



Examination of Optimal Administration of Arsenic Trioxide in Continuous Renal Replacement Therapy During Acute Promyelocytic Leukemia Treatment

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Background and Aim

Acute promyelocytic leukemia (APL) has a good prognosis with remission in > 80% of cases¹⁾. Arsenic trioxide (ATO) is reportedly effective and safe for initial or recurrent APL^{2) 3)}. In vitro, at a plasma arsenic concentration (PAC) of 7.4–37.6 ng/mL, APL cells were induced to differentiate, and at a PAC of 37.6–150 ng/mL, they were induced to undergo apoptosis⁴⁾. For APL patients with normal renal function, ATO is administered daily at 10 mg or 0.15 mg/kg. As APL can cause acute kidney injury (AKI) and respiratory failure owing to disseminated intravascular coagulation syndrome (DIC) or differentiation syndrome (DS) during induction therapy, continuous renal replacement therapy (CRRT) may be considered for fluid management. The dosage of ATO for managing APL in patients during intermittent hemodialysis (IHD) is recommended at 10 mg three times a week after dialysis⁵⁾. The study revealed that 38% of PAC are reduced following dialysis; however, redistribution from tissues to the blood results in PAC gradually rising. Yamamoto et al. have also published similar findings⁶⁾. Till date, only one patient has received ATO while undergoing CRRT⁷⁾. The optimal ATO dosage for patients undergoing CRRT has not been established. We evaluated the appropriate ATO dosage for these patients. We further determined the optimal timing of administration to achieve the therapeutic ATO range.

Patients and Methods

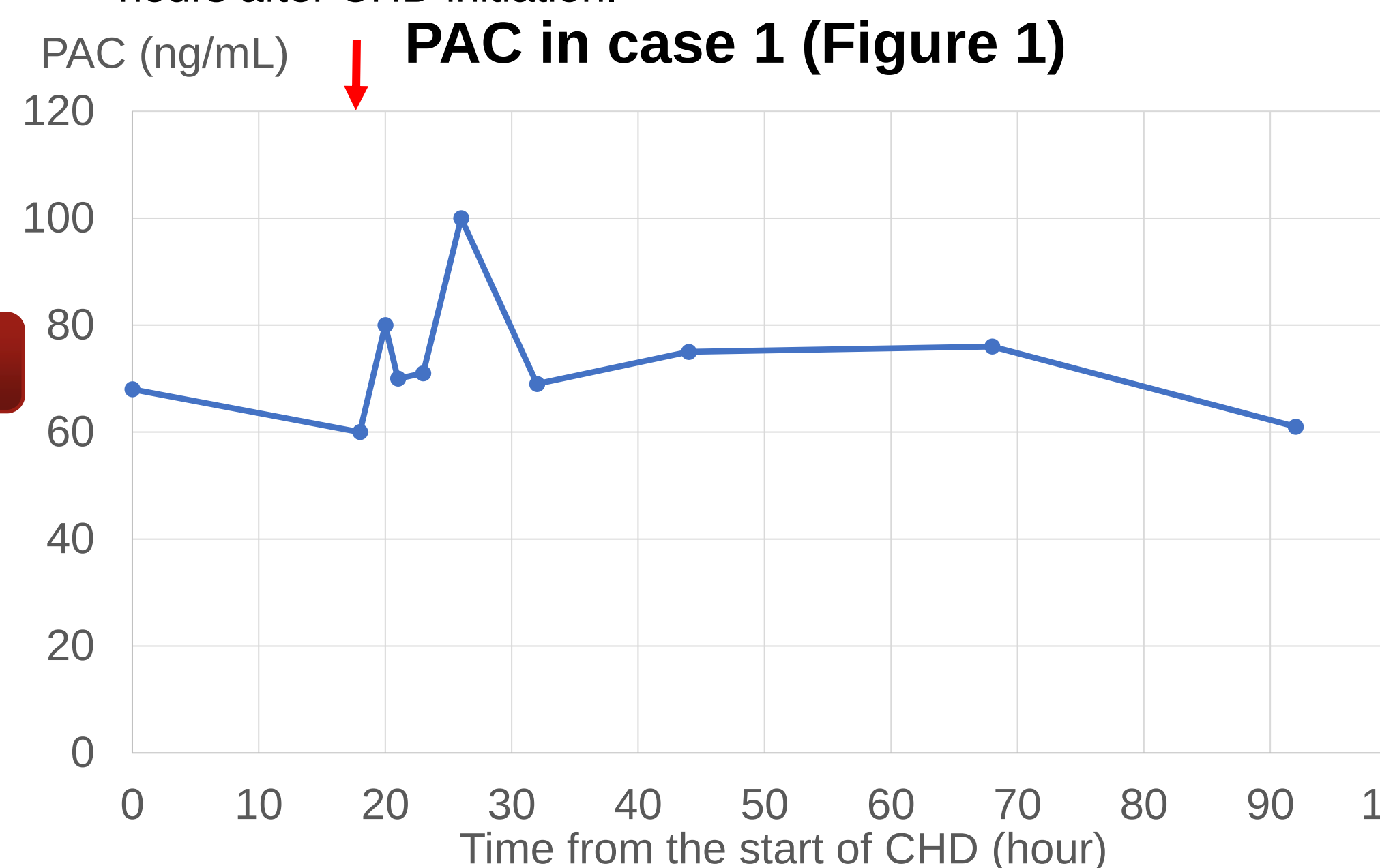
We enrolled two APL patients undergoing CRRT during ATO therapy at our institution. We obtained written informed consent from patients or their family. We measured PAC in patients using inductively coupled plasma mass spectrometry (ICP-MS). PAC measured included inorganic arsenic and methylated metabolites.

