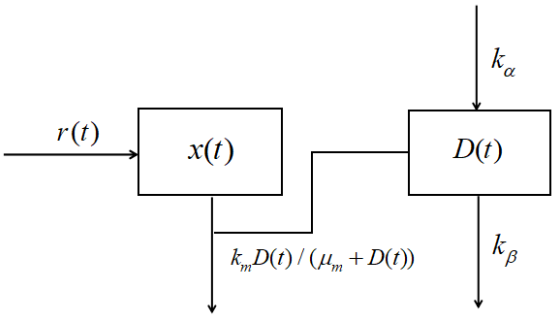

Figure 3. Relationship between albumin and indirect bilirubin.

The albumin in the human body has the effect of binding indirect bilirubin. Due to the insufficient content in the newborns, the indirect bilirubin binding is converted into bound bilirubin to be excreted with urine or bile by importing albumin. This binding ability does not increase indefinitely, that is, as the concentration of albumin in the blood gradually increases, its ability to bind bilirubin gradually becomes saturated [21]. In clinical practice, albumin is infused 1 h before

transfusion, 1 g/kg each time. The exchange of blood can increase the amount of indirect bilirubin exchange, thereby reducing the number of exchanges and the time of phototherapy. Figure 3 shows the relationship between albumin and indirect bilirubin.

The content of albumin in newborns is insufficient, and albumin needs to be instilled to bind its total bilirubin. The absorption process can be considered as consistent with the one-compartment pharmacokinetic model. Albumin is evenly distributed into the blood immediately after entering the body, and combines with the free bilirubin in it, thereby reducing the indirect bilirubin in the body. Considering the saturation reaction of drug binding indirect bilirubin, the saturation binding rate is set to $k_m D(t)/(\mu_m + D(t))$. Where k_m, μ_m is a positive constant. Assuming that the instillation time is T and the dosage is $\bar{D}$ per kilogram of body weight, within the time $[t_0, t_0 + T]$, a mathematical model of drug treatment of neonatal hyperbilirubinemia is established. The relevant parameters are shown in Table 4.

$$\begin{cases} x'(t) = r(t) - \dfrac{k_m D(t)}{\mu_m + D(t)} x(t) \\ D'(t) = k_\alpha - k_\beta D(t) \\ x(t_0) = x_0, D(t_0) = D_0 \end{cases} \tag{5}$$

Table 4. Formula (5) related parameters.

Parameter representation	Parameter meaning	Unit
$x(t)$	Total bilirubin level of newborns at time t	$\mu mol/L$
k_α	Albumin intravenous drip rate	$g/L \cdot h$
$r(t)$	The natural growth rate of neonatal total bilirubin at time t	$\mu mol \cdot L^{-1} \cdot h^{-1}$
$D(t)$	Albumin content at time t	$g/L \cdot kg$
k_β	The primary elimination rate of albumin	h^{-1}
D_0	The body's own albumin content	$g/L \cdot kg$

From the second equation of model (5), the albumin content in $[0, T]$ can be calculated as

$$D(t) = \frac{k_\alpha}{k_\beta}(1 - e^{-k_\beta t}) + D_0 e^{-k_\beta t} \tag{6}$$

Substituting formula (6) into the saturated combination ratio $k_m D(t)/(\mu_m + D(t))$, it can be simplified as

$$\frac{k_m\left(\frac{k_\alpha}{k_\beta}(1 - e^{-k_\beta t}) + D_0 e^{-k_\beta t}\right)}{\mu_m + \frac{k_\alpha}{k_\beta}(1 - e^{-k_\beta t}) + D_0 e^{-k_\beta t}} = \frac{1 + \left(\frac{k_\beta}{k_\alpha} D_0 - 1\right) e^{-k_\beta t}}{C_1 + C_2 e^{-k_\beta t}} \tag{7}$$

where C_1, C_2 parameter to be estimated.

In time $[t_0, t_0+T]$, substituting formulas (7) into (5), the solution can be obtained as follows

$$x(t)=e^{\int_{t_0}^{t}\frac{k_m(\frac{k_\alpha}{k_\beta}(1-e^{-k_\beta s})+D_0e^{-k_\beta s})}{\mu_m+\frac{k_\alpha}{k_\beta}(1-e^{-k_\beta s})+D_0e^{-k_\beta s}}ds}\left(x_0+\int_{t_0}^{t}r(s)e^{-\int_{t_0}^{s}\frac{k_m(\frac{k_\alpha}{k_\beta}(1-e^{-k_\beta \tau})+D_0e^{-k_\beta \tau})}{\mu_m+\frac{k_\alpha}{k_\beta}(1-e^{-k_\beta \tau})+D_0e^{-k_\beta \tau}}d\tau}ds\right) \tag{8}$$

The initial value of $x(t_0)$ is total bilirubin level measured, when the newborn is admitted to the hospital, and the change rule of the total bilirubin level of the child within $[t_0, t_0+T]$ can be calculated by formula (8).

3. Estimation of parameters in the model

By data fitting method and search method, the parameters of models (1), (3) and (5) are estimated. First, the natural growth rate of bilirubin levels is fitted according to actual data (from the lower limit of the intervention standard of phototherapy and blood exchange therapy). Then, according to the clinical data and parameter desirable range, some parameters in the model are fixed to adjust the parameters to be estimated for several times, and the numerical approximation method is applied to gradually search the parameter values. Let us set the basic parameters of light intensity and excretion rate as $L=1, d=0.001$ in the model.

3.1. The natural growth rate of bilirubin $r(t)$

By "Expert Consensus on the Diagnosis and Treatment of Neonatal Hyperbilirubinemia" (abbreviated as "Expert Consensus") [22], The standard intervention value of neonatal total bilirubin level is given clinically and to determine the treatment method. When total bilirubin of newborn exceeds the lower limit of intervention standard value, certain treatment measures must be taken. The intervention standard values of total bilirubin levels in phototherapy and blood exchange therapy are shown in Table 5 [23]. The corresponding scatter points are shown in Figures 4 and 5, respectively.

Table 5. Intervention standard of phototherapy and exchange transfusion for total bilirubin level of newborns at different ages.

Age (h)	~24h	~48h	~72	> 72h
The intervention standard value $x_1(t)$ of total biliary red level of phototherapy （$\mu mol/L$）	≥ 103	≥ 154	≥ 205	≥ 257
The intervention standard value $x_2(t)$ of total bile red level of blood exchange （$\mu mol/L$）	≥ 205	≥ 291	≥ 342	≥ 376

In the absence of treatment, hypothesis $r(t)$ is the rate of change per unit time of neonatal total bilirubin level. Taking into account the trend of data scatter and the saturation of changes in total bilirubin level, hyperbolic function is selected to characterize neonatal total bilirubin levels. Therefore, the lower limit values of the intervention standards are taken to fit the data as follows,

which is the total bilirubin levels of neonates at different ages of light therapy and blood exchange therapy in Table 5

$$x_1(t) = \frac{381.3t + 4150}{t + 91.79} \qquad 0 \le t \le 168 \tag{9}$$

$$x_2(t) = \frac{517.9t + 165}{t + 38.22} \qquad 0 \le t \le 168 \tag{10}$$

where, $x_1(t)$ and $x_2(t)$ respectively represent the fitting function of total bilirubin level in neonates with time light therapy and blood exchange therapy. The fitting function curves of Eqs (9) and (10) are shown in Figures 4 and 5.

