Clinics in Surgery

Research Article
Published: 07 Mar, 2017

Pre- and Post-Operative Hypomagnesaemia and Association with Adverse Outcomes in Elective Vascular Surgery

Sillo T[1], Ahmad M[1], Becker H[2], Garnham A[1] and Wall M[1]*

[1]Department of Vascular Surgery, Russells Hall Hospital, UK

[2]Department of Vascular Anaesthesia, Russells Hall Hospital, UK

Abstract

Objectives: We aimed to establish the incidence of pre- and post-operative hypomagnesaemia in patients having major elective vascular surgery, and the association with post-operative complications.

Design: A prospective analysis of patients undergoing major elective vascular surgical procedures in a regional vascular centre was performed over an eight-month period.

Materials and Methods: On-line electronic patient records (EPR) were used to obtain pre-operative serum magnesium levels, as well as first and second day post-operative titers. Hypomagnesaemia was identified as serum magnesium <0.7 mmol/L. Adverse outcomes were identified using a combination of EPR and written records.

Results: We identified 256 patients. The commonest procedures were lower limb bypass, carotid endarterectomy (CEA), endovascular aneurysm repair (EVAR), femoral endarterectomy and open aortic aneurysm repair (OAR). Pre-operative hypomagnesaemia was found in 9.0%. Post-operative hypomagnesaemia was detected in 31.3%. De novo post-operative hypomagnesaemia occurred in 26.7%. The relative risk (RR) of cardiovascular complications in hypomagnesaemic patients was 2.20 (95% confidence interval (CI) =1.10–4.40, p=0.03). The RR of non-cardiovascular complications was 1.76 (95% CI=1.04–2.98, p=0.05). The combined RR of any complications in hypomagnesaemic patients was 2.07 (95% CI 1.40–3.08, p=0.0007). The mean post-operative length of stay (LOS) was 6.7 days in hypomagnesaemic patients, and 4.3 days in other patients (p =0.0018).

Conclusion: Pre- and post-operative hypomagnesaemia are common in patients undergoing elective vascular surgery. Post-operative hypomagnesaemia is associated with post-operative complications and increased length of stay.

Keywords: Vascular diseases; Magnesium; Cardiovascular abnormalities; Postoperative complications; Length of stay

OPEN ACCESS

***Correspondence:**
T O Sillo, Department of Vascular Surgery, Black Country Vascular Network, Russells Hall Hospital, Dudley, West Midlands, United Kingdom DY1 2HQ, Tel: +44 (0)7889925303; E-mail: toritseju.sillo@doctors.org.uk

Received Date: *05 Jan 2017*
Accepted Date*: 28 Feb 2017*
Published Date*: 07 Mar 2017*

Citation:
Sillo T, Ahmad M, Becker H, Garnham A, Wall M. Pre- and Post-Operative Hypomagnesaemia and Association with Adverse Outcomes in Elective Vascular Surgery. Clin Surg. 2017; 2: 1356.

Introduction

Magnesium plays a key role in cellular metabolic processes. All reactions that require the release of energy from adenosine triphosphate (ATP) require binding to a magnesium ion. It is a factor in the sodium-potassium ATPase pump, helping to maintain cellular resting potential [1]. The association between low serum magnesium and major adverse cardiovascular events in humans is recognized [2,3] and additionally, animal studies have shown that magnesium deficiency (hypomagnesaemia) intensifies oxidative stress and the inflammatory response [4]. The prevalence of serum hypomagnesaemia is about 7% in the general population, but is significantly higher in those who are critically ill in the post-operative period [5-7]. Common causes of hypomagnesaemia include drugs, alcohol excess, diarrhoea, malabsorption and tubulopathies [8]. Hypomagnesaemia is common after cardiac surgery [9], with a significant fall in magnesium levels reported after cardiac procedures, especially coronary artery bypass grafting [9,10]. These patients are reported to be at increased risk of major adverse cardiac events [9]. Patients with pre-existing cardiac conditions, diabetes mellitus and renal disease, and those on certain drugs (e.g. diuretics, proton pump inhibitors [11]) are at higher risk of hypomagnesaemia following major cardiac procedures, subsequent morbidity from arrhythmias [12] and mortality from ventricular tachy-arrhythmias

Table 1: Surgical procedures performed.

