DOI: https://doi.org/10.5114/ait.2022.123137

Use of a combination of dexmedetomidine and magnesium sulfate as a multimodal approach to the treatment of alcoholic delirium

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Abstract

Background: The search for an effective sedation schedule in managing delirium tremens that would ensure an adequate sedation level and good safety profile is an urgent problem of modern intensive care medicine. In this respect, the use of dexmedetomidine combined with magnesium preparations seems to be promising.

Methods: A quasi-randomized prospective observational study was conducted on 80 patients with alcoholic delirium, who were divided into 4 groups. Assessment parameters were delirium duration, mean arterial pressure and heart rate, and plasma magnesium, urea, creatinine, transaminase, cortisol, and serotonin levels. The control-group patients underwent standard sedation therapy with benzodiazepines. In group 1, standard sedation was supplemented by magnesium sulphate. In group 2, dexmedetomidine infusion was used. In group 3, dexmedetomidine was supplemented by the correction of hypomagnesemia.

Results: The duration of delirium proved to be significantly shorter in all study groups (3.4 ± 0.6 days in group 1; 1.55 ± 0.61 days in group 2) as compared to the control (5.4 ± 1.48 days), $P < 0.001$, being the shortest in group 3 (1.1 ± 0.18 days), $P < 0.001$. Cases of hypotension were detected only in the control group (2 cases [10%]) and group 1 (4 cases [20%]). The patients of groups 2 and 3 showed significant improvement in plasma levels of cortisol (16.7 ± 2.25 nmol L^{-1}; 15.62 ± 1.63 nmol L^{-1}) compared with the control (18.77 ± 2.76 nmol L^{-1}), $P = 0.019$; $P = 0.003$. Serotonin level was higher in the experimental group 3 (87.8 ± 7.32 ng mL^{-1}) as compared to the control (62.81 ± 9.81ng mL^{-1}) and group 2 (71.73 ± 9.61 ng mL^{-1}), $P < 0.001$.

Conclusions: Dexmedetomidine infusion combined with magnesium sulphate proved to be effective in the treatment of patients with alcohol delirium.

Key words: alcohol withdrawal, delirium tremens, sedation, dexmedetomidine, magnesium.

Anaesthesiol Intensive Ther 2022; 54, 5: 365–368

Received: 12.10.2021, **accepted:** 04.10.2022

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Alcohol dependence is known to be one of the leading causes of death among the adult population both in Ukraine and other countries of the world [1]. The World Health Organization (WHO) places Ukraine in the highest category in terms of "years of life lost" due to the harmful use of alcohol [2]. The problem of alcoholism in our country makes a significant contribution to the overall mortality of the population, particularly among men [3]. The issue of the consequences of ethanol abuse is made especially relevant by the situation with the war, which was launched by Russia against Ukraine more than 8 years ago and is now in its hottest and largest phase [4]. The most severe and remarkable consequences of alcohol addiction are mental and behavioural disturbances in the form of delirium. The main factors of mortality in alcoholic delirium are determined by hyperthermia and the use of physical restraints in patients [5]. Nowadays, many published studies on alcoholic withdrawal delirium are focused on the review of pathogenetic processes in the central nervous system (CNS) in chronic heavy drinking as well as the search for an optimal sedation schedule, which would allow it to achieve its optimal level but does not lead to respiratory depression and mechanical ventilation [6]. In this context, dexmedetomidine seems to be promising, and its beneficial effect has been widely discussed in scientific medical literature for many years [7]. Another controversial issue is the influence of hypomagnesaemia on the quality of treatment [8]. Because the bioavailability of magnesium sulphate is quite low

TABLE 1. Analysis of randomization

Factor	Control group ($n = 20$)	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)	*P*-level
Age, years	46.9 ± 8.1	44.3 ± 9.8	47.5 ± 10.4	41.3 ± 9.2	0.230
MAP (day 1), mmHg	107.93 ± 9.25	105.33 ± 8.25	102.17 ± 6.72	109.33 ± 8.98	0.281
HR (day 1), bpm	97.75 ± 7.28	93.85 ± 8.87	92.20 ± 9.02	91.35 ± 4.95	0.196
Magnesium (day 1), mmol L^{-1}	0.65 ± 0.18	0.67 ± 0.17	0.68 ± 0.17	0.64 ± 0.12	0.942
Cortisol (day 1), nmol L^{-1}	22.42 ± 3.48	22.20 ± 3.69	22.15 ± 3.29	22.53 ± 3.21	0.993
Serotonin (day 1), ng mL^{-1}	39.92 ± 9.85	39.91 ± 7.61	39.55 ± 8.5	39.46 ± 9.87	0.999

Indices are presented as M ± σ, where M is mean value and σ – standard deviation.

and can be less than 50%, there is still no consensus as to its dose regimen [9]. Such a discrepancy leads to the administration of either a low dose of magnesium sulphate, which is ineffective, or its overdose, causing side effects such as hypotension, bradycardia, respiratory disorders, and uncontrolled sedation [10]. Some studies have presented convincing evidence that uncorrected plasma magnesium levels lead to an increased one-year mortality rate in patients with alcohol withdrawal [11]. Also, when intravenous magnesium sulphate is used, the target level of sedation can be achieved with lower doses of sedative agents for anaesthesia in minor surgical procedures [12]. The aim of our study is to test the efficacy and safety of a combination of dexmedetomidine and magnesium sulphate for the treatment of alcoholic delirium.

