



Opinion



# Magnesium Supplementation with Special Reference to Alcohol-Related Conditions: Experience from Russia

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## Abstract

Intravenous infusions of magnesium-containing solutions were routinely applied in Russia as treatment of alcohol withdrawal syndrome and other alcohol-related conditions. However, this indiscriminate approach is unfounded and may cause more harm than benefit. Magnesium deficiency is associated with certain circulatory, neuropsychiatric and metabolic conditions. The frequency of hypomagnesemia is enhanced in cases of chronic alcoholism. However, moderate deficiency does not necessarily require parenteral magnesium supplementation. Iatrogenic hypermagnesemia is associated with adverse effects. Endovascular manipulations in conditions of suboptimal procedural quality assurance can cause transmission of viral hepatitis. To decide if an intravenous magnesium supplementation is indicated, it should first be determined whether there is a deficiency and, if so, whether it can be compensated by diet or by oral intake of magnesium-containing drugs.

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Magnesium (Mg) is an intracellular cation involved in ATP metabolism. Mg is an essential element required as a cofactor for numerous enzymatic reactions and is necessary for the biochemical functioning of many metabolic pathways.<sup>1</sup> Various foods and drinking water are sources of Mg.<sup>2</sup> Chlorophyll, as found in green vegetables, is rich in magnesium. In cases of adequate nutrition, Mg deficiencies are unlikely.<sup>2,3</sup> However, in cases of poor diet, Mg deficiencies are common.

Mg deficiency has been associated with certain circulatory, metabolic and neuropsychiatric conditions, arterial hypertension, and alcoholism. Some drugs such as antibiotics, diuretics, digitalis, and others may cause Mg wasting.<sup>2-14</sup> Mg deficiency can develop in renal and gastrointestinal disease (Table 1).<sup>1-7,15,16</sup> The frequency of hypomagnesemia among inpatients was estimated to range from 7–11%<sup>3,16</sup>

or 9–65% according to another review, and these statistics are higher in intensive care units.<sup>7</sup> The prevalence of hypermagnesemia among inpatients was estimated to be in the range 5.7–9.3%, associated with increased mortality.<sup>7,11</sup> The incidence was reported to be 17% in the emergency room of one study.<sup>17</sup> Mild Mg depletion does not necessarily require supplementation. Indications for prophylactic Mg intake by large population strata are questionable because of the risk of hypermagnesemia associated with adverse effects.<sup>18-21</sup> Both low and excessive serum Mg concentrations may be unfavorable for osseous metabolism.<sup>20,22</sup> High Mg concentrations have been shown to stimulate osteoclasts and inhibit osteoblast differentiation *in vitro*.<sup>18,23</sup> Another study demonstrated that Mg consumption above the recommended dietary allowance was associated with an elevated risk of fractures.<sup>24</sup> For example in one study, postmenopausal women in the upper quintile of Mg consumption had a greater risk of wrist fracture.<sup>19,20</sup> Hypermagnesemia may also contribute to osteomalacia in renal failure, adynamic bone disease, and other disorders.<sup>3,11,22</sup>

Many studies have found enhanced frequency of hypomagnesemia in alcoholism or alcohol-related liver disease, and the potential underlying mechanisms are reported to inadequate nutrition, malabsorption, diarrhea, vomiting, and increased renal excretion.<sup>6,12,13,16</sup> The prevalence of hypomagnesemia among chronic alcoholics was estimated at ~30%<sup>3,25,26</sup> or higher.<sup>27,28</sup> An inverse relationship between serum concentrations of Mg and ethanol was found in healthy volunteers consuming alcohol.<sup>29</sup> However, a study of 60 alcoholic men could not confirm a statistically significant reduction in Mg levels, with Mg levels reported to be within the normal range irrespective of the duration of alcohol consumption and abstinence.<sup>30</sup> In a study of 129 alcohol-dependent individuals, 84 had normal, 37 had decreased, and 8 had excessive blood magnesium concentrations.<sup>9</sup> High-risk patients, such as those with chronic diarrhea, receiving parenteral nutrition or diuretics, and those who are habitual alcohol consumers, should have their blood Mg checked and supplemented when indicated.<sup>2,3</sup> Reportedly, Mg treatment may accelerated a decrease in serum aspartate-aminotransferase in patients with alcohol withdrawal symptoms, thus decreasing the risk of alcoholic liver disease.<sup>31</sup> At the same time, the recommended therapy of Mg depletion in patients with alcoholic liver cirrhosis does not significantly differ from that of other Mg-depleted patients.<sup>13</sup>