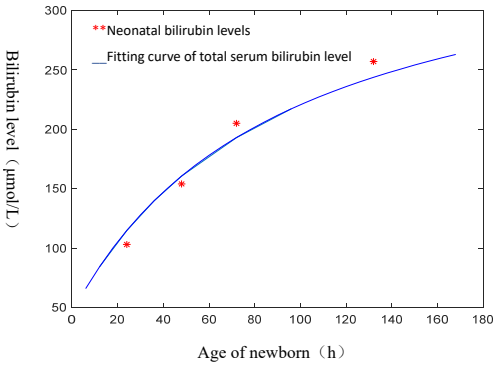

Figure 4. Fitting diagram of neonatal phototherapy bilirubin level.

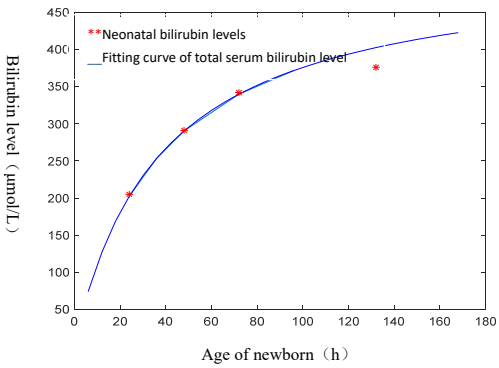

Figure 5. Fitting diagram of bilirubin level in neonatal exchange transfusion.

The change rate of total bilirubin level per unit time ($\mu mol \cdot L^{-1} \cdot h^{-1}$) is defined as natural growth rate. According to Eqs (9) and (10), $r_1(t)$ and $r_2(t)$ of natural growth rate of total bilirubin under phototherapy and blood exchange therapy are obtained respectively.

$$r_1(t) = \frac{30849.527}{(t + 91.79)^2} \qquad 0 \le t \le 168 \tag{11}$$

$$r_2(t) = \frac{19629.138}{(t + 38.22)^2} \qquad 0 \le t \le 168 \tag{12}$$

Note: formula (11) should be substituted into model (2), and formula (12) should be substituted into models (3) and (5).

3.2. Estimation of bilirubin decomposition product reversal rate σ, conversion rate k_{12}, k_{21} and light decomposition rate k

According to [19], $\sigma = 0.75\mu$ can be generated and eliminated from the body, but a small part will be reversed and returned to the body for circulation [24]. The smaller part of the reversal is described μ. It may be assumed to be percolated in the range $10.2 < \mu < 0.5$. According to the principle of pharmacokinetics and literature [25], the conversion rate of neonatal total bilirubin and transcutaneous bilirubin k_{12}, k_{21} is "not much different". Assume that k_{12}, k_{21} is in the range of

(0.18, 0.23). The light decomposition coefficient fluctuates between 0.026 and 0.04 [26,27]. Within the parameters hypothesis, the parameters fixed will be estimated through other disturbed the parameters. The initial value of $y(0)=327.25\mu mol/L$ is from Table 1, $y(t)$ is calculated by formula (2), $y_i\ (i=1,2,3)$ are obtained in the percutaneous bilirubin levels in Table 1, there is

$$\min \sum_{i=1}^{3} \left| y(t_i) - y_i \right| \tag{13}$$

as target estimation parameters.

When the parameter values are $\mu=0.343$, (k_{12},k_{21})=(0.2, 0.23), $k=0.026$, the error is the smallest. Numerical simulation of percutaneous bilirubin curve $y(t)$ and scatter diagram of clinical phototherapy data $y_i\ (i=1,2,3)$ is shown in Figure 6.

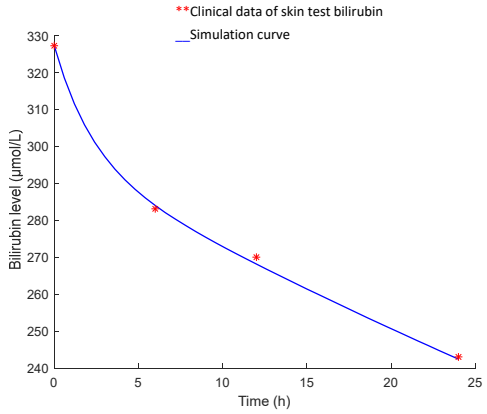

Figure 6. Simulated image of percutaneous bilirubin.

3.3. Estimation of the replacement rate of bilirubin v_2

Table 6. Changes of total bilirubin level under different exchange volume.

Replacement volume (ml/kg) / Group	Total bilirubin level after haplotransfusion ($\mu mol/L$)	Total bilirubin level after exchange blood between single and double ($\mu mol/L$)	Total bilirubin level after double transfusion ($\mu mol/L$)
Group I 298.8 ± 37.4 $\mu mol/L$	169.9 ± 62.5	164.8 ± 14.5	135.5 ± 30.7
Group II 466.3 ± 26.0 $\mu mol/L$	215.7 ± 84.5	197.7 ± 21.8	177.8 ± 29.3
Group III 567.0 ± 44.7 $\mu mol/L$	299.0 ± 55.1	214.4 ± 33.8	227.0 ± 39.6
Group IV 567.0 ± 44.7 $\mu mol/L$	380.4 ± 97.7	276.4 ± 62.0	285.7 ± 67.1
Average bilirubin replacement rate	35.3 ± 12.6%	51.3 ± 6.0%	52.1 ± 9.2%

The article [28,29] gives 118 neonates admitted to hospital with hyperbilirubinemia at the age of 4.9 ± 1.9 days from 2005 to 2011. The bilirubin levels before transfusion are in groups I to IV, and the transfusion is 2 hours. The bilirubin level and average bilirubin replacement rate are shown in Table 6.

The change of $x_i\ (i=1,2,3)$ in each group in the data in Table 6 reflects a positive correlation between the decrease in bilirubin level and the amount of exchange blood. It can also be seen that the bilirubin level after haplotransfusion for mild children is close to the standard of phototherapy, and subsequent phototherapy can be cured. For children with severe hyperbilirubinemia, it is necessary to exchange the blood volume between single and double. Comparing the bilirubin replacement rate of the two types of exchange blood, considering the treatment cost, postoperative infection rate and treatment effect comprehensively, two clinical standards for exchange blood treatment are given:

(1) If the initial bilirubin level is less than 428 $\mu mol/L$, use a single exchange volume.

(2) If the initial bilirubin level is greater than 428 $\mu mol/L$, exchange blood volume between single and double.