Results

The first case was of a woman in her 30s with recurring APL. Her renal function was normal on admission. She started ATO 0.15mg/kg administration as re-remission induction therapy. However, on the third day after treatment initiation, she developed AKI owing to severe DS and DIC, resulting in uncontrolled uremia and increased fluid volume. We started her on continuous hemodialysis (CHD) and discontinued ATO administration.

Her condition improved on day 10. She discontinued CHD and was administered ATO 0.15 mg/kg once. However, she experienced uremia again and resumed CHD on day 11. CHD was started 25 hours after the end of the final ATO administration. **Figure 1** shows PAC after CHD initiation. PAC at CHD initiation was 68 ng/mL. 18 hours after CHD initiation, we administered ATO 0.15 mg/kg over 2 hours. Her PAC before ATO administration was 60 ng/mL. Immediately after ATO administration, her PAC was 80 ng/mL. However, PAC gradually rose to 100 ng/mL. Thereafter, it decreased but remained constant at 60–70 ng/mL. ATO was not administered further, and CHD was completed within 92 hours. The CHD settings were not changed during the process. There was no ECG abnormality.

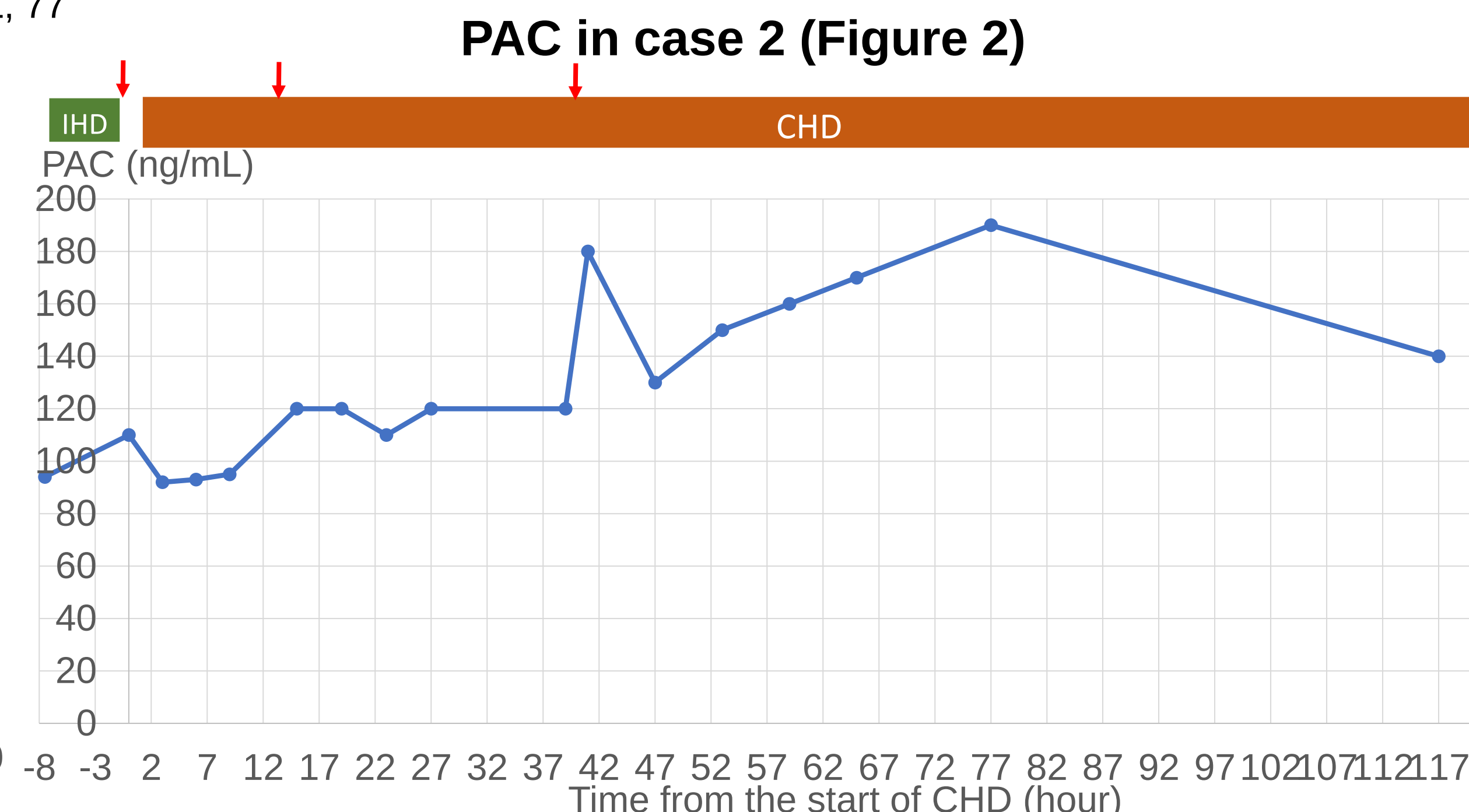
The second case was of a man in his 30s who had untreated APL. We started induction therapy with all-trans retinoic acid and idarubicin. He was admitted to the intensive care unit for starting treatment for respiratory failure with DIC and DS. As DS improved, we administered ATO 0.15 mg/kg for 2 days, but owing to AKI progression, he underwent IHD and immediately needed CHD. **Figure 2** shows the administration of ATO and PAC. PAC at CHD initiation was 110 ng/mL because ATO 0.15 mg/kg was administered twice before IHD initiation and once after IHD completion. 13 and 39 hours after CHD initiation, we administered ATO 0.15 mg/kg twice in total over 2 hours. After administration of ATO 39 hours after CHD initiation, PAC increased following a delay and peaked at 190 ng/mL, 77 hours after CHD initiation.



