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Title

Preferences for measurement and supplementation of magnesium, phosphate and zinc in ICUs: The international WhyTrace survey

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Abstract

Background. Patients admitted to Intensive Care Unit (ICU) often have low magnesium, phosphate and zinc levels. Monitoring of serum concentrations and supplementation may be important, but there is no consensus on optimal practice. The objective of the WhyTrace survey was to describe current practice regarding measurement and supplementation of magnesium, phosphate and zinc in ICUs.

Methods. A 54-item electronic questionnaire was developed in accordance with SURGE, SUrvey Reporting GuidelinE, to address international clinical practice in the ICU. National investigators recruited ICUs in ten countries with one physician responding per ICU using a unique e-mail distributed survey-link.

Results. The questionnaire was sent to clinicians in 336 ICUs of whom 283 (84%) responded. In 62% of the ICUs, a standard procedure was in place regarding measurement of serum magnesium levels, in 58% for phosphate and in 9% for zinc. Zinc was never or rarely measured in 64% of ICUs. The frequency of requesting serum levels varied from twice daily to once weekly. Regarding supplementation, 66% of ICUs had a standard procedure for magnesium, 63% for phosphate and 15% for zinc. Most procedures recommended supplementation when serum levels were below lower reference level, but some used the upper reference levels as the threshold for supplementation and others decided on a case-by-case basis.

Conclusion. The practice of measuring and supplementing magnesium, phosphate and zinc differed substantially between ICUs. Our findings indicate that there is a need for high quality prospective data on frequencies of measurements, treatment goals and effects of supplementation on patient-important outcomes.

Key words: Magnesium, Phosphate, Zinc, Trace elements, ICU, Critically ill

Ediorial Comment: Mineral elements are essential in the human body. Low levels of magnesium, phosphate and zink are commonly observed in critically ill patients, and these occurrences are associated with reduced survival likelihood. General supplementation is common, though without convincing evidence for effect on survival. Routines for plasma analyses and supplementation are vary widely between centres. These international survey findings describe this.

Background

Critically ill patients admitted to the Intensive Care Unit (ICU) often have low serum concentrations of magnesium, phosphate and zinc.[1-3] Very high incidences have been reported, for hypomagnesemia (52%)[3], hypophosphatemia (up to 100%)[1] and hypozincemia (up to 96%)[2] in critically ill patients indicating high clinical relevance of changes in these three elements. Decreased absorption and increased excretion are contributing to the low serum levels.[1,2,4] For magnesium and phosphate, compartmental redistribution plays a major role since serum contains only 0.3 and 0.1% respectively of total body stores, and low serum levels may not reflect body deficiency.[4,5]

Magnesium and phosphate are essential for energy storage, transport and utilization, and low serum levels have been associated with respiratory, cardiovascular and neuromuscular complications.[4,6-8] Zinc is important in the immune response, and low serum levels have been associated with recurrent episodes of sepsis, number of organ dysfunction and development of acute respiratory distress syndrome (ARDS).[2,9,10] Therefore monitoring of serum concentrations and supplementation of these elements may be important.

However, the optimal frequency of measuring serum levels of magnesium, phosphate and zinc and best practice of supplementation remain unclear. As a result, clinical practice may differ between ICUs. In the general ICU at Rigshospitalet in Copenhagen, Denmark, the procedure is to measure magnesium, phosphate and zinc levels twice weekly. During a literature search we found large variation in practice among Swedish and Dutch ICUs. [11-13]

Given the differences in routine practice even between ICUs in close proximity, we hypothesized that practice was likely to vary widely between ICUs in different countries. Thus, the objective of the WhyTrace survey was to describe differences in the routine procedures of measuring and supplementing magnesium, phosphate and zinc in general ICUs in numerous countries. The primary aim was to describe routine practice for general ICU patients as opposed to specific high-risk patient categories with known excessive losses (e.g. in dialysis, refeeding or burns patients), where intensive monitoring is often already in place.

