Combined Sodium Dimercaptopropanesulfonate and Zinc versus D-penicillamine as First-line Therapy for Neurological Wilson’s disease

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Abstract
Background: Even though recent research has achieved significant advancement in the development of therapeutic approaches for Wilson’s diseases (WD), the current treatment options available for the neurological symptoms of WD are significantly limited and yet to be standardized. Objective: The aim of this study was to compare the course of treatment for WD patients with neurological symptoms receiving either combined sodium 2, 3-dimercapto-1-propane sulfonate (DMPS) and zinc treatment or D-penicillamine (DPA) monotherapy as first-line therapy. Methods: The case records of 158 patients diagnosed with neurological WD were retrospectively analyzed. These patients were administrated with either intravenous DMPS + Zinc (group 1) or DPA (group 2) for 8 weeks. During the period of treatment, neurological symptoms were assessed using Global Assessment Scale (GAS), the key hematological and biochemical parameters (such as aminotransferase, serum ceruloplasmin, 24-h urine copper excretion), as well as adverse effects were recorded and analyzed. Results: 93 patients in Group 1, displayed decreased GAS scores consistently in comparison to the baseline (P < 0.01). Among them, 64 patients (68.1%) displayed a significant improvement in their neurological status after 8 weeks, while 10 patients (10.8%) experienced neurological deterioration. Among the 65 patients in Group 2, 30 patients (46.2%) displayed neurological improvements, while 21 patients (32.3%) displayed neurological deterioration. 6 patients discontinued their treatment midway due to their exacerbating neurological symptoms. A comprehensive comparison of the effectiveness of the two courses of treatment revealed that patients in Group 1 demonstrated a higher improvement ratio (P < 0.01) and lower worsening ratio of the neurological symptoms of the patients (P < 0.01) in comparison to the patients in group 2. Meanwhile, renal function, liver enzyme and the blood cell counts remained stabilized in group1. Conclusions: This study suggests that the combined therapeutic approach of treatment with DPMS and zinc should be the preferred first-line therapy in treating the neurological symptoms of WD, in comparison to the treatment with DPA as the experimental data demonstrates that it is significantly more efficient. Keywords: Wilson’s disease (WD), Sodium 2, 3-dimercapto-1-propane sulfonate (DMPS), D-penicillamine (DPA), Zinc, Global Assess Background
Wilson’s disease (WD) is a rare, genetic disorder in which the metabolism of copper is impaired. Mutations in a gene, called ATP7B, which encodes for a protein involved in copper-transportation, forms the genetic basis of WD. Thus, copper accumulation in different parts of the body is one of the primary physiological manifestations of WD. The accumulation of copper primarily affects the liver, brain and cornea. This leads to significant liver damage, as well as neurological and psychiatric symptoms. Neurological symptoms in WD are often accompanied by movement disorder or behavioral abnormalities. Although WD can be managed effectively with medications and dietary changes, if left untreated or delayed treatment can prove fatal within a few years from the onset of symptoms.

Even though recent research has achieved significant advancement in the development of therapeutic approaches for Wilson’s diseases (WD), the option of current pharmacological treatments available for WD are still limited, especially for WD patients with neurological symptoms. Copper chelators like D-penicillamine (DPA), trientine, sodium 2, 3-dimercapto-1-propane sulfonate (DMPS) and Zinc salts are the current initial therapies available for WD. DPA, a copper chelator, is the first oral treatment offered after the diagnosis of WD, and trientine is another copper chelator, which is a commonly used alternative to DPA for patients intolerant to DPA. All of these drugs facilitate the urinary excretion of copper and normalize the level of copper. Although the clinical benefits of treatment with DPA have been documented in detail, the serious side-effects and the initial exacerbation of the neurological symptoms, reported in 10-50% of patients with neurological WD, have vastly limited its widespread application. Trientine also has similar effects on the patients. In addition, its use is limited in developing countries due to its high cost and limited availability. DMPS is a water-soluble chelating agent, which binds to the copper ions in order to form a thiol compound. This enables the DMPS to excrete the extra copper through urine after filtration in the kidneys. Although it is not widely popularized in other areas, DMPS has been universally used as a routine treatment for WD in China for several decades. In addition, it is also used commonly used as an alternative treatment for WD patients, who are intolerant to the DPA treatment. Zinc also has a
relatively moderate anti-copper effect, which makes it an effective and safe therapeutic approach for the maintenance after the initial chelator therapy or as first-line therapy for asymptomatic and presymptomatic patients\textsuperscript{5, 14-17}.