In time $[t_{n-1},t_n]$, infuse the neonate with plasma containing a total bilirubin level of approximately $1.71\sim17.1\mu mol/L$ at a constant rate [30]. If a single exchange of blood takes 2 hours, the average bilirubin level infusion rate may be $v_1=4.7025\mu mol\cdot L^{-1}\cdot h^{-1}$. The initial value of total bilirubin level for single-fold exchange transfusion is $x(0)=336\mu mol/L$, and the initial value for single-double exchange transfusion is $x(0)=492.3\mu mol/L$. Calculate the total bilirubin level $x(t)$ of the model (4) from the formula (4), so that $min\sum_{i=1}^{3}\left|x(t_i)-x_i\right|$, to filter the parameters. The bilirubin simulation diagram and the data $x_i\ (i=1,2,3)$ in Table 6 are plotted in Figures 7 and 8.

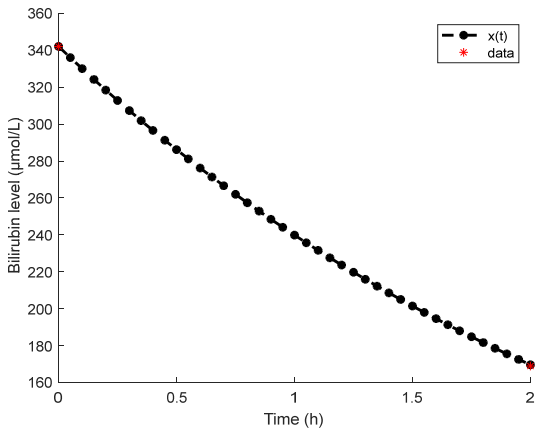

Figure 7. Simulation diagram of total bilirubin in single exchange transfusion.

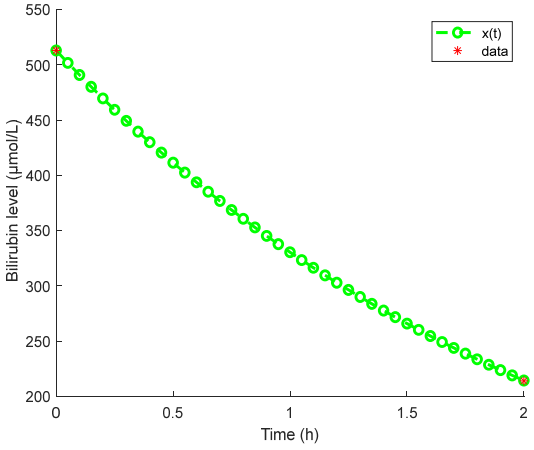

Figure 8. Simulation diagram of total bilirubin in exchange transfusion between single and double.

For the numerical simulation of single-fold exchange of blood, when $v_2=0.375h^{-1}$, the fitting error is 0.0011. For the simulation of single-double exchange of blood, when $v_2=0.4524h^{-1}$, the fitting error is 0.0008, and the fitting effect is better.

3.4. Estimation of the first-level albumin elimination rate k_β and parameters C_1, C_2

Clinically, albumin is generally infused at 1 g per kilogram of body weight before transfusion, the infusion time is T, and the dose is $\bar{D}$. If the newborn's weight is $w\,kg$, there is the calculation formula of albumin intravenous drip rate k_α

$$k_\alpha = \frac{\bar{D}}{T} \cdot w \tag{14}$$

According to the human albumin drug instructions, under normal circumstances, the average half-life of albumin is about 19 days [31]. According to [32], the formula for calculating the first-level elimination rate k_β of intravenous drip medication is as follows

$$k_\beta = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{19 \times 24} \approx 0.00152 h^{-1}$$

The article [33] gives the statistical data of bilirubin levels in full-term newborns with an average birth weight of 2000~2200 g and age $24 \sim 168h$ in the simple transfusion group and the transfusion plus albumin group. as shown in Table 7 and Figure 9.

Table 7. Comparison of total bilirubin level between two groups before and after treatment.

Group	Total bilirubin level before treatment ($\mu mol/L$)	Total bilirubin level for 2 hours of treatment ($\mu mol/L$)
Exchange blood transfusion group	426 ± 104	246 ± 69
Exchange blood transfusion + albumin group	423 ± 98	261 ± 78

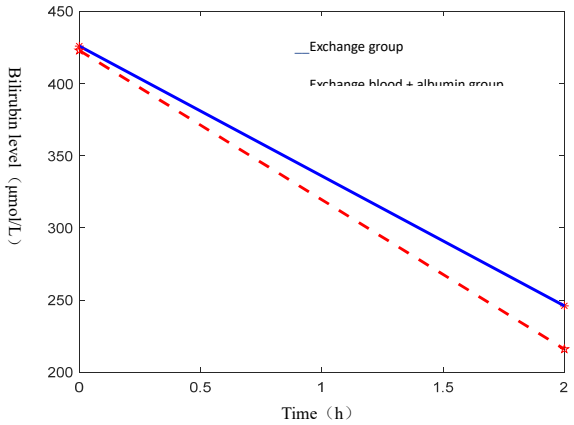

Figure 9. Bilirubin level curve of the two groups before and after treatment.

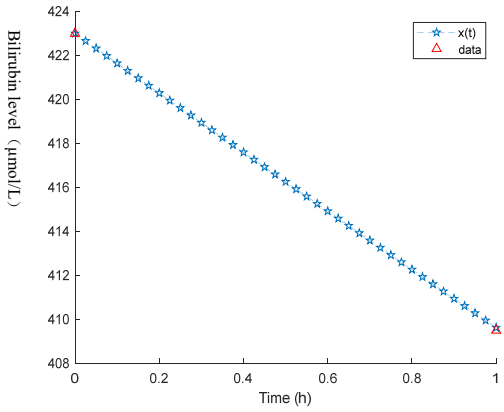

Figure 10. Numerical simulation diagram of bilirubin in vivo.

The difference in total bilirubin level data between the two groups in Table 7 and Figure 11 reflects that the difference is caused by albumin binding indirect bilirubin. Take the newborn's weight as $w = 2000g$ and substitute it into Eq (14) to get $k_\alpha = 1 \cdot 2/1 = 2g/L \cdot h$. Select the initial value of

bilirubin $x(0) = 423\mu mol / L$, substitute k_α into Eq (8), and numerically simulate screening parameters C_1, C_2. The model (5) numerical simulation total bilirubin $x(t)$ curve and the scatter plot of the data in Table 7 are plotted in Figure 10.

From Figure 12, the analysis of the fitting error between the clinical data and the theory shows that when $C_1 = 1.702$, $C_2 = 1.05$, the error of the simulation result is small.

3.5. Summary of model fitting parameters

Model (1) is obtained from Section 3.2–3.4, and the parameter summary Table of model (3) and model (5) is shown in model 8.

Table 8. Numerical table of model parameters.

