Can Convalescent Plasma Transfusion Reduce the COVID-19 Transmission?

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Abstract

With no vaccine available on the market, handling the COVID-19 pandemic is still a difficult problem to do. Preventive actions, such as wearing masks, distance guarding, frequent hand washing, and others are still the most important interventions in handling the transmission of this disease. Apart from disease transmission, the mortality rate is also an issue that has been widely studied in order to reduce its intensity. So far several countries have allowed the use of convalescent plasma transfusion (CPT) in the management of moderate and severe COVID-19 patients. Although this method is a fairly old method and is often used for other diseases, so far there have not been many studies on the impact of using CPT for COVID-19 on the population level. Several early studies of this use have yielded prospective results with reduced mortality rates. In this paper, we show by using a simple discrete mathematical model, that the uses of CPT for COVID-19 patients can also reduce the outbreak, in the sense of reducing the peak number of active cases and the length of the outbreak itself. The model used is the simplest discrete SIR and SEIR models. The completion of the model is done numerically through simulation on a spreadsheet to obtain general insight regarding the effect of the CPT application in COVID-19 management.

Keywords
Pandemic COVID-19, SIR, SEIR, Discrete Equations, Convalescent Plasma Transfusion.

1. Introduction

COVID-19 pandemic was officially announced less than a year ago by the WHO. The disease has been declared as a Pandemic by the World Health Organization (WHO) on March 11, 2020. However, disastrous impact to almost all aspects of human life becomes apparent from time to time. It is a very dangerous new disease in terms of health impact, economy, and other human aspects. COVID-19 so far is still regarded as a disease that difficult to understand, let alone to control, due to several reasons such as lack of data and confusing report (Caudill, 2020). This is among the reasons why so far most infected countries still struggling combating the disease. This disease is caused by the Corona SARS-2 virus and is thought to have originated in Wuhan, China. At that time, more than 118,000 cases were recorded in 114 countries with 4,291 people losing their lives (WHO, 2020). To see the widespread of the disease, we note that as of April 11, 2020, the figure has increased dramatically with a total number of more than 1.5 million cases of infection and more than one hundred fatalities and at the end of July 2020, there were 16,839,692 recorded positive cases of infection with 661,379 deaths, and even currently those number have reached to more than 65 million and one and a half million, respectivelly (Worldometer, 2020).

Since the announcement of the pandemic, almost every country has made very intensive effort to combat the disease, albeit with a wide variety of responses. Efforts are generally directed to handling cases of infection, prevention of transmission and development of early detection methods for monitoring transmission of the disease.

Currently the use of convalescent plasma transfusion (CPT) is being considered as one method that may reduce the number of transmission, especially in reducing the number of mortality of the moderate and severe patients. Several government have already recommended the use of this method to combating the COVID-19. For example Indonesia, USA, UK (CNN Indonesia), Australia (Detikcom), India (Agarwal, 2020), and many others. Convalescent plasma transfusion uses blood taken from people who have recovered from a disease infection to help other patients recover. Convalense is a condition when someone who previously contracted a disease heals or grows strong after the illness and convalescent means "recovering from sickness or debility" (Merriam Webster Dictionary). Since there is no approved treatment for COVID-19 so far, convalescent plasma therapy for people with coronavirus disease 2019 (COVID-19) is already allowed by the U.S. Food and Drug Administration (FDA). The blood is donated by people who have recovered from COVID-19. The blood has antibodies to the COVID-19 virus. The blood is processed by removing the blood cells to produce the liquid (plasma) and antibodies leaving behind. The resulting plasma can be given to people with COVID-19 to boost their ability to fight the virus, e.g. by transfusion and is usually called as the convalescent plasma transfusion (Mayo Clinic).

The use of CPT is not new. The CPT has been used for more than 100 years as a strategy of passive immunization in the prevention and treatment of epidemic infections (Garroud et al, 2016). The first documented use at least goes back to 1918-1920 in which it was applied during the Spanish influenza A (H1N1) pneumonia or could be further older than that (Marson et al, 2020). This method is regarded as a possible therapy for patients with COVID-19 infection (Cao and Shi, 2020). Even several studies showed that the convalescent plasma could reduce the mortality risk of a patient that given the CPT treatment (Salazar et al., 2020a,b).