Methods

Study design

We conducted an e-mail-distributed survey. The questionnaire was designed and distributed using SurveyXact (Ramboll, Denmark).[14] We developed the questionnaire in accordance with the SUrvey Reporting GuidelinE (SURGE).[15] The SURGE guideline is based on the STROBE (STrengthening the

Reporting of Observationally studies in Epidemiology) Statement.[16] However, in contrast to STROBE, it is designed uniquely for non-web-based surveys.[16]

All questions concerned the general clinical practice within the ICU, rather than the individual doctor's own preferences. Ethic approval was therefore not needed. All information was obtained in anonymized format and results are only presented by country and size of ICU. The e-mail addresses were not stored after data collection, neither were they shared or distributed further. Activation of the survey-link was regarded as informed consent to participate. Distribution in the first country started in April 2019 and the survey was closed in October 2019.

Study population

Using our established research network, we invited one clinician per country to act as national investigator. We sought to include general ICUs defined as a medical, surgical or mixed ICU which was not limited to a specific patient category only (i.e. burns, neurosurgical, cardiac surgery or cardiology). To ensure wide representation, we aimed to include a broad spectrum of ICUs differing in relation to medical vs. surgical patients, size and country.

The national investigators established direct contact with one physician per ICU, except in two countries, where the coordinating site initiated the first contact via e-mail based on a list provided by the national investigators. We only included participants who were able to read and write English. If a physician declined, another physician from the individual ICU was contacted when possible. No financial or other incentives were provided. If a clinician agreed to receive more information by e-mail, the coordinating site sent the e-mail with a unique link to the online survey. The unique links enabled us to avoid bias due to multiple answers from the same ICUs. In case of no reply or failure to complete the survey, at least three reminders were sent by the coordinating site and followed up by the national investigator.

To perform sub-analyses describing differences in practice between small, medium and large ICUs, we grouped ICUs based on quantiles (i.e. 2-10 beds, 11-22 beds and 23-127 beds). To assess differences between ICUs in developed vs. developing countries, we grouped ICUs according to the United Nations definition (Denmark, Finland, Iceland, Norway, Sweden, Switzerland and the UK as developed and Brazil, India and Saudi Arabia as developing countries).[17]

The questionnaire

The questionnaire consisted of 54 questions about general procedures related to measuring serum levels in the ICU and supplementing magnesium, phosphate and zinc. Throughout the questionnaire it was highlighted that responses should relate to general ICU patients and participants should refrain from

answers based on specific patient categories with known excessive losses (e.g. dialysis, refeeding or burns patients), which may not receive standard supplements (the questions are presented in Appendix S1). Each item on the initial list of questions was evaluated by several clinicians and research fellows at the coordinating site. Questions as well as response options were revised, added and deleted based on feedback from colleagues. Prior to distribution, the survey was pilot tested by six physicians from three different ICUs and the language was validated by a native English-speaking physician.

To reduce the number and complexity of questions, we used adaptive questioning where some questions were conditionally displayed based on previous answers. To ensure that the participants considered all questions, choosing a response was enforced before moving on. A non-response option as "I don't know" was added to reduce the number of incomplete answers. If a participant was interrupted during the process and started again later, the questionnaire would automatically continue with the question which was left incomplete. It was possible to go back through the questionnaire to review or change the answers. All items were simple descriptive questions about general procedures; hence, no formal psychometric validation was needed.

Unit conversions: When serum magnesium was provided as mg/dL, the units were converted to mmol/L by multiplying with 0.4114; mEq/L was multiplied with 0.5. Phosphate levels were converted from mg/dL to mmol/L by multiplying with 0.3226. In analyses of intravenous (IV) zinc supplementation, several replies on dosages were clearly given in micromole instead of millimole. Since no ICU would use 150 mmol IV zinc supplementation, we converted replies with a clearly 100 or 1,000 factor error from micromole to millimole.

Statistics

Descriptive statistics are presented as number (n) and percentages for categorical variables and as median and interquartile ranges (IQR) for continuous variables. Since we aimed to describe differences rather than testing for associations, a formal sample size calculation was not required, and sample size was therefore based on convenience.

In sub-analyses we used the non-parametric Kruskal-Wallis rank test for continuous variables when describing differences according to size of ICU, and the Mann-Whitney test when assessing developed vs. developing country and completed vs. uncompleted questionnaires. For categorical variables we used chi-square test, except when the expected number of values was less than five in any of the categories in which case we used Fisher's exact test. We used 95% confidence intervals (CI) to explore the differences further.