Parameter symbol	Value	Unit	Parameter symbol	Value	Unit
k_{12}	0.2	h^{-1}	k_{21}	0.23	h^{-1}
σ	0.25725	——	d	0.001	h^{-1}
L	1	——	k	(0.026,0.04)	h^{-1}
ν_1	4.0725	$\mu mol \cdot L^{-1} \cdot h^{-1}$	ν_2	0.375 (single) 0.4524 (between single and double)	h^{-1}
k_α	2	$g \cdot L^{-1} \cdot h^{-1}$	k_β	0.00152	h^{-1}
C_1	1.702	——	C_2	1.05	h^{-1}

4. Design of treatment plan for neonatal bilirubin

From Figures 4 and 5, the level of neonatal bilirubin increases rapidly from 0 to 96 hours of age, but slowly increased from 96 to 168 hours. According to the trend of its growth trend, $0\sim168h$ are divided into 5 age segments, which are denoted as $l_i : 24i\sim24(i+1)$ $(i = 0,1,2,3)$ and $24i\sim24(i+3)$ $(i = 4)$, and the numerical simulation takes the median value of l_i age. Namely, the real-time ages are 12, 36, 60,84 and 132 h, respectively.

The TcB percentile（$\mu mol / L$）of total bilirubin level of newborns at different ages are given in [34]. Among them, only the total bilirubin levels of 95% quantile group of each age exceeds the phototherapy intervention standards in Table 5. From this, without phototherapy intervention , total bilirubin level $\bar{x}(t)$ of the 95% quantile group in newborns is shown in Table 9.

Table 9. Total bilirubin level $\bar{x}(t)$ of the 95% quantile group in newborns without phototherapy intervention.

Age (h)	12	36	60	84	132
95% quantile total bilirubin level $\bar{x}(t)$（$\mu mol / L$）	103.61	178.99	219.1	243.84	272.82

4.1. Principles of phototherapy plan design

By ("Expert Consensus") [22], total bilirubin level of the children admitted to the hospital is in the range of $257\,\mu mol/L$ to $428\,\mu mol/L$, after using standard light intensity, the transcutaneous bilirubin level is lower than $171\mu mol/L$ and the total bilirubin level is lower than $222\sim239\mu mol/L$, and the phototherapy can be stopped. In each course of treatment, total bilirubin level $\bar{x}(t)$ without treatment is shown in Table 9 below and the difference between the total bilirubin level with treatment is not less than $50\,\mu mol/L$.

The treatment plan for the total bilirubin level of newborns whose age is $t_0 \in l_i$ should have the following constraints [22]:

1. The initial value of neonatal total bilirubin level exceeds the intervention value, and it is considered that $x_1(t_0) = y(t_0)$;

2. The discharge condition is the nth phototherapy $\left|\bar{x}(t) - x_1(t)\right| \geq 50(t \in [t_{n-1}, t_n)), x_1(t_n) \leq 222$, $y(t_n) \leq 171$;

3. It is predicted that $x_1(t) \leq 257(t \in [t_{n-1} + \tau_n, 168])$ after discharge, it can be considered that there is no rebound in the newborn's condition.

Combining clinical treatment experience and "Expert Consensus" treatment principles [22], the following two intermittent phototherapy plans are given:

Scheme 1: Irradiation for 6 hours with 6 hours intermittent;

Scheme 2: Irradiation for 12 hours with 12 hours intermittent.

4.2. Scheme design of transfusion and collaborative phototherapy

The incidence of severe and extremely severe hyperbilirubinemia is not very high (from the statistics of clinical cases from Heilongjiang Medicine in recent years, the incidence rate is 1~2%, but acute bilirubin encephalopathy will occur, which seriously harms health. Transfusion therapy can quickly and effectively reduce blood bilirubin, which is a treatment that cannot be replaced by other therapies. According to the "Expert Consensus", when the growth rate of neonatal bilirubin increases abnormally above $428\,\mu mol/L$, replacement of blood can quickly reduce the total bilirubin level $x(t)$. For neonates at age $t_i \in l_i$, after a single exchange of blood, monitor their total bilirubin levels to diagnose whether they need further phototherapy.

The design principles of transfusion cooperative light therapy are as follows:

1. If the child's total bilirubin level reaches the phototherapy standard $x_1(t)$ after a single exchange of blood, the treatment can be stopped;

2. If after a single exchange transfusion, the total bilirubin level of the child is slightly higher than the phototherapy standard $x_1(t)$ and lower than the 95% phototherapy standard $\bar{x}(t)$, or if slightly higher than the total 95% of the newborn When the bilirubin level phototherapy intervention standard is $\bar{x}(t)$, phototherapy is required to be below the standard.

Combining clinical treatment experience and "Expert Consensus" treatment principles [22], the treatment plan of transfusion and phototherapy is as follows:

1. The initial value of neonatal total bilirubin level exceeds the intervention value of transfusion $x_2(t)$, which is $x(t_i) \geq x_2(t)$, and simultaneous transfusion is performed. If the child's initial bilirubin level is less than $428\,\mu mol/L$, use a single exchange volume; if the child's initial bilirubin level is greater than $428\,\mu mol/L$, use a single-double exchange volume.

2. The time for a single exchange of blood is T, and the following 3 situations occur.

1) If $x(t_0+T)<x_1(t_0)$, stop treatment and discharge;

2) If $x(t_0+T)\in(x_1(t_0),\overline{x}(t_0))$ or $x(t_0+T)$ is slightly higher than $\overline{x}(t_0)$, then stop transfusion therapy and proceed with phototherapy;

3) If $x(t_0+T)>\overline{x}(t_0)$, first perform phototherapy for 6 hours. There is still $x(t_0+T+6)>\overline{x}(t_0)$ after phototherapy, and a second exchange of blood is required.

4.3. The design of the combined scheme of drug-assisted exchange transfusion and phototherapy

For the newborns with moderate and severe hyperbilirubinemia, albumin instillation is performed before exchange transfusion to reduce the total bilirubin level $x(t)$. After the end of the total bilirubin level as the initial value of transfusion, the next step of transfusion is combined with light therapy.

Aiming at the total bilirubin level of newborns at the age of $t_i\in l_i$, combining clinical treatment experience and "Expert Consensus" treatment principles [22], the following combined treatment plan is given:

1. The initial value of the total bilirubin level of newborns exceeded the intervention value of exchange transfusion $x_2(t)$, which is $x(t_i)\geq x_2(t)$, and is treated with albumin for 1 hour.

2. From the initial bilirubin level of exchange blood, choose single exchange blood or between single and double exchange blood volume. Set the time of a single exchange of blood as T, and perform exchange of blood in conjunction with phototherapy according to the following three conditions:

1) If $x(t_0+T+1)<x_1(t_0)$, stop treatment and discharge;

2) If $x(t_0+T+1)\in(x_1(t_0),\overline{x}(t_0))$ or $x(t_0+T+1)$ is slightly higher than $\overline{x}(t_0)$, then stop transfusion therapy and start phototherapy;

3) If $x(t_0+T+1)>\overline{x}(t_0)$, there is still $x(t_0+T+7)>\overline{x}(t_0)$ after 6 hours of phototherapy, a second exchange blood treatment is required.