The effect of CPT is basically acknowledged to be a clinical effect to the individual of the patient who is given the CPT treatment. Many references show that the effect is the reduction of mortality risk of the patient. The effect of the CPT application in the population level is not clear so far. Only a few mathematical model literature (e.g Huo et al., 2020) discusssing this issue using mathematical modeling approach. In this paper we present a simple mathematical model in assessing the impact of CPT into the disease transmission. The model is not COVID-19 specific model, but a more generic transmission model in the form of simple discrete time SIR and SEIR model.

2. Method

We use mathematical modeling approach in answering the question in the title of the paper. We reiterate the question "Can Convalescent Plasma Transfusion Reduce the COVID-19 Transmission?" Most papers in the literature show that there are positive results of the use of the CPT to COVID-19 patients. Many of the patients who are given the CPT treatment healed or recovered from COVID-19. The data in (Salazar et al. 2020) shows that the group of patients transfused with the plasma has lower mortality rate than those who did not. In the model we develop here we assume that the effect of the CPT is to increase the rate of recovery. Here we use the discrete time version of the SIR and SEIR epidemic model as discussed in Nykamp and Morrissey (2003). Other simple model such as in Switkes (2003) can also be used. The equilibrium solution of the model will be looked for and it's behaviour will be investigated analytically while the transient solution will be explored numerically.

3. Results and Discussion

3.1 The SIR Discrete Model

Let us assume a closed population with $N(t)=S(t)+I(t)+R(t)=N$ constant. The most simplest SIR model is given by

$$S(t+1)=S(t)-\beta S(t)I(t) \tag{1}$$

$$I(t+1)=I(t)+\beta S(t)I(t)-\alpha I(t) \tag{2}$$

$$R(t+1)=R(t)+\alpha I(t) \tag{3}$$

We are interested in looking at the steady state solution of the model. To find the steady state solution from (1) we have $I^* = 0$ and from (2) we have $S^* = \dfrac{\alpha}{\beta}$. Furthermore, since $N(t) = S(t) + I(t) + R(t) = N$ is constant, then we have $R^* = N - S^* - I^* = \dfrac{\beta N - \alpha}{\beta}$. Hence the steady state solution is given by $(S^*, I^*, R^*) = \left(\dfrac{\alpha}{\beta}, 0, \dfrac{\beta N - \alpha}{\beta}\right)$.

Next suppose that in the presence of CPT, the rate of recovery increases proportionally to the number of recovered people from COVID-19, say it follows the linear function $\alpha + \varepsilon R(t)$. Other form such as $\dfrac{\alpha + \varepsilon R(t)}{1 + R(t)}$ can also be used to take into account an upper bound or saturation of the effect of convalecents. Then we have the modified model in the form of

$$S(t+1) = S(t) - \beta S(t) I(t) \tag{4}$$
$$I(t+1) = I(t) + \beta S(t) I(t) - (\alpha + \varepsilon R(t)) I(t) \tag{5}$$
$$R(t+1) = R(t) + (\alpha + \varepsilon R(t)) I(t) \tag{6}$$

As before we can find the steady state solution, which from (4) we have $I_\varepsilon^* = 0$ and from (5) we have $S_\varepsilon^* = \dfrac{\alpha + \varepsilon R_\varepsilon^*}{\beta}$. Again, since $N(t) = S(t) + I(t) + R(t) = N$ is constant then we have $R_\varepsilon^* = N - S_\varepsilon^* - I_\varepsilon^* = \dfrac{\beta N - \alpha}{\beta + \varepsilon}$. Hence the steady state solution is $(S_\varepsilon^*, I_\varepsilon^*, R_\varepsilon^*) = \left(\dfrac{\alpha + \varepsilon R_\varepsilon^*}{\beta}, 0, \dfrac{\beta N - \alpha}{\beta + \varepsilon}\right) = \left(\dfrac{\alpha + \varepsilon N}{\beta + \varepsilon}, 0, \dfrac{\beta N - \alpha}{\beta + \varepsilon}\right)$. To see the effect of the CPT in the long-term transmission we could compare this steady state solution to the original SIR model in which the CPT absence. We found that the presence of the CPT increases the final size of susceptibles as shown in the following result.