Since WD is a rare genetic disease, it has been challenging to develop the best and most effective therapeutic approach for treating WD. In addition, the low incidence and the heterogeneous clinical presentation of the disease make it very difficult to design a randomized controlled trial. Thus, the degree of efficiency and safety of existing treatment options have been developed from studies based on clinical patients, which makes it complicated to devise definitive recommendations\textsuperscript{18}.

Until now, limited investigation of the combined therapeutic approach of DMPS + Zinc and DPA monotherapy in WD patients who manifested neurological symptoms. Therefore, the aim of this study was to fill the scientific gaps in this field of research by comparing the two different therapeutic approaches and identifying the more effective therapeutic approach.

**Methods**

**Patient Information**

In this retrospective study, the data of 158 WD patients who demonstrated neurological symptoms, was collected from the Department of Neurology at the first affiliated hospital of Anhui University of Traditional Chinese Medicine, during the time period of July 2015 to June 2018. Only those patients who had been recently diagnosed and had not received any initial treatment, were selected to be included in this study.

The diagnosis of the disease was based on the characteristic clinical manifestations of WD. It followed the following criteria: (1) positive family history, (2) the presence of K-F ring, (3) low serum ceruloplasmin levels (<200mg/l), (4) elevated 24-hour urinary copper excretion (>100μg/24h), elevated 24-hour urinary copper excretion (>100μg/24h, asymptomatic children>40 μg/24h can be suggestive); (5) elevated urinary copper excretion following the administration of the penicillamine (>1600μg/24h). Evaluation of K-F ring on slit lamp was performed by experienced ophthalmologists.

All the medical details of the patients, including the demographic data, family history, medical history and clinical features, were recorded in detail. The following hematological and hepatic criteria were
also analyzed and recorded: white blood cell (WBC) counts, platelet (PLT) counts, aminotransferase, urea, creatinine, ceruloplasmin (CER) and 24-hour urine copper. Any adverse effects of both the treatments being compared were also recorded. The neurological symptoms of the patients were assessed by applying the neurological subscale of Global Assessment Scale (GAS)\textsuperscript{19}, which is a multidimensional neurological evaluation system which evaluates the various neurological symptoms which might manifest as a result of WD.

**Treatment**

Intravenous DMPS + Zinc (group 1):

The initial dose at which DMPS was administrated to WD inpatients (n=93) was 5-10mg/kg per day. This dosage was then gradually increased to 20mg/kg per day during a period of 1 - 2 weeks. This dosage was further maintained for the experimental period of 8 weeks. Each treatment course comprised of 5 consecutive days of treatment with DMPS, and 2 days withdrawal period to promote tolerance\textsuperscript{11}. After intravenous treatment finished, Zinc sulfate was given as the maintenance therapy for 1 year. In case of zinc sulfate, the dosage administered was age dependent. For patients under 15 years old, 75 mg of zinc sulfate was divided over 3 doses during a period of 24 hours. For older children and adults, 150mg of zinc sulfate was administered over 3 doses during 24 hours.

DPA monotherapy (group 2):

The WD patients (n=65) who were either intolerant to DMPS (e.g. allergic to DMPS) or refused hospitalization for the long term DMPS + Zinc treatment were assigned to group 2 and were treated with the daily DPA monotherapy. In case of DPA, an initial dose of 5mg/kg/day was administered, following that it was gradually increased to 20mg/kg/day during a period of 1 - 3 weeks.