5. Numerical simulation of neonatal bilirubin treatment plan

5.1. Numerical simulation of treatment of neonatal bilirubin by exchange transfusion and phototherapy

According to the design standard of transfusion and collaborative phototherapy in Section 4.2, it is known that the determination of a personalized treatment plan is a process of dynamic change. According to the initial value of the child and the bilirubin level in the course of treatment, combined with the data in Tables 5 and 9, the curative effect is gradually judged, and the treatment plan is finally given (see Table 13). The initial value of the bilirubin level of the child is used to determine the single-fold exchange volume (80~100 ml/kg) or the single-double exchange volume (100~150 ml/kg). Follow-up phototherapy adopts the principle of 6 h intermittent 6 h.

The following is a step-by-step numerical simulation of the process of transfusion and phototherapy. The three groups of Initial bilirubin levels and corresponding blood exchange volume are selected:

Group I $x(0) = 342\mu mol / L$, using single blood exchange volume

Group II $x(0) = 513\mu mol / L$, exchange blood volume between single and double

Group III $x(0) = 612\mu mol / L$, exchange blood volume between single and double

1. Simulated numerical analysis of total bilirubin level after first-stage blood exchange therapy

Table 8 is substituted into formula (4), Table 10 shows the changes of total bilirubin levels in the three groups of neonates at different ages during blood exchange.

Table 10. Changes of total bilirubin levels in three groups of neonates at different ages.

Age (h) \ Group	Total bilirubin level after exchange blood in group I ($\mu mol / L$)	Total bilirubin level after exchange blood in group II ($\mu mol / L$)	Total bilirubin level after exchange blood in group III ($\mu mol / L$)
12	178.6^	222.7^	262.8^
36	173#	217.5^	257.5^
60	171*	215.5#	255.6^
84	170*	214.6#	254.7#
132	169.1*	213.8*	253.9#

After blood exchange, the total bilirubin levels of neonates by the three groups are in Table 10, they are compared with the intervention values of total bilirubin levels in Tables 5 and 9 respectively, and the data analysis found the following situations:

(1) In groups I and II, the total bilirubin level of markers (*) are lower than the phototherapy intervention standard, and the corresponding age children can be discharged directly after a single blood exchange.

(2) In groups I, II and III , the total bilirubin level of markers ($^{\#}$) are all higher than the light therapy intervention standards in Table 5, and the corresponding age children can be cured by light therapy once.

(3) In groups I, II and III , the total bilirubin level of markers (^) are all higher than the phototherapy intervention standard in Table 9. Children of corresponding age should continue to be treated after 1 phototherapy.

2. Simulation numerical analysis of the total bilirubin level after the second stage of phototherapy

The total bilirubin level in Table 10 is marked as (^), which is substituted into Eq (2) as the initial value, and the total bilirubin level after 6 hours of the second stage of phototherapy is numerically simulated, as shown in Table 11.

Table 11. The total bilirubin levels of the three groups after 6 hours of phototherapy.

Age (h) \ Group	Group I total bilirubin level ($\mu mol / L$)	Group II total bilirubin level ($\mu mol / L$)	Group III total bilirubin level ($\mu mol / L$)
12	207.6&	252.8&	293.8&
36	——	234.9&	275.9&
60	——	——	268.9&

By comparing Tables 9 and 11, it is found that 6h after phototherapy, the total bilirubin level of

children marked with ($^{\&}$) is still significantly higher than the intervention standard of phototherapy, and further treatment is still required. Secondary blood exchange therapy is discussed below.

3. Simulated numerical analysis of total bilirubin level after the third stage of secondary blood exchange therapy

The total bilirubin level marked ($^{\&}$) in Table 11 is substituted into Eq (4) as the initial value, and the total bilirubin level after the third stage of secondary exchange transfusion is calculated as shown in Table 12.

Table 12. Total bilirubin level after second exchange transfusion.

Group / Age (h)	The level of total bilirubin after the second transfusion in group I （$\mu mol/L$）	The level of total bilirubin after the second transfusion in groupII （$\mu mol/L$）	The level of total bilirubin after the second transfusion in group III （$\mu mol/L$）
12	112.5#	133.9^	153.2^
36	——	121.6*	140.9#
60	——	——	136*

Table 13. Table of neonates' blood exchange + phototherapy at different ages in the three groups.

Group	Parameter description	Age (h) 12	36	60	84	132
GroupI	Number of exchanges	2	1	1	1	1
	Replacement time (h)	4	2	2	2	2
	Number of phototherapy	2	1	0	0	0
	Duration of phototherapy (h)	36	42	——	——	——
GroupII	Number of exchanges	3	2	1	1	1
	Replacement time (h)	6	4	2	2	2
	Number of phototherapy	3	1	1	1	0
	Duration of phototherapy (h)	18	6	66	42	——
Group III	Number of exchanges	3	2	2	1	1
	Replacement time (h)	6	4	4	2	2
	Number of phototherapy	3	2	1	1	1
	Duration of phototherapy (h)	42	36	6	90	78

Note: Table 13 shows The number of exchanges and the duration of phototherapy required for neonates of mild and severe ages at different ages, they meet the constraints of neonatal bilirubin level intervention, and there is no rebound.

Similarly, comparing Table 12 with Tables 5 and 9 of the phototherapy intervention values, it is found that the children marked with (*) total bilirubin level can be discharged from the hospital. The children marked with ($^{\#}$) can stop the exchange transfusion treatment and continue phototherapy to be cured. The children marked with (^) have total bilirubin levels of $157.4\mu mol/L$ and

$163.3\mu mol/L$ after 6 hours of phototherapy. After the third single transfusion, the total bilirubin levels are $87.06\mu mol/L$ and $95.8\mu mol/L$ respectively, and the transfusion is stopped for phototherapy.

4. List of simulated numerical values of the three groups of treatment plans

Combining Tables 10 to 12, given the initial values of the bilirubin levels of the three groups of children, formulas (2) and (4) can be used to obtain the treatment plan for the time and frequency of exchange blood for newborns at various ages. (as shown in Table 13).

5.2. Numerical simulation of combined treatment of neonatal bilirubin

Considering the treatment needs of severe children, the principle of drug first is adopted , later secondary blood exchange and phototherapy. Take group III in Section 5.1 as an example, the drug albumin is instilled for 1 hour before the exchange of severe neonates, with an initial bilirubin level of $x(0)=612\mu mol/L$. By formula (8) of numerical simulation, the total bilirubin levels of different ages after drug treatment are shown in Table 14.

Table 14. Bilirubin levels of neonates of different ages under 1 hour of drug treatment.

Age (h)	12	36	60	84	132
Total bilirubin level（$\mu mol/L$）	593	589	587.6	586.9	586.2

According to formulas (2) and (3), numerical simulation of the change curve of bilirubin level of different ages in combination with transfusion and phototherapy is shown in the simulation diagrams 11.

The total bilirubin level in Table 14 are taken as the initial value of blood exchange, and Eqs (4) and (2) are still used, the same method as Section 5.1, taking 12 h as an example, the numerical simulation curve of bilirubin level in blood exchange combined with light therapy by phased is shown in Figure 11.