According to a recent systematic review,<sup>32</sup> no study has thus far investigated the management of Mg depletion in chronic alcohol-use disorders. Hypomagnesemia is mostly mild presenting with minimal or no symptoms. After intravenous administration, only a small portion of Mg

**Keywords:** Magnesium; Alcoholism; Alcohol withdrawal syndrome; Hypomagnesemia; Nutrition.

**Abbreviations:** ATP, adenosine triphosphate; Mg, magnesium; SU, Soviet Union; S-AST, serum aspartate-aminotransferase; Tb, tuberculosis.

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**Table 1. Causes of Mg deficiency**

| Categories                                   | Descriptions  |
|--|---|
| Reduced dietary intake                       | Poor food choices, malnutrition, demineralized water. <sup>1,3,5,7</sup>  |
| Reduced gastrointestinal absorption          | Bowel diseases and resection, malabsorption, vitamin D deficiency, drugs. <sup>3,5</sup>  |
| Increased losses from gastrointestinal tract | Diarrhea, vomiting, laxative use. <sup>3,5</sup>  |
| Increased renal losses                       | Congenital or acquired tubular defects, reduced reabsorption in old age, alcoholism, drugs. <sup>3–5</sup>  |
| Endocrine and electrolyte derangements       | Diabetes mellitus, primary hyperparathyroidism, hyperthyroidism, hyperaldosteronism, Bartter syndrome, severe burns, hypocalcaemia, phosphate depletion. <sup>3,5,6</sup>   |
| Drug-induced                                 | Diuretics, proton pump inhibitors, beta adrenergic agonists, certain antibiotics, antivirals, antifungals, antacids, chemotherapeutic agents, corticosteroids and some other hormones, phenytoin, phenobarbital, hydralazine, digoxin, pamidronate <i>etc.</i> <sup>1,2,3,5,6</sup> |
| Increased requirements                       | Growth, pregnancy, lactation, continuous stress, heat, prolonged exercise. <sup>1,3,6,7,16</sup>  |
| Others                                       | Aging is often associated with Mg deficit. <sup>1,4</sup><br>Chronic latent Mg deficiency in various clinical conditions. <sup>6</sup><br>Excessive sweating. <sup>16</sup><br>Mg-free intravenous infusions. <sup>3,7</sup><br>Genetic causes. <sup>3,5,6</sup>                    |

Mg, magnesium.

is retained, as most is excreted in the urine.<sup>33</sup> This is one reason why oral supplementation is preferable.<sup>32</sup> Oral administration is safer, being associated with a lower risk of hypermagnesemia.<sup>34</sup> Intravenous replacement may be required for symptomatic cardiac arrhythmias such as torsade de pointes or neuromuscular irritability.<sup>35</sup> Excessive intravenous infusions of Mg can lead to hypermagnesemia in alcohol-dependent patients. Fatal iatrogenic overdoses of intravenous Mg in patients with alcohol withdrawal have been reported; the life-threatening manifestations include cardiac conduction delays, asystole, apnea, and coma.<sup>36</sup> The difference between hangover and alcohol withdrawal syndrome should be considered. Although combinations are possible, a hangover is different from withdrawal syndrome, as the latter is a consequence of neuroadaptation to prolonged consumption.<sup>37</sup> In a hangover there is residual ethanol intoxication with circulating levels of ethanol's metabolites. Although withdrawal syndrome may resemble a hangover, it often presents with more pronounced and variegated symptoms in combination with alcohol cravings.<sup>38,39</sup> It should be noted that hangover and withdrawal syndromes have not been clearly distinguished from each other in the former Soviet Union.<sup>39,40</sup>