In addition, all the patients were recommended to follow a special diet with low copper. The follow-up checkups of the patients were conducted at 2 weeks, 4 weeks, 8 weeks and 1 year. During the period of the treatment, 6 patients quitting the DPA treatment and adjusting to DMPS therapy withdrew from
the study midway due to the exacerbating neurological symptoms.

**Statistical analysis**

All statistical analysis performed within the scope of this study was performed using the SPSS software version 22.0 (International Business Machines Corporation, Armonk, NY, USA). The results have been demonstrated as mean ± SD or as the median and range. The significance of the data obtained in this study was analyzed through t tests for quantitative data and χ² tests for qualitative data. All P values were based on two-tailed comparisons, and those less than 0.05 were considered statistically significant.

**Results**

**Baseline patient characteristics**

The primary characteristics of the patients prior to initiation of treatment are shown in **Table 1**. 93 patients (with mean age of 24.47 ± 8.00 years), out of which 64.5% were male, were assigned to group 1. These patients were scheduled to receive intravenous DMPS in combination with Zinc as the first-line therapy. 65 patients (with mean age of 26.93 ± 8.16 years) were assigned to group 2. Group 2 consisted of 50.8% male patients. They were scheduled to receive DPA monotherapy as the first-line therapy. All of the patients included in this study demonstrated manifestations of neurological symptoms, which included dystonia (100 cases, 63.3%), dysarthria (75 cases, 47.5%), salivation (81 cases, 51.2%), dysphagia (45 cases, 28.5%), tremor (108 cases, 68.4%), parkinsonism (89 cases, 56.3%), ataxia (45 cases, 28.5%) and epileptic seizures (5 cases, 3.2%). After the first 4-week treatment, 6 patients were quit the DPA treatment and adjusted to DMPS therapy for the emerging severe neurological symptoms.

The baseline characteristics of patients in both the experimental groups were relatively similar (**Table 1**). In case of group 1, the average time since first symptoms was 24 months (ranging between 3-60 months), whereas in case of group 2, the average was 23 months (ranging between 3-96). All patients included in this study presented with the common hallmark syndromes of WD, like corneal K-F rings, low serum ceruloplasmin levels, high 24-hour urine copper levels and abnormal MRI findings.
Structural brain MRI of these patients revealed that the patients presented with widespread lesions throughout the brain. The scans produced high-signal intensity on T2 weighted images and low-intensity on T1 scan in the basal ganglia (144 case, 91.1%), thalamus (37 cases, 23.4%), midbrain (19 cases, 12%), pons (21 cases, 13.3%) and cerebellum (23 cases, 14.6%).

**Serum ceruloplasmin and 24-hour urinary copper**

The levels of serum ceruloplasmin (normal range is 200-600mg/l) and 24-hour urine copper (normal ranges <100μg/24 h) of all patients during the period of this study are presented in Table 2. In case of both groups, the levels of serum ceruloplasmin were not significantly different in comparison to the experimental baseline. Comparison between the two experimental groups showed that there was no difference which was statistically significant, in the serum ceruloplasmin levels between the two therapeutic approaches at the 1-year follow up. After 2 weeks treatment, it was observed that the 24-hour urinary copper excretion sharply elevated for patients in either group ($P < 0.01$), and then gradually decreased after 4 weeks treatment, and statistically significant differences were observed between the two groups at the 2-week follow up ($P < 0.05$).