Results on sub-analyses are descriptively presented as median or percentage. Statistical analyses were performed in R version 3.6.2, and differences were considered significant at P-values below 0.05.

Results

We initially approached clinicians from 559 ICUs in ten countries. Of the 336 ICUs who agreed to receive the survey link, 283 responded (response rate 84%). In developed countries the response rate was 90.4% and in developing countries 76.4%. The majority of ICUs were mixed medical and surgical (91.5%), and the median number of beds was 16 (range 2-127) (table 1).

Place table 1 here

Measurement of serum levels

The median reference ranges of magnesium, phosphate and zinc among ICUs are presented in table 2.

Place table 2 here

Of the included ICUs, 176 (62.2%) had a procedure for measurement of magnesium levels in general ICU patients, while 102 (36.0%) measured magnesium at the discretion of the individual doctor, and four (1.4%) never or rarely measured magnesium. In most ICUs (98.6%), the method used included measurement of total serum magnesium; only four ICUs measured ionized magnesium.

Regarding phosphate, 159 (58.2%) ICUs had a procedure for measurement, 106 (38.8%) used individual orders and seven (2.6%) never or rarely measured serum levels.

Only 23 (8.6%) ICUs had procedures for measurement of zinc, 70 (26.2%) used individual orders and 170 (63.7%) never or rarely measured serum levels in general ICU patients. Of the ICUs without a procedure for measuring zinc levels in the general ICU population, several had procedures for measurement in specific patient categories (Appendix S2).

The most common practice was to measure magnesium (61.9%) and phosphate (62.3%) once daily, but practice differed from once weekly to twice daily in general ICU patients; more frequent measurements were done in specific patient categories (table 3). In the few ICUs where zinc was routinely measured, it was mainly done twice weekly.

Place table 3 here

Supplementation therapy

Of the participating ICUs, 171 (65.5%) had a procedure for magnesium supplementation in general ICU patients, 163 (63.4%) for phosphate and 39 (15.3%) for zinc supplementation (figure 1). Most procedures involved supplementation when serum levels were below the reference range. For magnesium and phosphate supplementation, some procedures aimed for the upper reference levels, either in general or in selected patient categories.

Place figure 1 here

The preferred administration route for supplementation therapy was IV (table 4). Frequencies of administration differed according to patient category or serum level, which was often monitored after supplementation.

Place table 4 here

In different specific patient categories, regular supplementation of especially magnesium and phosphate was done either more frequently or in higher dosages (Appendix S2).

There were substantial differences in the use of "as needed" (PRN) prescriptions between countries, ranging from 70.4% in some countries using PRN supplementation of magnesium and phosphate regularly, to other countries never using PRN prescriptions in 91.7% of ICUs. No ICUs used PRN zinc prescriptions regularly (table 5).

Place table 5 here

Size of ICU

The 25 ICUs which did not complete the full questionnaire did not differ from ICUs which completed regarding size. There were no differences in proportion of small, medium or large ICUs having procedures for measurement of serum magnesium, phosphate or zinc. The full results of sub-analyses with P-values from statistical tests, IQR on continuous variables and CI on percentages are available in Appendix S3. Daily measurement of magnesium was more common in larger than small ICUs. The same was seen for phosphate, although not statistically significant. Small ICUs used two-three weekly measurements of magnesium and phosphate.

A lower proportion of small ICUs had a procedure for magnesium and phosphate supplementation as compared with medium and large ICUs. The smaller ICUs more often had a clinician-led approach.

Daily dosages of magnesium supplementation did not differ substantially between small, medium and large ICUs.

Developed vs. developing countries

The proportion of responders who did not complete the full questionnaire was higher in developing countries than in developed countries (Appendix S3, page 10). In developed countries, ICUs more often had procedures for measurements of serum magnesium, phosphate and zinc. The frequencies for measuring serum levels did not differ though. The full results of sub-analyses are available in Appendix S3.

In developed countries, the decision to supplement magnesium or phosphate was more often clinician led without procedures.

Daily dosages of magnesium supplementation did not differ between developed vs. developing countries, but developed countries used higher dosages of daily phosphate supplementation. The use of PRN prescriptions for magnesium and phosphate tended to be more common in developed countries.