Result 1 (The Equilibrium Properties):

a. The final size of the susceptibles in the presence of CPT is higher than the final size in the absence of CPT.
b. The final size of the infectives in the presence of CPT as well as the final size in the absence of CPT is zero.
c. The final size of the recovers in the presence of CPT is lower than the final size in the absence of CPT.

Proof:

a. The ratio $\dfrac{S^*}{S_\varepsilon^*} = \left(\dfrac{\alpha}{\beta}\right) \div \left(\dfrac{\alpha + \varepsilon R_\varepsilon^*}{\beta}\right) = \dfrac{\alpha}{\alpha + \varepsilon R_\varepsilon^*} < 1$.
b. Obvious.
c. $\dfrac{R^*}{R_\varepsilon^*} = \left(\dfrac{\beta N - \alpha}{\beta}\right) \div \left(\dfrac{\beta N - \alpha}{\beta + \varepsilon}\right) = \dfrac{\beta + \varepsilon}{\beta} > 1$.

Result 1 only reveals the equilibrium behaviour of the solution. Here we will not attempt to proof the transient behaviour of the solution analitycally, instead we will give numerical examples in the section that follows.

3.2 The SEIR Discrete Model
Let us assume a closed population with $N(t) = S(t) + E(t) + I(t) + R(t) = N$ is constant. By modifying equations (1) to (3) we have and adding an equation for the dynamics of *E* then we have

$$S(t+1) = S(t) - \beta S(t)I(t) \quad (7)$$
$$E(t+1) = E(t) + \beta S(t)I(t) - \delta E(t) \quad (8)$$
$$I(t+1) = I(t) + \delta E(t) - \alpha I(t) \quad (9)$$
$$R(t+1) = R(t) + \alpha I(t) \quad (10)$$

As before we are interested in looking at the steady state solution of the model. To find the steady state solution from (10) we have $I^* = 0$ and from (8) and (9) we have $S^* = \frac{\alpha}{\beta}$. Furthermore, since $I^* = 0$ from (9) we have $E^* = 0$. Moreover, since $N(t) = S(t) + E(t) + I(t) + R(t) = N$ then we have $R^* = N - S^* - E^* - I^* = \frac{\beta N - \alpha}{\beta}$.

Hence, the steady state solution is given by $(S^*, E^*, I^*, R^*) = \left(\frac{\alpha}{\beta}, 0, 0, \frac{\beta N - \alpha}{\beta} \right)$.

Next, as before suppose that in the presence of CPT, the rate of recovery increases proportionally to the number of recover people from COVID-19, say it follows the linear function $\alpha + \varepsilon R(t)$. The modified SEIR model in the presence of the CPT then is given by

$$S(t+1) = S(t) - \beta S(t)I(t) \quad (11)$$
$$E(t+1) = E(t) + \beta S(t)I(t) - \delta E(t) \quad (12)$$
$$I(t+1) = I(t) + \delta E(t) - (\alpha + \varepsilon R(t))I(t) \quad (13)$$
$$R(t+1) = R(t) + (\alpha + \varepsilon R(t))I(t) \quad (14)$$

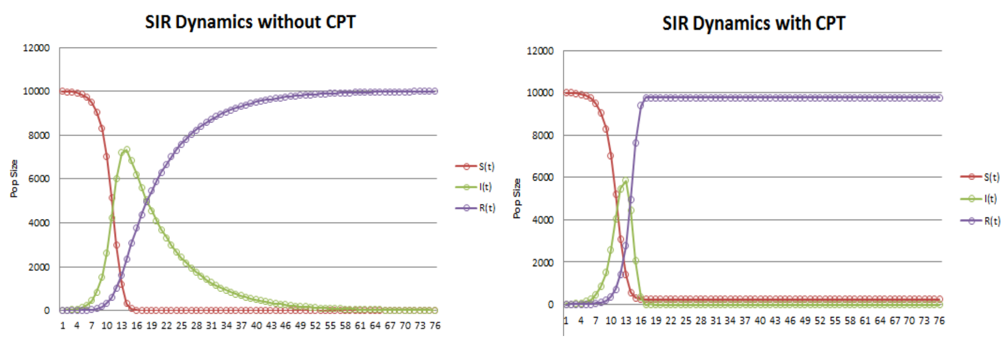
As in the case of SIR we can find the steady state solution, which is given by $(S_\varepsilon^*, E_\varepsilon^*, I_\varepsilon^*, R_\varepsilon^*) = \left(\frac{\alpha + \varepsilon R_\varepsilon^*}{\beta}, 0, 0, \frac{\beta N - \alpha}{\beta + \varepsilon} \right) = \left(\frac{\alpha + \varepsilon N}{\beta + \varepsilon}, 0, 0, \frac{\beta N - \alpha}{\beta + \varepsilon} \right)$. To see the effect of the CPT in the long-term transmission we could also compare this steady state solution to the original SEIR model in which the CPT absence and found that the presence of the CPT increases the final size of susceptibles. It is trivial to show that result similar to Result 1 also holds for this SEIR model.