The recommended duration of detoxifying treatment including intravenous infusions was 5–10 days, and even 10–12 days according to some recommendations.<sup>41,42</sup> It is common knowledge that alcohol and its derivatives are discharged spontaneously and dehydration can be compensated by an oral intake of liquids. Nonetheless, the following therapies were recommended and used to treat alcohol withdrawal syndrome: intravenous infusions of Mg sulfate, sodium thiosulfate, sodium chloride, glucose, and other solutions (7–10 infusions per day, sometimes combined with intramuscular or subcutaneous injections).<sup>43–47</sup> Detoxification therapy was deemed “indicated for almost all alcoholic patients, especially to those with prolonged withdrawal syndrome”.<sup>41</sup> Infusion therapy has been also recommended for patients with withdrawal syndrome of moderate severity.<sup>43</sup> Similar indications can be found in recent publications.<sup>48,49</sup> Certain methods were patented, including infusion therapy and transcerebral electrophoresis of Mg-containing solu-

tions as therapies for alcohol withdrawal syndrome.<sup>46,50–52</sup> Intramuscular injections have also been recommended, including Mg sulfate, glucose, sodium thiosulfate solutions, subcutaneous infusions of saline, extracorporeal ultraviolet irradiation of blood, sorbent hemo- and lympho-perfusion, “cerebrospinal fluid perfusion”, or “liquorosorption”.<sup>42,47,53–56</sup> Admittedly, some withdrawal symptoms are similar to those observed in Mg deficiency and may improve with supplementation. Among others, thiamine utilization in patients with alcohol withdrawal syndrome may be positively influenced by an adequate Mg status.<sup>27</sup> However, patients without Mg deficiency can develop the syndrome while delirium tremens may discontinue despite persistently low Mg levels.<sup>57</sup> Hypomagnesemia may persist for 2 weeks after the onset of abstinence, potentially justifying a nutrient supplementation,<sup>58</sup> but indiscriminate intravenous infusions could be contraindicated. The prescription of Mg for alcohol withdrawal including delirium tremens has been debated, and as such there is insufficient evidence to prescribe Mg in this setting.<sup>32,34</sup> Controlled trials have not demonstrated improvements in severity of alcohol withdrawal, delirium, or seizures with Mg use.<sup>59</sup> According to one Cochrane review, there is no sufficient evidence to administer Mg to treat or prevent alcohol withdrawal syndrome.<sup>60</sup>

Mg should be supplemented in cases of proven hypomagnesemia. In case of clinical indications, infusion therapy may be administered with monitoring of renal function and Mg levels.<sup>59</sup> There is an opinion that Mg infusions “can only be envisaged in intensive care units with careful monitoring of pulse, arterial pressure, deep tendon reflexes, hourly diuresis, electrocardiogram and respiratory recordings”.<sup>61</sup> The guidelines recommend checking electrolyte levels and correcting abnormalities where necessary,<sup>60</sup> or “in case of biological deprivation”.<sup>34</sup> Despite limitations, Mg serum levels are used as a standard assessment of Mg status.<sup>3,7</sup> Blood Mg levels can revert to normal levels at the time of delirium onset.<sup>13,62</sup> In the above-cited study, hypomagnesemia was detected in 42.3% of delirium tremens patients;<sup>9</sup> and other researchers have reported comparable or even higher rates.<sup>63,64</sup> Given that withdrawal syndrome may be hard to distinguish from Wernicke encephalopathy,