Procedure	Number
Lower limb bypass (infra-inguinal bypass)	59
Carotid endarterectomy	53
Endovascular aneurysm repair	46
Femoral and/or iliac endarterectomy	39
Open abdominal aortic aneurysm repair	24
Aorto-iliac bypass	19
Femoro-femoral bypass	7
Miscellaneous	6
Popliteal/femoral stent	3

Table 2: Distribution of age and sex in the commonest procedures.

Procedure	Number	% male	Average age (yrs)± SD
Lower limb bypass	59	76.3	68.7± 10.2
Carotid endarterectomy	53	73.6	71.7± 8.3
EVAR	46	82.6	77.5± 7.3*
Femoral endarterectomy	39	82.1	71.7± 8.7
OAR	24	91.7	70.9± 6.7
All	**256**	**77.7**	**70.8± 10.2****

*One-way ANOVA test p<0.05 **Chi-squared test p= 0.38

Table 3: A comparison of pre- and post-operative magnesium levels.

	Pre-operative magnesium (mmol/L)	Post-operative magnesium (mmol/L)
number of data points	144	477
Average	0.82	0.78
Median	0.83	0.77*
standard deviation	0.1	0.12

*difference is statistically significant; student's t test p <0.0001

[13]. Patients undergoing major elective vascular procedures are at an increased risk of cardiovascular disease, and hence adverse cardiovascular events [14-16]. A recent study done in our unit showed the prevalence of post-operative hypomagnesaemia in patients after elective open aortic aneurysm repair (OAR) was 73%, compared with 32% in patients having endovascular aneurysm repair (EVAR) [17]. We have broadened our topic of interest to include patients undergoing other major elective vascular procedures. We sought to establish the pre- and post-operative incidence of hypomagnesaemia in this population, and to correlate our findings with adverse cardiovascular and non-cardiovascular post-operative events.

Materials and Methods

Data was collected prospectively on all patients undergoing major elective vascular procedures in the unit between July 2015 and February 2016 in a tertiary vascular centre. Patient demographics, length of stay, blood test results, intra-operative and post-operative complications were collected from a combination of electronic patient records (EPR) and written patient notes. Serum magnesium levels were measured using the Johnson & Johnson Vitros-250 chemisty analyser (Ortho Clinical Diagnostics, Raritan, NJ, USA), with hypomagnesaemia defined as a level <0.7 mmol/L. Details of the pre-operative serum magnesium (collected within a month of the planned procedure), post-operative serum magnesium levels (collected in the first 24 hours post-operatively, and then within 24 and 48 hours post-operatively) and any magnesium infusions (peri-operative or within the first 24 hours post-operatively) were recorded. Details of adverse post-operative events were recorded and included interrogation of EPR and follow-up out-patient clinic notes to check for re-admissions within 30-days of the surgery. Any recorded complications were subsequently grouped as being cardiovascular or non-cardiovascular in nature. Statistical analysis was performed using GraphPad Prism (version 5) software (GraphPad, San Diego, CA, USA). Data was presented as mean and standard deviation (mean±SD). The D'Agostino-Pearson test was performed to test for normal distribution of data. The student's t-test was used to determine the significance of the difference between paired quantitative variables. One way ANOVA was used to compare more than two sets of quantitative data, with post-hoc analysis using Tukey's multiple comparison tests. The Chi-squared test was used to determine the significance of the difference between categorical variables. Statistical significance of the relative risk was determined using Fisher's exact test. Data on percentages was quoted to one decimal place, and on p-values to two decimal places. Differences between groups were deemed significant at the 95% level (p <0.05).