We do several simulation to assess the impact of the CPT in the transient solution. Let $S(t),\ E(t),\ I(t),\ R(t)$ be the solution of the system without the use of CPT and $S_\varepsilon(t),\ E_\varepsilon(t),\ I_\varepsilon(t), R_\varepsilon(t)$ be the solution of the system with the use of CPT, then the following properties holds for every discrete time $t \geq 0$: $S_\varepsilon(t) \geq S(t)$, $I_\varepsilon(t) \leq I(t)$, $R_\varepsilon(t) \geq R(t)$, both for the SIR and SEIR models. It can be proven by induction, but here we only show the illustration via numerical examples in the following section

3.3 Numerical Examples
In this section we present numerical examples to show the behaviour of the discrete SIR and SEIR model with and without the presence of the convalescent plasma transfusion. The results in general support the analysis of the SIR and SEIR solutions. First part gives the illustration for the SIR model and the second part gives the illustration for the SEIR model. Both are in agreement with our expectation that the practice of CPT indeed prospective in reducing the number infection. In this case we will show that the use of CPT will decrease the peak of the outbreak. To run the

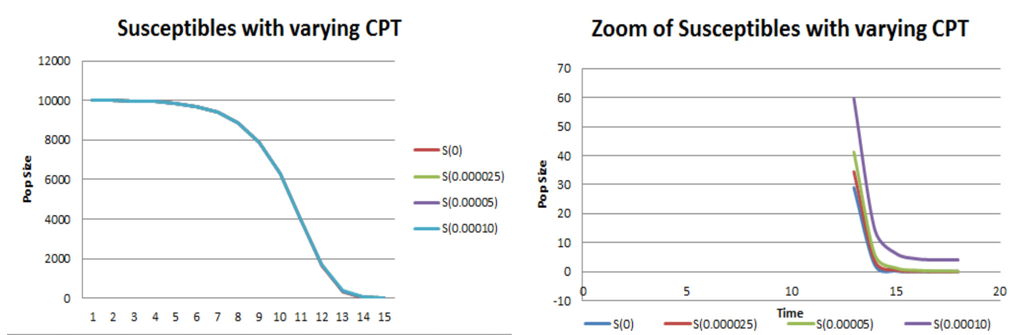
simulation we use hypothetical values of parameters as in Nykamp and Morrissey (2003) and various values of the CPT parameter as indicated in the figures.

Figure 1 shows the graph of the original SIR without CPT (a) and SIR with CPT (b). It is clear that there is an effect of the CPT application in reducing the peak of the epidemic, from 7,333(Fig.1.a) to 5,846 (Fig.b) using the CPT level (ε) = 0.0001. Figure 2 shows the graph of the susceptibles class from original SIR with varying degree of CPT (a). The effect of CPT is almost negligible visualy, but the close up of the graph around 15 unit time of the epidemic course (b) shows that indeed it increases the number susceptibles. Figure 3 shows the graph of the infectives class from original SIR with varying degree of CPT (a) and graph of recovered class with varying degree of CPT (b). These graphs show that the effect of CPT into the number of infectives and recovered is very obvious, i.e. reduces the peak number of infection (active cases) and increases the number of recovered. The same patterns also appear from SEIR model prediction (Figure 4). As in the SIR model, the effect to the susceptible is not visible (Figure 5.a), and also almost no effect to the exposed class (Figure 5.b). Meanwhile the effects to the infectives and recovered class is notable as in the SIR model (Figure 6). Figure 7 shows that the application of CPT clearly affects the number of daily new cases. We highlight the results which presented in Table 1, emphasizing the significant effect of the CPT application in reducing the peak of the outbreak.