Discussion

In this international survey we found that procedures for measurement of serum levels and supplementation of magnesium, phosphate and zinc differed substantially between 283 general ICUs in ten countries. Frequencies of measuring serum levels varied from twice daily to once per week. Many had established procedures for supplementation when serum levels were below the lower reference level, while others used the upper reference level or decided on a case-by-case basis.

Our results are in line with the findings of a survey on phosphate from 2012, where practice varied widely between ICUs in the Netherlands.[13] Although the awareness of monitoring magnesium and phosphate levels has increased over the last years,[18,19] our findings indicate that consensus on best practice has still not been reached. This is unfortunate, since more frequent measurements of serum levels may inflate expenses for laboratory tests and potentially result in unnecessary tests or supplementation, while less frequent measurements may cause complications from unrecognised deranged serum levels. Our survey was not designed to answer which frequencies are optimal to use in clinical practice. However, it is part of a full research program designed to provide some answers. As such, the results of the present study will inform the protocol for an RCT within this area.

Lack of specific recommendations in previous international guidelines may have contributed to the different routines.[18,20,21] In a document published in addition to the 2019 European Society for Clinical Nutrition and Metabolism (ESPEN) guideline, daily monitoring of magnesium and phosphate is recommended.[19,22] Despite this recommendation, our survey showed that only 62% of the ICUs with a procedure in place, performed daily measurements. The recommendations were developed by expert consensus though. The evidence was ungraded because of lack of studies comparing effects.[22]

National guidelines are likely to be more influential, but they differ. For example, the Danish Association for Anaesthesiology and Intensive Medicine (DASAIM) recommends magnesium and phosphate measurements twice per week in the general ICU population.[23] The UK National Institute for Health and Care Excellence (NICE)[24] recommends three measurements per week until stable and thereafter weekly. In our survey, 28% and 41% of the ICUs having procedures measured serum levels two-three times per week in accordance with these national guidelines, which may be deemed as more relevant by the individual ICU.

The influence of local guidelines becomes clear when evaluating the survey responses regarding zinc. Since only 9% of the ICUs had a procedure for measuring zinc levels, we explored these ICUs further; of the 23 ICUs, 17 were Danish. This is in line with DASAIM's national guideline,[23] which recommends twice

weekly measurement. In contrast, the UK NICE guidelines recommends zinc to be measured every two to four weeks,[24] the ESPEN guideline[19] only recommends measurement of zinc in selected cases and the American Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient provides no recommendation.[21] This may explain why 64% of the participating ICUs never or rarely measured zinc levels. "The consequences of low serum zinc levels are less acute compared with magnesium and phosphate, which may contribute to the lower proportion of measurements."[2,10]

In sub-analyses of magnesium and phosphate we found that small ICUs were less likely to measure serum levels daily than larger ICUs. Many of the small ICUs were placed in Nordic countries. It is possible that our finding of small ICUs measuring serum levels less often was confounded by the fact that Nordic countries include fewer measurements. However, the frequencies of measuring serum levels did not differ between developed and developing countries, hence, caution should be taken before assigning the variation in practice to geographical differences.

Around half of the ICUs with procedures for supplementation of magnesium or phosphate used the lower reference levels as their trigger. Based on recommendations stating "replace when needed",[21] a pragmatic approach could very well be to aim for levels within the reference range. ICUs of large size more often had practices based on lower reference levels, while in small ICUs, the decision was more often made on a case-by-case basis. The more widespread practice of using the lower reference level in large ICUs, may be explained by the higher proportion of large ICUs doing daily measurements. However, the daily dosages of supplementation did not differ between small and large ICUs. There may be a need for more formal procedures in larger departments while informal consensus can be reached more easily in smaller departments.

Our survey has several strengths. We only allowed one survey response per ICU and obtained a relatively high response rate. Also, we included a large number of ICUs with diversity in size and country. With participating ICUs from Europe, Brazil, India and Saudi Arabia, we were able to describe differences in clinical practice in a broad spectrum of cultures.