METHODS

The study was registered by the Academic Council of National Pirogov Memorial Medical University, Vinnytsia and approved by its bioethics committee. Written informed consent to participate in the study was obtained from all legal representatives of the patients.

The quasi-randomized prospective observational study was conducted on 80 patients at the university clinic for 18 months (1 September 2019 – 1 March 2020). The mean age of the patients was 45.8 ± 10.3 years (26 to 78 years) and the majority were males (71 [87.7%]). All patients were in approximately the same social and household conditions. To ensure adequate randomization, we used inclusion and exclusion criteria. The criteria for the inclusion of patients were as follows: age over 18 years; absence of concomitant clinically established mental illnesses; clinical diagnosis of alcoholic delirium established in accordance with DSM-5 criteria [13]; absence of bradycardia before treatment; absence of severe damage to the heart, liver, and kidneys; and informed consent from the patient or a relative. The criteria of the exclusion were as follows: severe liver failure with bilirubin level ≥ 101 μmol L^{-1}; severe renal failure with creatinine level ≥ 354 mmol L^{-1}; bradycardia that occurred against the background of treatment with a decrease in heart rate (HR) below 50 beats per minute; and a decrease in mean arterial pressure (MAP) against the background of treatment < 55 mmHg. None of the patients participating in the study during the entire course of treatment fell under any of the above exclusion criteria. They completed the full course of the proposed therapy. Neither the evaluators of the results nor the specialists who performed the analyses knew which research group the treated cases belonged to. The analysis of patients' initial parameters is presented in Table 1.

Individuals with alcohol withdrawal status according to DSM-5 diagnostic classification [14] and those who had scores of at least 20 according to the Clinical Institute Withdrawal Assessment of Alcohol Scale – Revised (CIWA-Ar) on admission were included in the study [15]. To assess withdrawal severity during the study period, the CIWA-Ar scale was used, the evaluation intervals being 8 hours. Alcohol withdrawal delirium was verified by the Confusion Assessment Method for Intensive Care Units (CAM-ICU) [16]. The level of sedation was evaluated using the Richmond agitation-sedation scale (RASS) [17] every 8 hours. According to the RASS scale, a sedation level of 0 to –2 was maintained in all the patients.

Standard monitoring of all study patients included continual assessment of mean arterial pressure (MAP), heart rate (HR) and oxygen saturation. Also, the following laboratory parameters were determined: blood plasma levels of transaminase, urea, creatinine, plasma cortisol, serotonin, and magnesium. Laboratory parameters were analysed and compared on the treatment's first and third days. The duration of the delirium episode was considered the primary indicator of treatment effectiveness.

All patients were randomly divided into 4 groups – 3 experimental groups and a control group. The control patients underwent standard sedation therapy: diazepam 10–20 mg every 4–6 hours. When sedation was considered insufficient, continuous intravenous infusion of sodium thiopental at a dose of 1–3 mg kg^{-1} h^{-1} was administered. In addition, all patients received thiamine 250 mg per day to pre-

vent Wernicke-Korsakoff syndrome; body hydration status was also controlled. In experimental group 1, standard sedation was supplemented with intravenous administration of 25% magnesium sulphate solution at a dose of 50 mg kg^{-1} [12] every 8 hours. In experimental group 2, after a single administration of diazepam 10–20 mg, a long-term dexmedetomidine infusion was instituted at the initial dose of 0.7 μg kg^{-1} h^{-1}, followed by its correction depending on the level of sedation according to the RASS scale. In experimental group 3, initial administration of 10–20 mg diazepam was followed by an intravenous 25% magnesium sulphate solution every 12 hours along with a continuous infusion of dexmedetomidine in a mode identical to that in experimental group 2.

The entire data array obtained was statistically processed using SPSS Statistica version 22 software [18]. To assess the statistical power of the sample, the one-sample binomial test was used. We used the Kolmogorov-Smirnov test to determine the type of data distribution. We found that the distribution of the data in our study did not differ from normal. To check the significance of statistical differences, we used the following criteria: Student's *t*-test for independent samples and one-way analysis of variance ANOVA for comparing 3 or more independent samples. The difference was considered statistically significant at $P < 0.05$.

RESULTS

A comparison of the average indicators of the duration of delirium in all groups by the ANOVA test showed a statistically significant difference (Table 2). A comparison of the duration of delirium of the control and magnesium groups also showed a significant difference. A similar comparison of the groups with dexmedetomidine and the combination of dexmedetomidine and magnesium also revealed a statistically significant difference.