oral Mg was recommended for severe cases;<sup>65</sup> but intravenous infusions in alcohol withdrawal syndrome have not been recommended.<sup>62</sup> It should be stressed that lengthy drip infusions are associated with discomfort. Some alcoholic patients considered such treatments as punishment; this motivation was apparently present among some medics.<sup>66</sup> It should be noted that repeated endovascular procedures may result in a transmission of hepatitis B and C, which has occurred in patients with chronic alcoholism. A combination of viral and alcohol-related liver injury is known to be associated with less favorable prognosis. The nosocomial transmission of hepatitis virus is a known problem. Thus, the reuse of injection equipment should be avoided.<sup>67</sup> There are preventive measures that can be applied in the healthcare settings.<sup>68</sup> In the absence of disposable needles and syringes, reusable instruments must be properly sterilized. However, this has not always been the case in some institutions. Unfortunately, attitudes towards alcoholic patients can be negative, resulting in potentially lower procedural quality assurance. Therefore, indications for intravenous and other invasive manipulations should be thoroughly evaluated.

Outdated and suboptimal methods have sometimes been applied in the former SU due to partial isolation from the international professional community, insufficient adherence to the principle of informed consent, paternalistic attitudes towards patients, lack of professional autonomy, autocratic or military managerial style discouraging criticism, and impartial polemics.<sup>69,70</sup> Suboptimal practices have been applied as per instructed and according to leading expert publications, and some examples have been discussed previously.<sup>70,71</sup> In brief, the overuse of Halsted and Patey mastectomy with excision of pectoral muscles, routine electrocoagulation of cervical ectropions without cyto- or histological examination for precancerous changes, extensive gastric resections for peptic ulcers, thoracic and abdominal surgery for bronchial asthma and diabetes mellitus,<sup>70</sup> overuse of surgery in tuberculosis (Tb),<sup>71</sup> mass bronchoscopy in conscripts with supposed pneumonia.<sup>72,73</sup> Some invasive methods with questionable indications were introduced or advocated by first generation military surgeons.<sup>70</sup> There is an opinion, that over-manipulation has sometimes been applied with the aim of personnel training. Alcohol-dependent people are convenient subjects of such treatments. Finally, it should be noted that patients suffering both Tb and alcoholism are often subject to the treatment described above. In some cases, vocal cord injuries were observed in such patients after repeated bronchoscopies due to suboptimal procedural quality assurance. It was reported that apomorphine-induced vomiting as emetic (aversive) therapy of alcohol dependence provoked hemoptysis.<sup>41</sup> In some official instructions, indications for surgery were broader in alcoholics than in other Tb patients;<sup>55</sup> surgery was recommended earlier, after a shorter period of medical therapy.<sup>74</sup> Reportedly, in 1994 about 60% of patients in a "phtisio-narcological" institution who were receiving compulsory treatment absconded and half were brought back by the police (militia).<sup>75</sup> The duration of compulsory treatment in such institutions was around one year or longer.<sup>42</sup> During the 1990s, the system of compulsory treatment was largely dismantled, but some experts recommended a return to the Soviet-time practices of compulsory treatment.<sup>76</sup> More details can be found in another review.<sup>71</sup>

## Conclusions

Patients with alcohol withdrawal syndrome and other alcohol-related conditions have been routinely treated in Russia by intravenous infusions of Mg-containing solutions. This sometimes entailed unfavorable physiological and psycho-

logical effects. Significant Mg deficiency should not be a priori assumed in all alcoholics.<sup>77</sup> To decide if a parenteral Mg supplementation is indicated, it should first be determined whether there is a Mg deficiency and, if so, whether it can be compensated by diet or by oral intake of Mg-containing drugs or dietary supplements. More research on the effects of exogenous Mg in alcohol-related disorders is needed, including withdrawal syndrome and delirium tremens, taking into account blood Mg levels and other indices such as Mg content in red blood cells, loading test, and 24-h urinary excretion.

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## Author contributions

Single author (SVJ): Concept and design, writing, and approval of the manuscript.

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