Effectiveness of Continuous Veno-Venous Hemofiltration and Intermittent Hemodialysis in the Treatment of Severe Acute Phenobarbital Poisoning

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Abstract

Background: Phenobarbital poisoning is common in Vietnam. The aim of this study was to compare the effectiveness of continuous veno-venous hemofiltration (CVVH) and hemodialysis (HD) on clinical outcomes in the treatment of severe acute phenobarbital poisoning.

Methods: This was a retrospective observational historically controlled study. 42 patients with severe phenobarbital poisoning were enrolled. 21 patients were treated with HD and 21 with CVVH. Both groups received similar supportive therapies consisting of mechanical ventilation, forced alkaline diuresis and multiple-dose activated charcoal.

Results: Following one course of treatment with HD (4 hours) or CVVH (~19.5 hours) the mean (SD) blood phenobarbital concentration (BPC) had decreased to 3.9 (2.5) and 3.2 (2.3) mg/dL respectively (P=0.232). Mean percentage decrease in BPC after HD and CVVH were 62.7 (12.4) and 61.5 (22.0) % respectively, showing no significant difference (P=0.782). Mean duration of coma and mechanical ventilation in CVVH group was 31.9 (26.6) and 39.7 (27.9) hours, significantly shorter than those in HD group with 66.1 (32.5) and 66.7 (32.2) hours (P=0.002; 0.001) respectively.

Conclusion: One course of treatment with CVVH and HD decreased the BPC to a similar extent but this was not associated with similar clinical outcomes. Although, CVVH was not associated with rapid fall in blood phenobarbital level, it clearly had clinical advantages by shortening the duration of coma and mechanical ventilation and with lack of coma recurrence in severe phenobarbital poisoning.

Keywords: Phenobarbital; Poisoning; Continuous Veno-Venous Hemofiltration (CVVH); Hemodialysis (HD)

INTRODUCTION

In Vietnam, poisoning with sedative medications is the leading cause of pharmaceutical poisoning accounting for 76.3% of cases (1). Of these, the majority of severe cases are due to ingestion of phenobarbital for the purpose of suicide. Large doses of phenobarbital causes very high blood phenobarbital concentration (BPC) and consequently serious complications such as loss of consciousness, deep coma, hypotension and respiratory failure may occur (2). These are major causes of death in patients with acute phenobarbital poisoning.

Most cases of mild or moderate phenobarbital poisoning can be treated with multiple-dose activated charcoal (MDAC), intravenous fluids, forced alkaline diuresis and other supportive therapies (3,4). However, in cases of life-threatening phenobarbital poisoning, extracorporeal techniques including hemodialysis (HD) and continuous veno-venous hemofiltration (CVVH) can be used for enhanced elimination in order to decrease the duration of hospitalization and complications (4-7). HD is proven to be effective in the treatment of phenobarbital poisoning, but use of this procedure is complicated in patients with hypotension. Successful use of continuous veno-venous hemodiafiltration (CVVHDF), which is a similar method to CVVH, for a severely phenobarbital poisoned patient with hypotension, was reported by Lal et al. (8). Therefore, CVVH has been regarded as an alternative modality with better safety potentials.

At Bach Mai Poison Control Center in Vietnam, severely phenobarbital poisoned patients with high BPC are treated by supportive therapies and HD or CVVH. The aim of this study was to investigate the differences in clinical outcomes between CVVH and HD in the treatment of severe acute phenobarbital poisoning.

METHODS

Study Design

This was a retrospective observational historically controlled study. 42 severely phenobarbital poisoned patients who were admitted to Bach Mai Poison Control Center during 2003-2010 were enrolled. Criteria for
exclusion were concurrent poisoning with other sedatives and coma due to other reasons.

Indications for commencing the treatments were acute phenobarbital poisoning with BPC above 4 mg/dL and/or deep coma with stage 3 or 4. Coma was graded according to following definitions (1,9):

Stage 1. Responsive to painful but not to verbal stimulus
Stage 2. Unresponsive to all stimuli but normal reflexes and vital signs
Stage 3. Unresponsive, areflexic, stable vital signs except hypoventilation
Stage 4. Unresponsive, areflexic and unstable vital sign

Patients were categorized into 2 groups. Group 1 (study group) included 21 patients presenting between 2006 and 2010 who were treated with CVVH. Group 2 (control group) included 21 patients presenting between 2003 and 2005 who were treated with HD. Both groups received similar supportive therapies consisting of mechanical ventilation, forced alkaline diuresis and MDAC.

Intubation and mechanical ventilation were performed for all patients. Criteria for weaning off from mechanical ventilation were regaining consciousness up to Glasgow coma scale (GCS) over 13, no respiratory compromise, pCO2 less than 40 mmHg and pO2 over 85 mmHg. Criterion for stopping CVVH was regaining consciousness with GCS over 13. Hypotension was defined as systolic blood pressure below 90 mmHg.

Study facilities
CVVH: Prismaflex (Gambr 0.5 L filter and Diacap (B-Braun) machine with Diacap Acute filter were used. Blood flow rate was 150-180 mL/min and replacement fluid rate was 35-45 mL/kg/h. The anticoagulant used was heparin.

HD: Artificial kidney machine AK95 with polyflux 14 L filter was used. Blood flow rate was 180 mL/min and dialysate flow rate was 500 mL/min. The anticoagulant used was heparin.