Hypomagnesaemia on the first day of treatment was detected in 40 patients, which accounted for 50% of the total number of treated cases. This proportion remained unchanged in all experimental groups.

MAP indicators on the third day of treatment did not statistically differ in the global comparison. In a similar analysis of HR indicators, we found a significant difference. In a pairwise comparison, the HR in the second experimental group was significantly higher than in the control group. Similarly, the HR in the second group differed from the third. During the treatment, we clinically observed cases of hypotension that required correction. In the control group, 2 cases (10%) of hypotension were recorded; in the first experimental group, 4 patients (20%) with hypotension were found. At the same time, MAP indicators in these cases did not reach the limits of the exclusion criterion and were corrected after a volaemic load of 500 mL of stabilized polyionic solution. Hypotension cases were not detected in the second and third experimental groups.

In a global comparison of mean cortisol values on the third day between all groups, we found a significant difference. A pairwise comparison with the control showed that cortisol was significantly lower in the second and third experimental groups. A similar result was obtained in a pairwise comparison with the first group. The level of cortisol in the second and third groups was statistically comparable.

Serotonin indicators on the third day differed significantly in the global comparison. A pairwise comparison of the level of serotonin with the control showed that it was significantly higher in the second and third experimental groups. The level of serotonin in the third group was significantly higher than in the second group. After comparing the indicators of the state of the kidneys and liver on the third day of treatment between all groups, we did not find significant differences in any of them.

DISCUSSION

After analysing the obtained results, we saw that the optimization of the control points of our study (duration of delirium, cortisol and serotonin levels) occurred in those groups where dexmedetomidine was used. The best result was obtained in the group with a combination of dexmedetomidine and magnesium sulphate.

TABLE 2. Global comparison.

Factor	Control group ($n = 20$)	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)	*P*-value
Delirium duration, days	5.40 ± 1.48	3.40 ± 0.60	1.55 ± 0.61	1.10 ± 0.18	< 0.001
MAP (day 3), mmHg	92.69 ± 6.72	90.00 ± 8.22	95.17 ± 5.38	92.83 ± 9.09	0.497
HR (day 3), bpm	79.90 ± 6.92	84.10 ± 9.29	89.55 ± 8.31	81.90 ± 8.70	0.022
Magnesium (day 3), mmol L^{-1}	0.73 ± 0.14	0.91 ± 0.11	0.73 ± 0.15	0.90 ± 0.09	< 0.001
Cortisol (day 3), nmol L^{-1}	18.77 ± 2.76	18.84 ± 2.08	16.70 ± 2.25	15.62 ± 1.63	< 0.001
Serotonin (day 3), ng mL^{-1}	62.81 ± 9.81	64.95 ± 9.54	71.73 ± 9.61	87.8 ± 7.32	< 0.001

Indices are presented as M ± σ, where M is the mean value and σ is the standard deviation.

Dexmedetomidine is already used in the treatment of alcoholic delirium and has shown its effectiveness both in our study and in other trials [19].

In our opinion, hypomagnesaemia is an underestimated link in the pathogenesis and treatment of alcohol withdrawal with delirium. Although we found laboratory-confirmed hypomagnesaemia in only half of our patients, we should not forget that magnesium is an intracellular electrolyte, and its deficiency cannot always be verified in the laboratory [20]. We can see that in our study when magnesium sulphate was added, the duration of delirium was shortened, and when dexmedetomidine and magnesium sulphate were combined, it was significantly lower than in the other groups.

Having analysed the obtained data on the effect of each of the schemes on haemodynamics, we are inclined to believe that the correction of hypomagnesaemia in combination with controlled sedation by dexmedetomidine in patients with alcoholic delirium adequately normalizes MAP and HR and also makes the development of complications in the form of hypotension and bradycardia less likely, which occur with the isolated use of both dexmedetomidine and magnesium sulphate.

Specific biochemical markers that indicate the severity of delirium and are sensitive to sedative therapy are the level of free cortisol and serotonin in the plasma because one of the links of this pathological process is hyperactivation of the sympathoadrenal system [21]. According to the obtained data, we believe that the use of a combination of dexmedetomidine and magnesium sulphate showed better dynamics of these biomarkers.

The dynamics of indicators of the functional state of the kidneys and liver in all groups were unreliable, i.e. none of the schemes we used harmed these vital organs.

CONCLUSIONS

We believe that using magnesium has a significant positive effect on the treatment outcome, improving the effectiveness of both standard therapy and dexmedetomidine sedation. Using a combination of dexmedetomidine and magnesium sulphate helps shorten the duration of delirium as much as possible. This combination, in our opinion, has no adverse effect on haemodynamics, is safe for the kidneys and liver, and does not cause breathing disorders. The combined use of dexmedetomidine and magnesium sulphate influenced plasma cortisol and serotonin levels towards their normalization.

ACKNOWLEDGEMENTS

1. Assistance with the article: none.
2. Financial support and sponsorship: none.
3. Conflicts of interest: none.
4. Presentation: none.

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