**Neurological outcome**

The temporal trend of neurological outcomes of the WD patients are shown in Table 3. No significant differences were found between the GAS scores of the two groups at the baseline ($P > 0.05$). In comparison with the baseline, the GAS scores of group 1 patients remained stable after 2 weeks of DMPS treatment ($P > 0.05$) and then gradually decreased after 8 weeks of treatment ($P <0.01$). The neurological outcome of the patients in group 1 was similar to the baseline after 2 weeks of treatment. Thirty-seven patients (39.8%) demonstrated improvements in their neurological symptoms after 4 weeks treatment. By 8 weeks, the number of patients showing neurological improvements increased to 64 (68.8%). And by the 1-year follow up, the number increased to 82 patients (88.2%). However, 11 patients (11.8%) from group 1 presented deterioration in their neurological conditions after 4 weeks of treatment. In addition, most of these patients (i.e. 8 out of the 11) with the
neurological deterioration did not recover to the baseline by the 1-year follow up.

No patient demonstrated neurological deterioration and eighty patients (8/93) gradually exhibited neurological improvements during zinc maintenance therapy, as indicated by an increase of 1-2 points on the GAS.

In case of patients in group 2, the GAS scores were significantly higher compared to the baseline ($P < 0.05$) in the first 4 weeks ($P < 0.05$) after treatment. By 8 weeks pot treatment, the GAS scores of the patients were slightly decreased ($P > 0.05$). In this group, after the first 4-weeks of DPA monotherapy, 22 patients (33.8%) exhibited significant neurological deterioration. Six of these patients quitted the DPA treatment regime due to the severe exacerbation of their neurological symptoms. By the 1-year follow up, 17 patients (26.2%) still exhibited significant neurological deterioration. Finally, 37 patients (58.5%) demonstrated significant improvements in their neurological symptoms at the 1-year follow up post the DPA treatment.

Thus, the comparative analysis of the two groups demonstrated that after 1 year of therapy, the neurological improvement ratio of the patients in group 1 was significantly better than that of in group 2 ($P < 0.01$). In addition, the deterioration ratio in group 1 was remarkably lower than that of in group 2 ($P < 0.01$). It is noteworthy that some of the neurological symptoms like dysarthria, dysphagia and dystonia have a higher predisposition to deteriorate during the courses of both the therapeutic approaches compared in this study.

**Liver function and Renal function**

No significant difference observed between the serum concentrations of alanine aminotransferase (ALT) and aspartate transaminase (AST) in case of the two experimental groups at baseline ($34.85 \pm 20.45 \text{IU/L} \text{ vs } 36.45 \pm 26.75 \text{IU/L}, P > 0.05; 28.43 \pm 9.95 \text{IU/L} \text{ vs } 31.37 \pm 14.29 \text{IU/L}, P > 0.05$) (Figure 1). After 4 weeks of the commencement of the therapy, the ALT and AST levels were mildly elevated in both groups in comparison to the baseline ($P > 0.05$). By 8 weeks post treatment, the ALT and AST levels decreased gradually in both groups ($P > 0.05$). No significant differences in the serum ALT or AST levels were observed in between the WD patients two groups 1 by the 1-year follow up ($30.37 \pm$
There were also no significant differences in the serum levels of creatinine (Cr) and blood urea nitrogen (BUN) between the two groups at baseline ($P > 0.05$). The same was true at the 4-week, 8-week and 1-year follow-ups ($P > 0.05$) (Figure 1). Renal function remained stable for patients in both experimental groups throughout the study.