There are some limitations to our survey. First, the recruitment of countries and ICUs were by interest and clinicians from the ICUs who agreed to receive the survey may have a higher interest in the subject. Hence, we don't know if different results would have been obtained in other settings. Also, the need for supplementation and therefore procedures may vary in different parts of the world, especially for zinc where deficiency is common in countries with low intake by food. Therefore, our findings may not be applicable worldwide. Interestingly, we did not find increased attention to zinc measurements in Indian

ICUs where 73% of respondents never or rarely measured zinc despite a lower zinc intake compared to European countries.[25] Second, we had some outliers in the responses to reference levels. However, sensitivity-analyses excluding unrealistic values did not change median values or IQRs. Third, most of the participating ICUs had a mix of medical and surgical patients, and we were not able to assess differences in practice between patient categories. Fourth, the very low proportion of ICUs where zinc levels were routinely measured hampers further detailed analyses. Finally, in a survey design we explored the content of ICU procedures, which may deviate from the actual routine clinical practice at the bedside.

In conclusion, we found that the procedures for measuring and supplementing magnesium, phosphate and zinc in general ICU patients who were not at increased risk of depletion due to dialysis, refeeding or burns, differed substantially between ICUs. The wide differences in procedures likely reflect differences in the guidelines, which are based on low-level evidence. Our findings therefore highlight the need for high quality data from randomized clinical trials investigating the effects of optimal frequencies for measurements and supplementation therapy and goals in the ICU setting.

Authors contributions

G.K.V. and A.P. contributed to the design of the study.
M.O; S.N.M; Y.M.A; M.S; F.G.Z; M.C; J.C.S; F.S; E.A.B; M.B; K.M.T. and G.K.V. communicated with national participants from each own country.
G.K.V. Managed the data collection in SurveyXact and drafted the initial manuscript.
M.O; S.N.M; Y.M.A; M.S; F.G.Z; M.C; J.C.S; F.S; E.A.B; M.B; K.M.T. and A.P. critically revised the manuscript. All authors approved the paper in the current form.

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Tables in the article:

Table 1. Characteristics of the 283 participating ICUs

	n	(%)
Size of ICU		
-Small 2-10 beds	94	(33.2)
-Medium 11-22 beds	92	(32.5)
-Large 23-127 beds	97	(34.3)
Medical / surgical ICU		
-Medical	19	(6.7)
-Surgical	5	(1.8)
-Mixed	259	(91.5)
Country		
-Brazil	31	(11.0)
-Denmark	27	(9.5)
-Finland	16	(5.7)
-Iceland	3	(1.1)
-India	50	(17.7)
-Norway	19	(6.7)
-Saudi Arabia	32	(11.3)
-Sweden	27	(9.5)
-Switzerland	19	(6.7)
-UK	59	(20.8)
Developed country	170	(60.1)

ICU: Intensive care unit. n: number

Table 2: Serum reference levels in the participating ICUs

	Lower level		Upper level	
	median	(IQR)	median	(IQR)
Magnesium, mmol/L	0.70	(0.66-0.71)	1.00	(0.94-1.07)

Phosphate, mmol/L	0.80	(0.74-0.81)	1.45	(1.40-1.50)
Zinc, mmol/L	10.0	(10.0-17.0)	19.0	(18.4-19.1)

ICU: Intensive care unit, mmol/L: Millimoles per Liter, IQR: Interquartile range, n: number

Table 3: Frequencies of measuring serum levels in ICUs with procedures for measurements

	Magnesium		Phosphate		Zinc	
	n	(%)	n	(%)	n	(%)
In the general ICU patient:						
Twice daily	4	(2.3)	3	(1.9)	0	(0.0)
Once daily	109	(61.9)	99	(62.3)	1	(4.3)
Three times per week	17	(9.7)	11	(6.9)	1	(4.3)
Twice per week	32	(18.2)	30	(18.9)	12	(52.2)
Weekly	6	(3.4)	7	(4.4)	7	(30.4)
Specific patient categories with more frequent measurements:						
Renal replacement therapy	71	(25.1)	75	(26.5)	7	(2.5)
Burn patients	33	(11.7)	27	(9.5)	2	(0.7)
Alcohol abuse (known/suspected)	46	(16.3)	50	(17.7)	4	(1.4)
Refeeding syndrome	90	(31.8)	105	(37.1)	8	(2.8)
Other specific patient categories *)	58	(20.5)	33	(11.7)	5	(1.8)