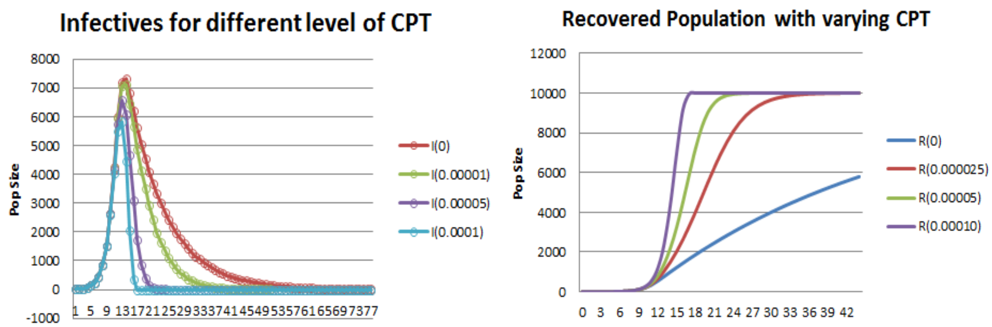
(a) (b)

Figure 1. The graph of the original SIR without CPT (a) and SIR with CPT (b). The SIR parameters are β=0.0001, α=0.1, and ε=0.0001 with initial values S_0=10,000, I_0=10, and R_0=0.



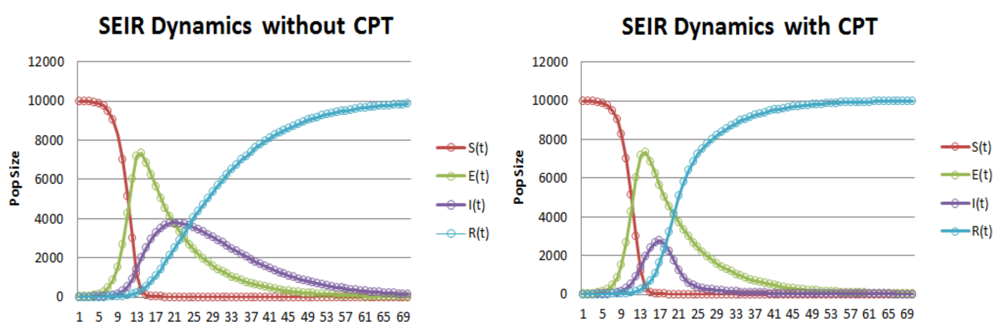
(a) (b)

Figure 2. The graph of the susceptibles class from original SIR with varying degree of CPT (a) and the close up of the graph around 15 unit time of the epidemic course (b) with the SIR parameters as in Figure 1.



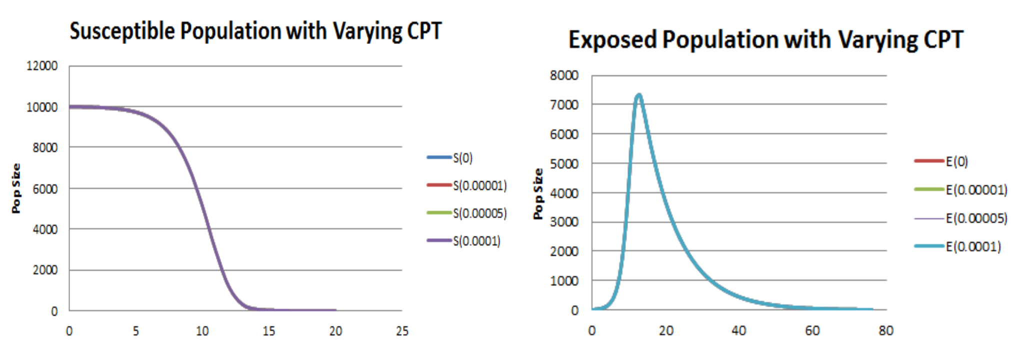
(a) (b)

Figure 3. The graph of the infectives class from original SIR with varying degree of CPT (a) and graph of recovered class with varying degree of CPT (b) with the SIR parameters as in Figure 1.