Subsequently, DS relapsed, and ATO was discontinued. At 117 hours after CHD initiation, his PAC was 114 ng/mL, which was within the optimal range. The CHD settings were not changed during the process. There was no ECG abnormality.

Discussion

ATO methylates in the liver, and both inorganic arsenic and methylated metabolites are said to induce apoptosis of APL cells⁸⁾. The mechanism of excretion of arsenic after ATO administration remains unclear. Fujisawa et al. showed that repeated administration of ATO results in a 60% urinary excretion rate of inorganic arsenic and methylated metabolites⁹⁾. Sweeney et al. showed that excretion of methylated metabolites decreased urinary excretion in patients with impaired renal function¹⁰⁾. Therefore, the kidney plays an important role in arsenic excretion after ATO administration, but there appear to be excretion routes other than the kidney. There are few reports of ATO being administered during CRRT, but the appropriate dosage remains unknown. Perreault et al. reported that 38% of PAC are reduced by hemodialysis⁵⁾. However, our study showed that there was no significant reduction in PAC during CHD. This is probably because the dialysis efficiency of CHD is lower than that of IHD and the volume of distribution of arsenic is large. Concerning case 2, we administered ATO every 24 hours, but PAC increased continuously and decreased over time since the last dose.



Thus, PAC may be in the effective range even if ATO during CRRT is administered every 48–72 hours. This may be owing to an increase in or redistribution of methylated metabolites. According to Gao et al. who reported on the pharmacokinetics of arsenic during CRRT in APL patients, PACs were stable, eliminating the need for ATO dose adjustment⁷⁾. We also had stable PACs with a single dose of ATO; however, PAC increased with multiple doses, suggesting that the number of doses should be reduced. PAC may be influenced by the different methods of ATO administration in their and our studies. We only measured PACs during CHD and cannot gauge changes that will occur with other CRRTs such as continuous hemofiltration and continuous hemodiafiltration. Given the mechanism of CRRT, the molecular weight and volume of distribution of inorganic arsenic and methylated metabolites, we speculate that ATO dosage does not vary significantly with the type of CRRT. We believe that additional studies are needed on the ATO dosage method during CRRT.

Conclusions

Based on these two cases, there was no significant decline in PAC due to CHD. The increase in PAC appeared following a delay. Therefore, the dosage of ATO during CHD should be every 48–72 hours.

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