ICU: Intensive care unit, n: number

*) Regarding magnesium, other patient categories were mostly cardiac patients, patients with arrhythmias, persistent hypokalaemia, malnutrition or who had received magnesium substitution due to e.g. eclampsia/pre-eclampsia. For phosphate, others most often were patients on mechanical ventilation, weaning failure, malnutrition, abnormal serum levels, diabetic ketoacidosis or sepsis / multi organ failure. For zinc, the few ICUs mentioning other patients referred to malnutrition, impaired wound healing and surgical patients.

Table 4. Administration route and dosages for supplementation therapy in the

participating ICUs

	Magnesium		Phosphate		Zinc	
Preferred administration route	n	(%)	n	(%)	n	(%)
Intravenous	199	(76.5)	158	(62.5)	31	(33.7)
Oral	4	(1.5)	18	(7.1)	34	(37.0)
Interchangeable	56	(21.5)	75	(29.6)	21	(22.8)
A fixed dose for most patients	245	(94.2)	223	(88.1)	66	(71.7)
Daily dosages *)	median	(IQR)	median	(IQR)	median	(IQR)
mmol, intravenous	20	(10-29)	20	(20-40)	0.15	(0.15-0.16)
mg, intravenous	2000	(1000-2000)	-	-	-	-
mmol, per oral	20	(20-30)	40	(20-45)	1.23	(0.44-1.40)
mg, per oral	720	(475-1000)	1000	(600-1000)	45	(22-118)

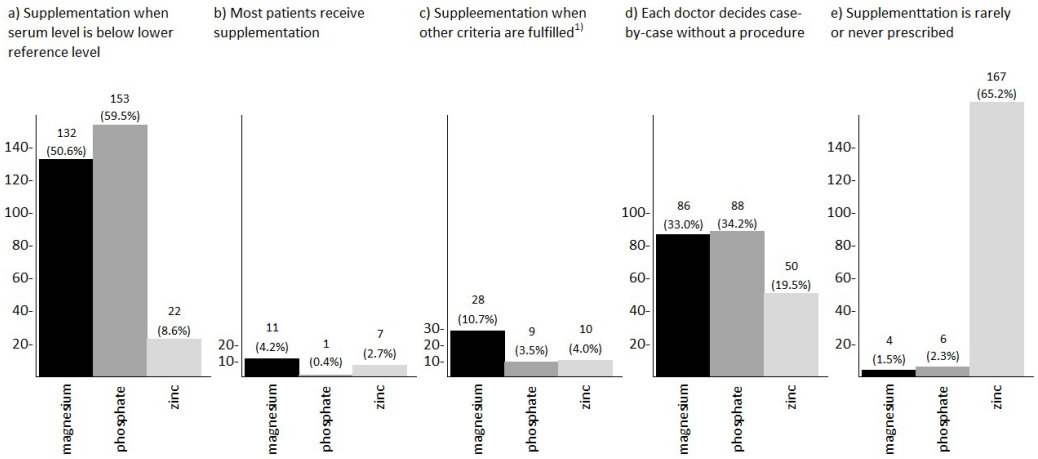
ICU: Intensive care unit, mg: milligrams, mmol: millimoles, n: number, IQR: Interquartile range

*) Magnesium was mostly administered once daily when intravenous and twice per day when oral. Phosphate and zinc mostly once daily.

Table 5. Number of ICUs using "as needed" (PRN) prescriptions of supplementation

	Magnesium n (%)	Phosphate n (%)	Zinc n (%)
Never	159 (62.1)	166 (65.6)	82 (90.1)
Regularly	61 (23.8)	54 (21.3)	0 (0.0)
In rare cases	31 (12.1)	26 (10.3)	2 (2.2)

ICU: Intensive care unit, n: number



1) Regarding magnesium, other criteria most often were patients with arrhythmias, hypokalaemia or supplementation sooner than lower limit of reference level. For phosphate, other criteria were most often respiratory difficulties or supplementation sooner than lower reference level. For zinc, other criteria were most often wound healing or parenteral nutrition.

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