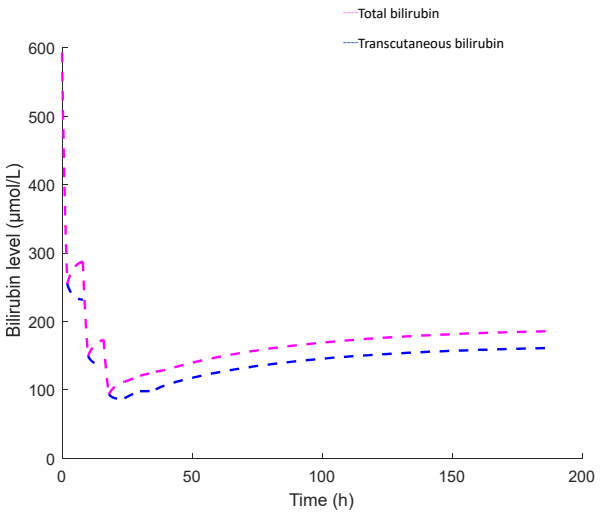

Figure 11. The level of bilirubin in children with exchange transfusion + phototherapy at age 12 h.

Table 15. Details of blood exchange + phototherapy for neonates at different ages in group III.

Age（h）	12	36	60	84	132
Number of exchanges	3	2	1	1	1
Replacement time（h）	6	4	2	2	2
Number of phototherapies	3	1	1	1	——
Duration of phototherapy（h）	30	6	90	78	——

As can be seen from figure 11, the children aged 12 h received comprehensive treatment of drug coordinated blood exchange and phototherapy for 37 h. Total bilirubin levels eventually drops to the point $124.8\mu mol/L$, where treatment is discontinued. According to Eq (2), the highest bilirubin level is predicted to be no rebound possibility after the cessation of phototherapy. Similarly, the details of drug-assisted blood exchange and phototherapy treatment programs in other age groups of group III can be calculated, as shown in Table 15.

By compared with the combined blood exchange and phototherapy group, the combined treatment group can reduce the phototherapy time 6–78 h effectively. For children aged 60 h, one frequency of blood exchange is reduced. Therefore, it can be obtained that drug therapy is an effective treatment method in transfusion therapy. By reducing the frequency of transfusion and the duration of phototherapy, it can effectively reduce the treatment risk and treatment cost.

6. Clinical treatment case analysis

The following two clinical treatment data are used to verify the feasibility of the model. When the expected treatment effect of the model is not achieved due to individual reasons, the initial value of the total bilirubin level of the children is adjusted according to the differences of the children, and the actual treatment results can still be consistent. The numerical simulation results can also be used to predict the feasibility of personality therapy.

6.1. Analysis of clinical treatment cases of transfusion and phototherapy

Medical record number 81013180: Male, aged 144 h at birth, weighing 3 kg. The child is admitted to the neonatal department of the hospital due to jaundice. Clinical diagnosis: hyperbilirubinemia, intracranial hemorrhage with scalp hematoma. Upon admission, the transcutaneous bilirubin is determined to be 470.25 $\mu mol/L$, and the total bilirubin is determined to be 574 $\mu mol/L$.

Table 16. Treatment bilirubin level of children.

Bilirubin level（$\mu mol/L$） \ Date	9.25	9.26	9.27	9.28	9.29
Total bilirubin level	294.5	278	223	—	193.2
Transcutaneous bilirubin levels	—	—	196.65	—	172.71

Clinical treatment plan: use one exchange of blood for 2 hours, then blue light irradiation for 12 hours, with an interval of 12 hours. The changes of bilirubin during the treatment of children are shown in Table 16.

The following is to take the clinically given treatment plan of transfusion combined with phototherapy, and theoretically calculate the change rule of bilirubin level during treatment. First take the initial total bilirubin level of 574 $\mu mol / L$, exchange blood for 2 hours, the total bilirubin level drops to 277.7 $\mu mol / L$, which is used as the initial value of total bilirubin during phototherapy, and the parameters of formula (12) and Table 8 are substituted into formula (2) and In formula (4), the theoretical value is simulated numerically, and the fitted curve and measured data are plotted in Figure 12.

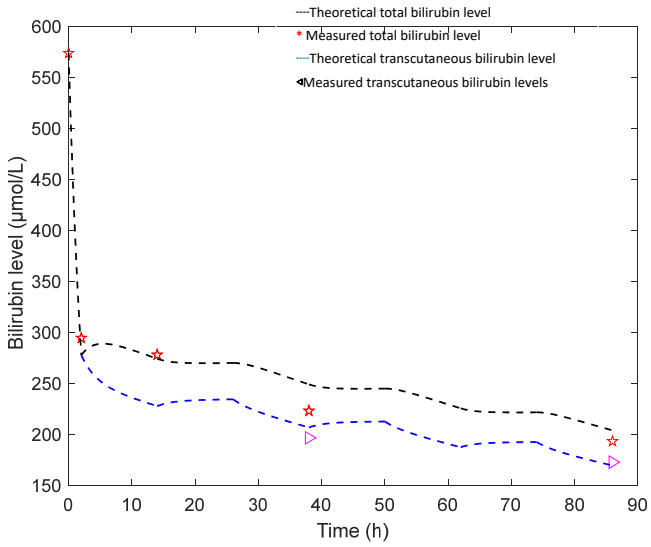

Figure 12. Bilirubin level of children under clinical practice and theoretical treatment.

It can be seen from Figure 12 that after the exchange of blood for 2 hours and 84 hours of phototherapy, the actual and theoretical values of bilirubin levels are 193.2 $\mu mol / L$ and 203.9 $\mu mol / L$ respectively, and transcutaneous bilirubin are 172.71 $\mu mol / L$ and 169.4 $\mu mol / L$ respectively. Meet the discharge standards for phototherapy. The error of total bilirubin level and transcutaneous bilirubin level are 0.0207 and 0.0151, respectively. The available theoretical treatment is consistent with the actual clinical treatment duration, which verifies the rationality of the model.

6.2. Analysis of clinical treatment cases of drug combined exchange transfusion and phototherapy

Medical record number 81011644: Male, aged 48 h at birth, weighing 2.8 kg. The child is admitted to the neonatal department of the hospital due to jaundice. Clinical diagnosis: hyperbilirubinemia. Upon admission, the transcutaneous bilirubin is determined to be 418.95 $\mu mol / L$, and the total bilirubin is determined to be 489.4 $\mu mol / L$.

Clinical treatment plan: first instill albumin for 1 hour, then exchange blood for 2 hours, and then irradiate blue light for 12 hours with an interval of 12 hours. The changes of bilirubin during the treatment of children are shown in Table 17.

Table 17. Bilirubin level of children treated with combined therapy.

Date (day)	14	15	16	17	18	20	21	22	24	25
Total bilirubin level（$\mu mol/L$）	249.4	379.8	383.9	370.1	—	—	317.7	—	205	—
Transcutaneous bilirubin levels（$\mu mol/L$）	—	304.4	—	278.7	285.6	282.2	148.8	253	—	136.8

1. Numerical simulation of bilirubin levels under clinical combined treatment regimens

For children aged 48 h, the clinically given combined treatment plan is adopted: drugs (1 h infusion), exchange blood (2 h) and phototherapy (12 h light, 12 h intermittent). The initial bilirubin level is $x_0 = 489.4\mu mol/L$, and the parameters in Table 8 are substituted into formulas (2), (4) and (8) respectively. The fitting curve of the data simulating the bilirubin level at each stage of the combined treatment is plotted in Figure 13.