**Blood cell counts**

No significant differences were discovered in the platelet (PLT) and white blood cell (WBC) counts of patients from both groups at baseline ($P > 0.05$) (Figure 2). In case of both experimental groups, the PLT counts remained stable throughout the period of the study, and no significant differences were observed between two groups ($P > 0.05$). The WBC counts in case of patients from group 1 were mildly decreased in comparison to the baseline by 2 and 4 weeks (5.01 ± 1.61 vs 4.91 ± 1.29, $P > 0.05$; 5.01 ± 1.61 vs 4.85 ± 1.09, $P < 0.05$). By the 8-week follow up, the WBC count gradually elevated and reached up to the baseline (5.01 ± 1.61 vs 4.94 ± 1.13, $P > 0.05$). In case of group 2, the WBC count of patients decreased in the first 4 weeks after treatment (4.97 ± 1.50 vs 4.47 ± 1.47, $P < 0.01$; 4.97 ± 1.50 vs 4.40 ± 1.61 $P < 0.01$), however, by the 1-year follow up, it still failed to recover to baseline (4.97 ± 1.50 vs 4.45 ± 1.10, $P < 0.01$). Analysis of the differences in the WBC counts between the two groups at each follow up time point revealed that there was a significant difference between the two groups at the 2-week, 4-week, 8-week and 1-year follow up time points (4.91 ± 1.29 vs 4.47 ± 1.47, $P < 0.05$; 4.85 ± 1.09 vs 4.40 ± 1.61, $P < 0.05$; 4.94 ± 1.13 vs 4.63 ± 1.45, $P < 0.05$; 4.92 ± 1.09 vs 4.45 ± 1.10, $P < 0.05$).

**Neuroimaging data**

All patients with neurological manifestations of WD had brain pathology on baseline MRI. Forty-five patients (45/93, 48.4%) in group 1 exhibited significant improvements after 1-year combined treatment, which were demonstrated as decrease or disappear in abnormal signal intensity. In case of
patients in group 2, 20 patients (20/65, 30.8%) exhibited significant changes after 1-year treatment. Thus, the comparative analysis of the two groups demonstrated that after 1 year of therapy, the MRI improvement ratio of the patients in group 1 was significantly better than that of in group 2 ($P < 0.05$).

**Adverse effects**

The main adverse effect recorded in case of patients from both groups were certain gastrointestinal symptoms, like pain in the abdomen, nausea, and vomiting. These symptoms could easily be alleviated by dosage adjustment and modifying the time line of the administration of the medicine. However, no gastrointestinal hemorrhage was recorded in patients of either experimental group. In group 1, 6 patients with splenomegaly suffered from myelosuppression, 13 patients from group 1 suffered from the gastrointestinal symptoms only during the oral Zinc treatment, but most of those were alleviated by a simple dosage adjustment or by modified medication schedule. In group 2, 10 patients suffered from the gastrointestinal symptoms discussed earlier. 5 patients developed myelosuppression and this was not successfully alleviated after 1 year of the DPA treatment.

**Discussion**

It has been challenging to develop an universally accepted therapeutic approach to address WD, due to its heterogeneous clinical manifestation$^1$. Currently, the best therapeutic approach for treating each specific presentation of WD depends on different factors like the opinion of the physician, the availability of the drug and patient acceptance. This study showed that the efficacy and safety of a combination therapeutic approach in which DMPS + Zinc as an initial treatment for the WD patients manifesting neurological symptoms.

88.2% of the patients receiving intravenous DMPS+Zinc as the first-line therapy showed gradual neurological improvement after 1 year of treatment, while only 58.5% of the patients undergoing the DPA monotherapy group exhibited neurological improvements. This data demonstrates that the combinatorial therapeutic approach using DMPS and Zinc as the initial therapy was significantly more effective than DPA monotherapy in case of patients of WD manifesting neurological symptoms.
It has been reported that the neurologic symptoms would be deteriorated with the chelating agents due to the re-distribution of copper ions and increase free serum copper levels\textsuperscript{20}. This study shows that only 8.6\% of the patients in the combination therapy group presented with neurological deterioration at the 1-year follow up, however, in the DPA monotherapy group, 26.2\% of patients demonstrated neurological deterioration. This demonstrates that the combination therapy is safer than that of the DPA monotherapy as an initial treatment in patients with neurological WD. In case of most of the patients, hepatic function improved slightly kept constant after treatment. This study also shows that the WBC and PLT counts remain stable in the combination therapy group of patients during the 1 year of follow up period post treatment, which indicates that there was no hematological toxicity to the treatment regimes.