BPC: Blood phenobarbital concentration was measured with HP Agilent 6310 Ion Trap LC/MS systems using HPLC/MS method.

**Ethics**
This study was one part of a research project approved by the ethical and scientific committees of Bach Mai hospital and Ministry of Health of Vietnam.

**Data analysis**
Fischer Exact test was done for ratio comparison. Mann Whitney test and Sign test were done for comparison of percentage and continuous variables. Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) was used for data analysis. P<0.05 was considered as significant.

**RESULTS**

**Demographic**
Of 42 patients, 26 (61.9%) were males and the average age was 34.4 (15.1) ranging from 13 to 77 years. Most cases (95.2%) were due to self-poisoning. All patients were in deep coma (stage 3-4). Mean duration of procedure with CVVH was 19.5 (8.3) hours, which was approximately 15 hours longer than HD (Table 1). As it is illustrated in table 1, there were no significant differences in baseline characteristics.

**BPC Changes during Extracorporeal Therapy**
After 4 hours of treatment, mean BPC in HD group was 3.9 (2.5), significantly lower than mean BPC in CVVH group with 5.4 (2.9), reflecting a quicker method to decrease BPC (Table 2). However, at the end of CVVH, BPC was

| Table 1. General features of subjects before procedure |
|---------------------------------|-----------------|-----------------|
|                                | HD              | CVVH             |
| Number of patients             | 21              | 21              |
| Age, mean (SD)                 | 35.9 (17.6)     | 32.8 (12.3)     |
| Male/Female                    | 1.6 (13/8)      | 1.6 (13/8)      |
| GCS before procedure, mean (SD)| 4.1 (1.5)       | 3.5 (0.9)       |
| Stage of coma (Stage 4/total)  | 13/21 (59.1%)   | 9/21 (40.9%)    |
| BPC before procedure (mg/dL), mean (SD) | 10.1 (3.9) | 8.8 (4.9)      |
| Duration of procedure (hours), mean (SD) | 4 | 19.5 (8.3) |
| Intention of Poisoning (Suicide/Total) | 95.2 (20/21) | 95.2 (20/21) |

| Table 2. Changes in blood phenobarbital concentration during procedure |
|------------------|-----------------|-----------------|-----------------|
|                  | BPC             | HD (mg/dL), mean (SD) | CVVH (mg/dL), mean (SD) | P Value |
| BPC before procedure | 10.1 (3.9) | 8.8 (4.9) | 0.134 |
| BPC after 4 hours of procedure | 3.9 (2.5) | 5.4 (2.9) | 0.021 |
| BPC at the end of procedure | 3.9 (2.5) | 3.2 (2.3) | 0.232 |
| Decrease in BPC after 4 hours of procedure | 62.7 (12.4) | 36.3 (18.6) | 0.001 |
| Decrease in BPC at the end of procedure | 62.7 (12.4) | 61.5 (22.0) | 0.782 |

| Table 3. Comparison of Duration of coma and mechanical ventilation between two groups |
|----------------------------------|-----------------|-----------------|-----------------|
|                                | HD (hour), mean (SD) | CVVH (hour), mean (SD) | P Value |
| Duration of coma                | 66.1 (32.5) | 31.9 (26.6) | 0.002 |
| Duration of mechanical ventilation | 66.7 (32.2) | 39.7 (27.9) | 0.001 |
Phenobarbital poisoning may cause coma and respiratory compromise (2). Hence, we considered duration of coma and mechanical ventilation to evaluate clinical effectiveness of HD and CVVH. We found that duration of coma and mechanical ventilation in CVVH group was significantly shorter than HD group, revealing CVVH is more effective. Moreover, hypotension and recurrence of coma were not observed following CVVH, implying a safer method.

It has been ascertained that many of the sedative-hypnotic medications have a redistribution phase following initial distribution (13). This is because they are dispersed and accumulated in other body tissues, especially adipose tissue (13). Therefore, after initial distribution, they reenter into blood circulation and can cause rebound manifestations. CVVH is a long extracorporeal therapy. Hence, it is capable of filtering out the redistributed phenobarbital. Conversely, HD is a shorter technique. Therefore, redistribution of phenobarbital and as a result, recurrence of coma is more probable after HD. In these situations, extra courses of HD may solve the problem; though we treated our patients conservatively with only mechanical ventilation and forced alkaline diuresis.

**LIMITATIONS**

The control group in the study was retrospectively studied. Therefore, some bias could not be avoided. We suggest that future studies about comparison of elimination of BPC with CVVH and HD or CVVH and MDAC to be designed as randomized controlled trials. Moreover, in this study, BPC at the time of coma recurrence was not determined. Therefore, we propose measurement of BPC at the time of coma recurrence in routine practice and future studies. In addition, phenobarbital concentration in dialysis fluid was not measured. Thus, exact clearance of phenobarbital for both modalities could not be estimated.

**CONCLUSION**

One course of treatment with CVVH and HD decreased the BPC to a similar extent but this was not associated with a similar clinical outcomes. CVVH is safer and more effective than HD on treatment of severe acute phenobarbital poisoning as it shortens the duration of coma and mechanical ventilation with fewer complications. Therefore, using CVVH is recommended for treatment of severe cases of acute phenobarbital poisoning especially those with deep prolonged coma and refractory hypotension.

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**Conflict of interest:** None to be declared.

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