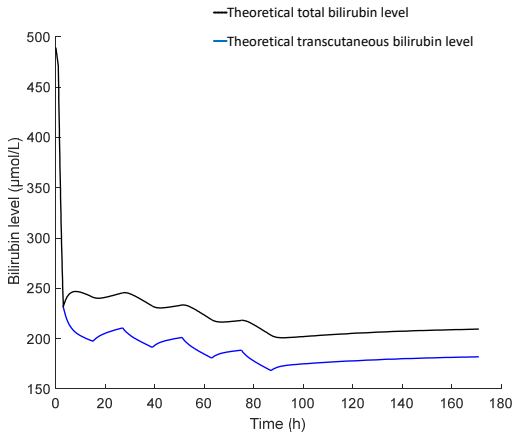

Figure 13. Bilirubin level of children under theoretical combined treatment.

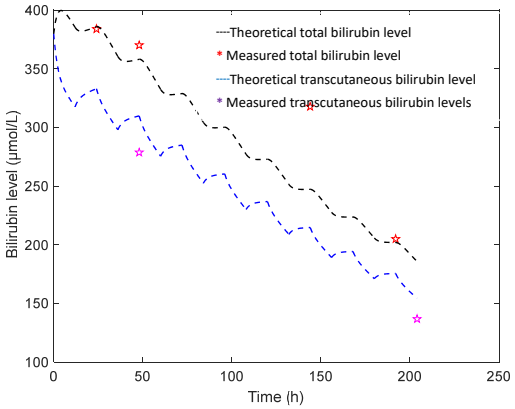

Figure 14. Bilirubin level of children under clinical practice and theoretical treatment.

It can be seen from Figure 13 that the total treatment duration of the combined treatment

program is 87 hours. At the end of the treatment, the total bilirubin level and transcutaneous bilirubin level are calculated to be 203.4 $\mu mol / L$ and 168.3 $\mu mol / L$ respectively, which met the discharge standards for phototherapy.

2. Analysis of the difference between numerical simulation and clinical actual treatment data

From the treatment data in Table 17, it can be found that after the child is admitted to the hospital, the total bilirubin level dropped from $x_0 = 489.4 \mu mol / L$ to 231.7 $\mu mol / L$ after the treatment of albumin infusion and exchange transfusion on the 14th. Explain that the two methods can quickly reduce the level of bilirubin, and compare the clinical treatment data with theoretical values, which are consistent. On the 15th, phototherapy is started, and the total bilirubin level abnormally increased to 379.8 $\mu mol / L$, which deviated from the theoretical value. It is known from the case that the child is too young, the partial pressure of oxygen after birth increased, and the excessive oxygenated red blood cells are destroyed, resulting in excessive bilirubin production, while the liver cells had poor ability to process bilirubin, and abnormally increased. After medication and exchange blood treatment, bilirubin levels are still rising. By adjusting the initial value of phototherapy bilirubin, re-simulate its changing law numerically and compare the actual observation value. Therefore, $x_0 = 379.8 \mu mol / L$ is selected as bilirubin. Similarly to the numerical simulation of 1, the fitting curve between the measured data and the theoretical value is plotted in Figure 14.

It can be seen from Figure 14 that both the theoretical calculation value and the actual clinical light therapy have passed 192 h. After the treatment period, the theoretically calculated in vivo and transcutaneous bilirubin levels are 185.7 $\mu mol / L$ and 154.4 $\mu mol / L$, respectively, in line with the light therapy discharge standards. The error between the modified initial value and the actual treatment in vivo and transcutaneous bilirubin levels in Table 17 are 0.082 and 0.01072, respectively. Therefore, the theoretical treatment is consistent with the actual clinical treatment time, which verifies the rationality of the combined treatment.

Due to the different individual conditions of patients, the model may not achieve the expected effect. But the initial value of total bilirubin level can be adjusted to get the actual treatment results.

3. Numerical simulation of recommended treatment plan

From Figure 14, it is found that the total bilirubin level of the child has abnormally increased after the drug exchange transfusion treatment, and he needs to be treated with light for up to 192 h. The initial value of $x_0 = 379.8 \mu mol / L$ is now selected for single exchange transfusion plus light therapy. The theoretical treatment simulation curve is shown in Figure 15.

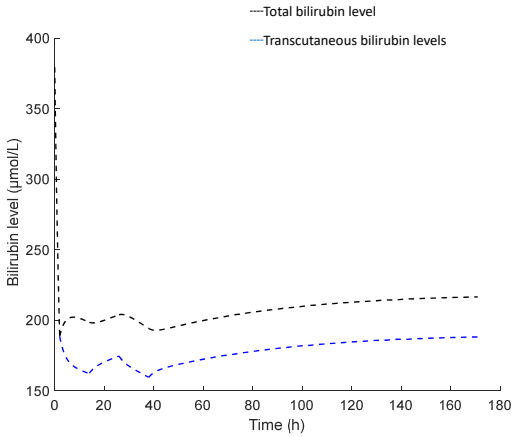

Figure 15. Simulation curve of theoretical treatment for children.

Comparing Figures 14 and 15, it is found that if the second single-fold exchange blood is combined with light therapy, the treatment time is 38 hours, which is much smaller than 192 hours of light therapy alone, and no secondary rebound occurs. Through this case analysis, when the total bilirubin level of the child is high after the first exchange transfusion, it is recommended to use the second exchange transfusion combined with light therapy, but the child's bearing capacity should also be followed.

Considering the patient's personality needs (tolerance, treatment time, treatment cost, etc.), the treatment plan is suggested by numerical simulation. Although it can shorten duration of the treatment, there are many factors involved in the choice of treatment, which is only a reference for doctors and patients' families. The answers to questions 6 and 7 of the reviewers are as follows, and have been modified in the paper.

7. Conclusions

In this research, three types of mathematical models for the treatment of neonatal hyperbilirubinemia are established according to the mechanism of the combination of light, exchange blood and drugs with bilirubin. The expression of the real-time change of bilirubin level is provided. From the clinical treatment data, a numerical approximation algorithm is used to identify the relevant parameters in the model. Two types of treatment plans are numerically simulated, which are 1) the change curve of neonatal bilirubin level under different age and disease treatment plans, and 2) the simulation results can provide theoretical suggestions for clinical treatment plans. Finally, this study has compared the clinical treatment case data and the model calculation data，the result verifies the feasibility of the proposed model.

Acknowledgments

This work was supported by the project of Nature Scientific Foundation of Heilongjiang Province (A2016004), National Natural Science Foundation of China (11801122).