Studies have shown that DMPS is one of the best copper-chelators used for medicinal purposes. This can be attributed to its characteristic of a very low probability to cause allergic reactions, low hematological toxicity and its efficiency in excreting copper from the patient’s body\textsuperscript{10}. This study showed that the 24-h urine copper levels increased significantly during intravenous DMPS treatment without having any adverse effect on the platelet counts and renal function of the patients. However, intravenous DMPS is primarily used as a first-line treatment after the diagnosis of WD in order to effectively alleviate severe symptoms in acute stages of the disease. Once the initial symptoms have been alleviated, the patients are shifted to an oral medications therapy accompanied with a low copper diet.

In developing countries, DPA has been primarily used as a first-line drug for WD patients for several decades now, as DPA is a very powerful copper chelator. However, DPA is also prone to causing several adverse effects, including serious conditions like bone marrow depression and anemia/leucopenia. Studies have also shown it to cause a potential initial deterioration of the neurological symptoms of WD\textsuperscript{2, 21}. Moreover, the copper-excreting efficacy of DPA has also been shown to gradually decrease during long-term clinical applications. Zinc has extremely low neurotoxicity and is considered safety in treating WD with neurological syndromes. However, the use
of Zinc alone is also not a preferred method of treating WD with symptomatic patients, as its capability to excrete sufficient amount of copper from the bodies of WD patients is highly limited. Therefore, it has been commonly used as maintenance treatment or reserved as a first-line drug for asymptomatic and pregnant patients. Trientine is an efficient alternative when WD patients become intolerant to DPA, however, its high cost and limited availability has made its use in the developing countries vastly difficult. Scientific reviews have reported that 24.4% of the patients treated with DPA based therapy display adverse effects, with the manifestation of severe side effects in about 50% of those patients. Recent reports have suggested that neurologic worsening occurred in over 10% for all kinds of WD treatments.

This study showed that 33.8% of the patients treated with DPA monotherapy experienced exacerbated neurological symptoms by the 4-week follow up time point and no significant recovery (e.g. 5 out of the 22) was recorded in most of the patients by the 1-year follow up time point. Besides, 6 excluded patients discontinued DPA treatment in the midway for severe adverse events and changed their therapeutic regime. Thus, the results of this study along with the published literature about DPA as a first-line treatment for WD suggests that DPA has a considerable amount of neurotoxic effect and some serious side effects, which make it a suboptimal first-line medical therapy for treating WD with neurological symptoms.

Numerous studies on several different groups of WD patients have demonstrated that Zinc therapy is considerably safe and inexpensive. The mechanism of zinc chelates with copper is different from that of iron chelators. The mechanism of chelation by zinc involves inducing liver cell metallothionein and intestinal, which binds to copper with a great affinity and inhibits the transfer of copper into the portal circulation. Since zinc has extremely low toxicity and is also cost effective, it is an optimal therapeutic choice. It has been successfully used as first-line treatment for treating pre-symptomatic and pregnant patients for maintaining their copper levels consistently, and in pediatric WD patients with hepatic presentation. As for neurological WD patients, large cohort studies for zinc
monotherapy as first-line treatment were hardly reported. For its limited efficacy in eliminating sufficient amount of copper from the body of the patient, zinc therapy has been proved difficult to prevent the progression of WD\textsuperscript{14, 26}.

It has been reported that 29.4\% of the neurological patients with a history of DPA intolerance, treated with Zinc based monotherapy show neurological worsening, while only 11.8\% of them exhibit neurological improvements. Noteworthily, the combination of DMPS and zinc treatment was reported to be superior to that of zinc monotherapy in patients with neurological WD\textsuperscript{13}. Therefore, it can be safely concluded that zinc monotherapy is not a preferential treatment regime for neurological symptoms as first-line medical therapy, and should be used as a maintenance therapy after copper chelators treatment\textsuperscript{26}. Meanwhile, the American Association for the Study of Liver Diseases (AASLD) recommend that the initial therapy of symptomatic WD patients should include a chelating agent\textsuperscript{5}. In this study, no patient demonstrated neurological deterioration and eighty patients gradually exhibited neurological improvements during zinc therapy, which indicated that zinc agent is of great value as maintenance therapy.

