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Application of genetic algorithm for hemodialysis schedule optimization

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ABSTRACT

Background: The conventional hemodialysis (HD) schedule has been used for decades, even though new modalities have been introduced. Many reasons limit practices of frequent dialysis, such as patients' environments and unknown optimal schedules for each patient. This research provides a theoretical recommendation of HD schedule through genetic algorithm (GA).

Methods: An end-stage renal disease (ESRD) with various dialysis conditions was modeled through a classic variable-volume two-compartment kinetic model to simulate an anuric patient, and GA was implemented to search for an optimal HD schedule for each individual considering and ignoring burden consumption of each dialysis session. The adequacy of the optimized HD schedules through GA was assessed with time average concentration (TAC) and time average deviation (TAD).

Results: While ignoring the burden of dialysis sessions, GA returned schedules with slightly improved values of adequacy criteria (EKRc and std Kt/V), compared to the conventional regular uniform HD schedules. The optimized HD schedules also showed decreased TAC and TAD values compared to the conventional regular uniform HD schedules. It showed that frequent dialysis resulted in more effective treatment and higher fitness values. However, when burden was considered, less frequent dialysis schedules showed better fitness value.

Conclusions: Through this research, GA confirmed that at least 12 h of dialysis should be conducted for a week. The optimized schedules from GA indicated that evenly distributing the intervals amongst sessions is efficient, and that scheduling a session at the start and end of a week is optimal to overcome a long weekend interval. The theoretical optimal schedule of HD may help distribution of frequent dialysis and provide more schedule options to patients.

1. Introduction

For over half a century, the conventional hemodialysis (HD) schedule of three times a week has been used as the standard modality to treat end-stage renal disease (ESRD) despite the high mortality rate and the poor quality of life. To overcome these drawbacks, an innovative technological changeover that reduces the time and resource consumption, and that provides dialysis treatment at the optimal dose for each individual patient is strongly desired. Therefore, various modalities, such as daily HD, nocturnal HD, and continuous HD treatment, have been developed for ESRD patients and new technologies have been applied in HD. More frequent HD was assumed to be more physiological and to better mimic the biological function of the kidneys, yet only recently it was confirmed that more frequent HD improves dialysis efficacy compared with conventional HD [1]. Reduced dialysis-induced myocardial stunning with frequent HD compared to conventional HD was reported [2] and improvements in hyperphosphatemia and hypertension control were also reported with fre-

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quent HD [1,3]. Several computer simulation studies predicted that increased frequency or increased dialysis duration could increase molecular clearance [4–7]. Moreover, previous works have shown that frequent or longer dialysis not only decreases time average concentration (TAC) in body, but also decreases time average deviation (TAD), which denotes that those modalities are more physiological than the conventional HD schedule [8,9]. Therefore, a short daily HD seemed to be a good clinical alternative to conventional HD [10]. However, there was some skepticism regarding the effectiveness of frequent HD in every case [11]. Therefore, the optimal hemodialysis schedule that suits each patient must be identified and verified. However, to be treated with a more frequent HD schedule, patients must be assigned to more days of clinical visits and more medical resources must be utilized, which increases both the burden of time and the cost for patients [12–14]. Also, each patient has their own lifestyle and circumstances related to dialysis treatment, and the optimal treatment schedule may vary among patients. There are innumerable possible combinations, since various parameters such as duration, interval, and dosage must be considered for frequent HD scheduling. However, it is impossible to perform a clinical trial to identify which frequent HD schedule is suitable for a specific individual. Therefore, new HD modalities are not widely accepted in clinical practices, even though theoretical and clinical results have shown that these modalities have definite advantages. Recently, the computational modeling has been in the spotlight for the proof of theories. The Cobelli research group developed a simulator of type 1 diabetes mellitus (T1DM), which was accepted as a substitute for preclinical trials by the Food and Drug Administration (FDA) [15,16].

In this study, we propose a method to search for optimal intermittent and frequent HD schedules for individuals using mathematical modeling. For this purpose, we applied genetic algorithm (GA) to extract optimal scheduling solution from innumerable combinations. GA is a global optimization algorithm that employs the evolutionary processes found in nature, such as inheritance, selection, crossover, and mutation [17,18]. Compared to other optimization algorithms, GA shows strength in large multi-parameter optimization problems with non-linear, objective stochastic functions. Moreover, GA is operated with a set of parameters in a parallel environment, so it is suitable for problems with multiple local optima. Therefore, GA is utilized in various applications such as flow shop scheduling, image optimization, robotics, optimal power flow searching, and bankruptcy prediction modeling [18–22].