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. B. D. Gaqg, N. S Kabra, H. Balasubramanian, Role of massage therapy on reduction of neonatal hyperbilirubinemia in term and preterm neonates, a review of clinical trials, *J. Matern.-Fetal Neonat. Med.*, **32** (2019), 301–309.
2. V. K. Bhutani, A. Zipursky, H. Blencowe, R. Khanna, M. Sgro, F. Ebbesen, et al., Neonatal hyperbiliru-binemia and Rhesus disease of the newborn, incidence and impairment estimates for 2010 at regional and global levels, *Pediatr. Res.*, **74** (2013), 86–100.
3. J. E. Lawn, H. Blencowe, S. Oza, D. You, A. C. Lee, P. Waiswa, et al., Every newborn, progress, priorities and potential beyond survival, *Lancet*, **384** (2014) , 189–205.
4. J. Li, Application of metalloporphyrin to reduce bilirubin production in neonatal hyperbilirubinemia, *J. Pediatr. Pharm.*, **20** (2014), 53–56.

5. C. Y. Zhou, The effect of nursing intervention on blue light treatment of neonatal jaundice, *Chin. Primary Med.*, **19** (2012), 638–639.
6. Y. Ji, Application and related problems of phototherapy in neonates with hyperbilirubinemia, *Int. J. Pediatr.*, **40** (2013), 272–274.
7. Z. L. Peng, Comparative study on the efficacy and safety of intermittent and continuous blue light irradiation in the treatment of neonatal jaundice, *Primary Med. Forum*, **21** (2017), 4815.
8. T. P. Vogl , T. Hegyi , I. M. Hiatt, Intermittent Phototherapy in the Treatment of Jaundice in the Premature Infant, *J. Pediatr.*, **92** (1978), 627–630.
9. C. Q. Xu, J. Bai, G. U. Wei, Clinical effect of exchange blood therapy on neonatal hyperbilirubinemia, *Med. Rev.*, **25** (2019), 3313–3316.
10. X. X. Zuo, A. M. Xue, L. Na, Single and double circulating blood volume exchange transfusion for severe neonatal hyperbilirubinemia, *J. Henan Univ. Sci. Technol. (Med. Ed.)*, **35** (2017), 129–131.
11. L. X. Yang, X. L. Zheng, H. Y. He, Study on the effect of single and double blood transfusion on neonatal hyperbilirubinemia, *Chongqing Med.*, **46** (2017).
12. L. H. Long, L. Q. Li, J. L. Yu, Multi-factor analysis of the effects of exchange transfusion therapy on neonatal hyperbilirubinemia and the occurrence of adverse events, *J. Pract. Pediatr.*, **14** (2011), 38–40.
13. M. Ge, J. Tang, D. Z. Mu, Clinical study of the effect of exchange blood therapy and enhanced phototherapy on the nervous system of newborns with severe hyperindirect bilirubinemia, *Chin. J. Neonatol.*, **34** (2019), 8–13.
14. L. Y. Fan, Y. H. Xu, Research progress of neonatal bilirubin encephalopathy, *J. Pediatr. Pharm.*, **22** (2016), 50–54
15. M. Shahian, M. A. Moslehi, Effect of albumin administration prior to exchange transfusion in term neonates with hyperbilirubinemia--a randomized controlled trial, *Indian Pediatr.*, **47** (2010), 241–244.
16. M. Ge, J. Tang, Progress in treatment of neonatal severe hyperbilirub- inemia, *Chin. J. Matern. Child Clin. Med. (Electr. Version)*, **14** (2016), 360–365.
17. S. Thayyil, D. W. A. Milligan, Single versus double volume exchange transfusion in jaundiced newborn infants, *Cochrane Data. Syst. Rev.*, **4** (2006), 4592.
18. C. Q. Xu, J. Bai, G. U. Wei, Clinical Effects of Blood Exchange Therapy in Treatment of Neonatal Hyperbilirubinemia, *Med. Recapitul.*, **25** (2019), 3315–3316.
19. Z. P. Fang, Y. Lei, S. M. Wu, Phototherapy and its parameters for neonatal jaundice (review), *J.Clin. Pediatr.*, **3** (1992), 196–198.
20. X. H. Lu, Q. M. Meng, Parallel comparative study of intensive light therapy in the treatment of neonates with hyperbilirubinemia, *Chin. Med. Sci.*, **18** (2017), 68–71.
21. M. T. C. Ambat, E. M. Ostrea, J. V. Aranda, Effect of ibuprofen L-lysinate on bilirubin binding to albumin as measured by saturation index and horseradish peroxidase assays, *J. Perinatol. Off. J. Californ. Perinat. Associat.*, **28** (2008), 287.
22. Neonatology Group, Pediatrics Branch of Chinese Medical Association. Expert consensus on diagnosis and treatment of neonatal hyperbilirubinemia, *Chin. J. Pediatr.*, **52** (2014), 745–748.
23. H. M. Ye, K. L. Wei, Summary of the National Symposium on Neonatal Jaundice and Infection (with the recommended intervention plan for neonatal jaundice), *Chin. J. Pediatr.*, **39** (2001), 184–185.

24. C. M. Zhang , L. Z. Du, J. Yu, Determination of the correction factor of unbound photoisomer of bilirubin by high performance liquid chromatography and its clinical significance, *J. Zhejiang Univ. (Med. Ed.)*, **29** (2000), 105–107.
25. A. Knudsen, The Cephalocaudal Progression of Jaundice in Newborns in Relation to the Transfer of Bilirubin from Plasma to Skin, *Early Human Dev.*, **22** (1990),23–28.
26. Q. Y. Dai, Observation of the effect of intense light therapy and traditional light therapy on neonatal hyperbilirubinemia, *Chongqing Med.*, **46** (2017) ,1828.
27. J. LI, Comparison of efficacy and safety of intense light therapy and traditional light therapy on neonatal hyperbilirubinemia, *New Med. Knowl.*, (2019), 56–58.
28. B. Y. Zhang, Analysis of dose-effect relationship and influencing factors of exchange transfusion therapy in neonates with hyperbilirubinemia, *Guangxi Med. Univ.*, 2012.
29. M. C. Chen, K. Cai, Analysis of the effect of blood exchange on the blood index of severe neonatal hyperbilirubinemia, *Int. J. Laborat. Med.*, **8** (2013), 966–967.
30. X. M. Shao, H. M. Ye, X. S. Qiu, Practical Neonatology (Fifth Edition), *Beijing: People's Med. Publ. House*, (2019), 112–446.
31. A. Zorzi, S. Linciano, A. Angelini, Non-covalent albumin-binding ligands for extending the circulating half-life of small biotherapeutics, *Med. Chem. Commun.*, **10** (2019), 1068–1081
32. S. J. Huang, M. T. Li, R. Z. Chen, Dosage design for individualized admini- stration, *New Med.*, **34** (2003), 21.
33. M. L. Zhang, The effect of albumin on the treatment of hyperbilirubinemia by exchange blood transfusion, *Hebei Med.*, **33** (2011), 2613–2614.
34. X. P. Li, F. Wu, L. Chang, Transcutaneous bilirubin levels in the first 120 hour in term an neonates, *J. Pediatr. Pharm.*, **19** (2013), 4–6.