In the present study, we applied DMPS as initial therapy and Zinc as maintenance therapy for neurological WD patients. This combined therapeutic approach improved the neurological symptoms, while lowering the incidences of neurological deterioration. The adverse effects of the combined therapeutic approach were relatively mild, which primarily included gastrointestinal symptoms and transient increase in serum aminotransferases. The elevation of the transaminase levels in the patients participating in this study were similar to the findings of another recent study conducted in China. The incidence of myelosuppression as a side effect of the DMPS and zinc combined therapeutic approach was quite low and all cases which presented with myelosuppression had splenomegaly previously. Leukopenia can be alleviated by dosage adjustment. The findings of this study suggest that the combined therapy is more efficient and relatively safer compared to the DPA monotherapy as the first-line therapeutic approach for treating neurological symptoms of WD.

The 48.4\% of patients receiving combined therapeutic approach exhibited significant improvements
in MRI after 1-year treatment, while only 30.8% of the patients undergoing the DPA monotherapy group exhibited neurological improvements. Noteworthily, no obvious changes in MRI abnormal signal intensity were detected for the patients who demonstrated neurological deterioration in both groups after 1-year therapy.

Among this study, all the WD patients shows no psychiatric symptoms except 9 patients with mild psychiatric symptoms (anxiety and mild cognitive impairment). For these 9 WD patients, no specific treatments were given. With the ongoing of the treatment, most of these psychiatric symptoms gradually disappeared. For those with serious dystonia and poor life quality, consistent symptomatic treatment (e.g. anticholinergic drugs and baclofen) were given in both groups.

Dietary restriction is helpful in controlling copper excess\(^7\). Lifelong treatment, compliance with treatment, safety assessment and concomitant medications are also very important for WD patients\(^27\). In addition, earlier diagnosis and therapy is of great significance for preventing the neurological worsening in WD disease. Delayed diagnosis is one of the most important factors that determines poor treatment outcome\(^5, 17, 28\).

**Conclusions**

The findings of this study demonstrate that the safety and efficacy of the combined therapeutic approach of treatment with DPMS and zinc as a first-line therapy is more optimal in comparison to the DPA monotherapy for the treatment of WD patients manifesting neurological symptoms. There are a few limitations to the scope of this study. The retrospective nature of data collection poses a key limitation to the introduction of diversity within the dataset. The devising of studies with multi-cycle therapies and longer follow-up periods would be useful to shed more light upon the clinical value and potential side effects of the combination therapy. Finally, the genetic aspects of both the therapeutic approaches compared in this study have not been analyzed.

**Abbreviations**

- **WD**: Wilson’s disease
- **DMPS**: Sodium 2, 3-dimercapto-1-propane sulfonate
- **DPA**: D-penicillamine
**GAS:** Global Assessment Scale

**ALT:** alanine aminotransferase

**AST:** aspartate transaminase

**PLT:** platelet

**WBC:** white blood cell

**Declarations**

**Ethics approval and consent to participate**

The Ethics Committee of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine approved the protocol used in this study. All adult patients and the parents or guardians of pediatric patients consented to participate in this retrospective observational study. Informed consent was obtained in writing from each adult patient and from the parents or guardians of the pediatric patients.

**Consent to publish**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study can be provided by the corresponding author on request.

**Competing interests**

The authors declare that there is no competing interest.

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**Authors’ contributions**

JZ: Study conception/design; data collection; drafting of manuscript.

LX: Critical revisions for important intellectual content; supervision.

WY: Study conception/design, data interpretation; drafting of manuscript; critical revisions for
important intellectual content.