We implemented GA for optimal HD scheduling by considering the genes as the dialysis sessions and the chromosomes as the weekly dialysis schedule. As a result, a search space of around 10 million combinations was created, so GA was an adequate candidate for solving this problem. The corrected equivalent renal clearance (EKRc) and standard Kt/V (std Kt/V), which are dose measuring parameters widely used to compare the efficacy of dialysis modalities, were used to calculate a fitness function for GA. The searched optimal schedule was evaluated using TAC and TAD to assess its adequacy [8,9]. Lastly, we introduced the idea of burden, and examined its effect on searching for the optimal HD schedule.

2. Methods

2.1. Mathematical model of anuric patient

Anuric patients were modeled using a classic variable-volume two-compartment kinetic model [4], as described in our previous work [6,23]. Several assumptions were made for the model. The dry weight and total body water volume of the patients were set to 60 kg, 70 kg, and 80 kg, and 30 l, 35 l, and 40 l, respectively. The water volume distribution ratio of urea in the intracellular fluid, as the non-perfused compartment, and the extracellular fluid, as the perfused compartment, was assumed to be 2:1. The ultrafiltration rate (Q_{uf}) was set in order to maintain dry body weight after each dialysis session. The removal (J_v) and intake (I_w) of water, and the generation (G) and removal (J_s) of urea only occurred in the perfused compartment. The daily water intake was set to 1.5 l, and the rate of urea nitrogen generation was assumed to be 6.25 mg/min [4,24].

The dialysis clearance (K_d) was adjusted to 178 ml/min, barely enough to achieve the HEMO standard dose equivalent of EKRc $\geq$ 13.8 ml/min and std Kt/V $\geq$ 2.29 with a conventional HD schedule consisting of 4-h, three times a week [25]. The solute transfer rates for urea between the compartments were expressed in the form of inter-compartment clearance (K_{ic}) and the values were assumed to be 600 ml/min [4,24,26]. The initial concentrations of blood urea nitrogen in the compartments were assumed to be 100 mg/dl.

2.2. Dialysis schedule variables

Several options were considered in scheduling HD. Three available sessions were assigned for each day, separated into a morning session (start at 9 a.m.), an early afternoon session (start at 1 p.m.), and a late afternoon session (start at 5 p.m.). As a result, 21 sessions were available over the course of a week. The options for dialysis duration of each session were 4-h, 3-h, and 2-h. Also, two scheduling preferences were considered: the number of dialysis sessions performed per week ($N_{d/wk}$) with possible values between three and seven, and the number of sequential days not assigned to dialysis ($N_{d/ns}$) which represented whether dialysis was performed on any day of the week ($N_{d/ns} = 0$), only on Monday through Saturday ($N_{d/ns} = 1$), or only on Monday through Friday ($N_{d/ns} = 2$). Also, a cost factor, α, was assigned as either 0 or 1 for not considering or considering the burden of hemodialysis, respectively. It is an arbitrary number that represents the burden of time, money, quality of life, and other difficulties that patients may experience through hemodialysis treatment. Over 200 million schedule combinations were created with these variables. The search space of GA was reduced to around 10 million combinations, which is still a large search space, by restricting the schedule to only assign one HD sessions per day.

2.3. Genetic algorithm

Genetic algorithm is an adaptive metaheuristic search algorithm that mimics Charles Darwin's "survival of the fittest" concept in nature. GA is described in the two following sections: GA population and GA operation.

2.3.1. GA population

The GA searches through population that evolve over generations for an optimal solution. The population of GA contains a set of chromosomes which consist of genes. For the HD schedule optimization problem, the genes represented HD sessions while the chromosomes represented weekly dialysis schedules. Since 21 sessions were available in a week, a chromosome was composed of 21-digit genotype from Sunday to Saturday, i.e. xxx-xxx-xxx-xxx-xxx-xxx-xxx. Every gene in a 21-digit chromosome had four options of dialysis duration in each session: 4-h, 3-h, 2-h, and 0-h. A short 1-h dialysis duration was not considered, because it is not physiologically and clinically significant. Each dialysis duration was coded as 4, 3, 2, and 0, respectively, and 0 indicated that a dialysis was not assigned for a given session. For example, the conventional HD chromosome structure, consisting of 4-h HD on Monday, Wednesday, and Friday, with only morning sessions, was represented as 000-400-000-400-000-400-000, as shown in Fig. 1.