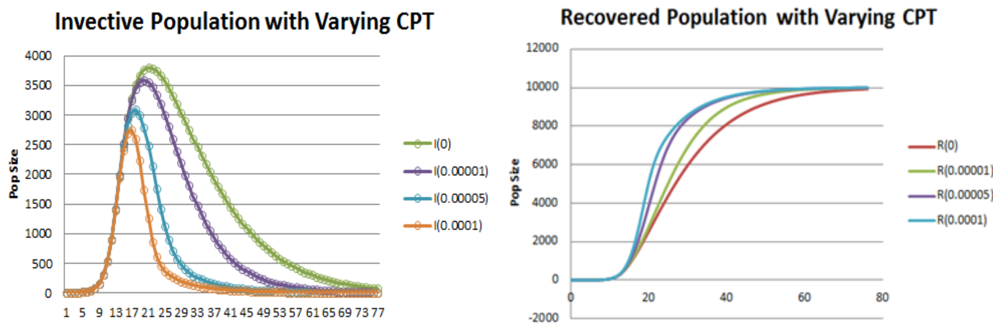
(a) (b)

Figure 4. The graph of the original SEIR without CPT (a) and SEIR with CPT (b). The SEIR parameters are β=0.0001, α=δ=0.1, and ε=0.0001 with initial values S_0=10,000, E_0=10, I_0=0, and R_0=0.



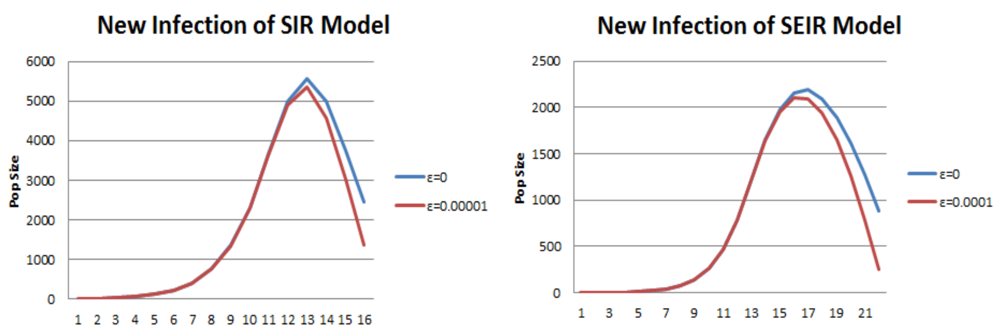
(a) (b)

Figure 5. The graph of the susceptibles class (a) and the exposed class (b) from original SEIR with varying degree of CPT application rate and the SEIR parameters as in Figure 4.



(a) (b)

Figure 6. The graph of the infectives class (a) recovered class (b) from SEIR with varying degree of CPT application rate and the SEIR parameters as in Figure 4.



(a) (b)

Figure 7. The graph of the daily new infection of SIR model (a) and SEIR model (b). Compare these to Figures 3.a and 6.a

Table 1. Model Prediction Hightlight

Level of CPT	**SIR Model**			**SEIR Model**			
	S (14)	*I* (peak)	*R* (14)	*S* (14)	*E* (peak)	*I* (peak)	*R*(14)
0	2	7,332	1,003	88	7,333	3,795	550
0.00001	4	7,108	1,496	88	7,333	3,583	561
0.00005	6	6,583	2,198	88	7,333	3,094	606
0.0001	15	5,845	4,376	88	7,333	2,757	667

Note:
S (14): The number of susceptibles at day 14-th
I (peak): The highest number of infectives
R (14): The number of recovered at day 14-th
E (peak): The highest number of exposed

4. Conclusion

We have presented a simple discrete time version of SIR and SEIR epidemic models with the effect of the convalescent plasma transfusion (CPT). The models revealed both the SIR and SEIR models predict that the use of CPT is indeed prospective in reducing the number infection. In this case it could decreases the peak of the outbreak as well as the length of the epidemic period. With the progress on the clinical investigation of the use of CPT in COVID-19, related data may soon available and further refinement and parameterization of the model should be done to obtain prudent insight of the model prediction.

Acknowledgements
This research was funded by the Indonesian Government through the scheme "PENELITIAN HIBAH RISET DAN TEKNOLOGI / BADAN RISET DAN INOVASI NASIONAL" with contract number: 1827 / UN6.3.1 / LT / 2020.

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