All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of the study population stratified by chelation therapy

| Characteristic                              | Group 1 (N=93) | Group 2 |
|---------------------------------------------|----------------|---------|
| Age (years)                                 | 24.47 ± 8.00   | 26.93 ± |
| Female (n, %)                               | 33(35.5%)      | 32 (49.2) |
| Time since first symptoms (months)          | 24(3-60)       | 23(3-96) |
| Psychiatric symptoms (n, %)                 | 5(5.4%)        | 4(6.1%) |
| Hepatic dysfunction at diagnosis (n, %)      | 23(24.7%)      | 19(29.2%) |
| Kayser-Fleischer corneal rings (n, %)        | 93(100%)       | 65 (100%) |
| Serum ceruloplasmin (<200mg/L)              | 93(100%)       | 65(100%) |
| Abnormal brain MRI (n, %)                   | 93 (100%)      | 65(100%) |

Group 1: treated by sodium 2, 3-dimercapto-1-propane sulfonate in combination of Zinc; **Group 2**: treated by D-penicillamine; MRI: magnetic resonance imaging

Table 2. Serum ceruloplasmin and 24 h urine copper in all patients with Wilson’s disease during treatment.

| Indicator                        | Time      | Group 1 (N=93) | Group 2 |
|----------------------------------|-----------|----------------|---------|
| Serum ceruloplasmin(mg/L)        | Baseline  | 79.34 ± 18.10  | 84.62 ± |
|                                  | 8 weeks   | 82.24 ± 8.24   | 82.15 ± |
|                                  | 1 year    | 81.75 ± 7.63   | 84.17 ± |
| 24-hour urinary copper(ug/24h)   | Baseline  | 393.23.7 ±213.94 | 395.16 |
|                                  | 2 weeks   | 1775.29 ± 665.92 | 1550.7 |
|                                  | 4 weeks   | 1509.21 ± 567.69 | 1598.0 |
|                                  | 8 weeks   | 799.36 ± 279.42 | 874.01 |
|                                  | 1 year    | 168.77 ± 80.72 | 176.69 |

Group 1 :treated by sodium 2, 3-dimercapto-1-propane sulfonate in combination of Zinc; **Group 2**: treated by D-penicillamine; Compared with Group 2, *P <0.05; In Group 2**: Baseline, 2 and 4 weeksN=65, 8 weeks and 1 year: N=59.
Table 3. Neurologic outcomes using the GAS scoring system in all patients with Wilson’s disease during treatment.

| Group | Baseline | 8 weeks | 1 year |
|-------|----------|---------|--------|
|       | N=93     | N=93    | N=93   |
|       | 8.74 ± 2.99 | 8.79 ± 2.27** | 5.89 ± 2.11** |
|       | 8.40 ± 3.49 | 8.17 ± 3.57 | 7.89 ± 3.76 |
| Group 1 | N=93     | N=93    | N=93   |
| Deterioration (n, %) | 10/93 (10.8%) | 8/93 (8.6%) |         |
| Improvement (n, %) | 84/93 (68.8%) | 82/93 (88.2%) |         |
| Group 2 | N=65     | N=59    | N=59   |

**P < 0.01, N.S. = not significant.
Deterioration (n, %)

\[ \frac{21}{65}(32.3\%) \quad \frac{17}{65}(26.2\%) \]

Improvement (n, %)

\[ \frac{30}{65}(46.1\%) \quad \frac{37}{65}(58.5\%) \]

Group 1: treated by sodium 2, 3-dimercapto-1-propane sulfonate in combination of Zinc; Group 2: treated by D-penicillamine; Global Assessment Scale, GAS.; Compared with baseline, *\( P < 0.05 \), **\( P < 0.01 \).

Figures
Figure 1

Liver function and Renal function in all patients with Wilson’s disease during treatment.
Figure 2

The white blood cell (WBC) and platelet (PLT) counts in all patients with Wilson’s disease during treatment.