Results

265 patients were identified in the study period, of whom seven were excluded as they had no recorded magnesium levels. A further two were excluded as they were still in-patients at the time of data analysis. This left 256 patients, of whom 199 (77.7%) were male. The age range was 24 to 92 years, with mean age 70.8±10.2 years. Details of surgical procedures performed are shown in Table 1. The EVAR patients were significantly older than the other groups (One-way ANOVA test p<0.05). Otherwise there were no significant age differences between the groups, and no significant difference in the sex distribution between groups (Chi-squared test, p=0.38) (Table 2). Pre-operative magnesium levels were available in 56% (n=144) and post-operative levels for all patients. The range of pre-operative magnesium was 0.49 mmol/L to 1.02 mmol/L (mean±SD=0.82 mmol/L±0.10 mmol/L). The range of post-operative magnesium was 0.44 to 1.43 mmol/L (mean±SD=0.77mol/L±0.12 mmol/L). There was mean reduction in magnesium post-operatively by 0.045 mmol/L (95% confidence interval (CI) 0.024-0.066 mmol/L, t-test p <0.0001) (Table 3). Post-operative hypomagnesaemia was recorded in 30.3% (n=80). Of the 131 patients with normal pre-operative magnesium levels, 26.7% (n=35) developed post-operative hypomagnesaemia. Of the thirteen patients with pre-operative hypomagnesaemia, this was found to persist post-operatively in 53.8% (n=7). The incidence of post-operative hypomagnesaemia appeared to be dependent on the procedure performed, however one-way ANOVA analysis with post-hoc analysis using Tukey's multiple comparison test did not detect any statistically significant difference in the post-operative magnesium levels across the five procedures analysed (Table 4). Complications

Table 4: Incidence of post-operative hypomagnesaemia in the five commonest procedures.

Procedure	Post-operative hypomagnesaemia (n)	Post-operative hypomagnesaemia (%)	Mean Mg (±SD) (mmol/L)
Lower limb bypass	21	35.5	0.75 (± 0.10)
OAR	15	62.5	0.74 (± 0.17)
Femoral / iliac endarterectomy	14	35.9	0.74 (± 0.10)
EVAR	12	26.1	0.75 (± 0.09)
CEA	5	9.4	0.78 (± 0.08)
Total	80	31.3	*

*p= 0.18 (one way analysis of variance)

Table 5: Post-operative complications.

Cardiovascular events	n	Non-cardiovascular events	n
Uncontrolled systolic hypertension/ hypotension	12	Hospital-acquired pneumonia	7
Brady/tachyarrhythmias	11	Wound infection	6
Myocardial infarction	3	Minor bleeding/haematoma	4
Peri-operative cardiac arrest (survived)	2	Urinary tract infection	4
		Failure of procedure – amputation	3
		Nerve palsy	3
		Seroma/lymph leak	2
		Acute kidney injury	2
		Failure of procedure – re-exploration	2
		Prolonged post-operative pain	2
		Type 1 endoleak (after EVAR)	2
		Electrolyte imbalance	2
		Graft infection	1
		Pulmonary embolism	1
		Bowel ischaemia	1
		Ileus	1
		Unexplained pyrexia	1
		Death	1
Total	**28**		**45**

Table 6: Incidence and relative risk of complications.

	Hypomagnesaemia (n)	Normomagnesaemia (n)	Relative risk (95% CI)
Cardiovascular complication	14	14	2.20 (1.10-4.40) p = 0.03
Non-cardiovascular complication	20	25	1.76 (1.04-2.98) p = 0.05
Any complication	32	35	2.01 (1.35-3.00) p = 0.001

were divided into cardiovascular and non-cardiovascular events. 28 patients had cardiovascular complications, including three myocardial infarctions (MIs) and two peri-operative cardiac arrests (both with successful return of spontaneous circulation and recorded to be alive at discharge). 45 patients had non-cardiac complications (Table 5). There was one post-operative death. In total, 67 patients (26.2%) developed post-operative complications of the 28 patients with cardiovascular complications 14 had recorded post-operative hypomagnesaemia. Of the 45 patients with non-cardiovascular complications 20 had post-operative hypomagnesaemia. The relative risk (RR) of developing a cardiovascular complication in hypomagnesaemic patients was 2.20 (95% CI 1.10-4.40, p=0.03). The RR of developing a non-cardiovascular complication in hypomagnesaemic patients was 1.76 (95% CI 1.04-2.98, p=0.05). The combined RR of developing any complication in hypomagnesaemic patients was 2.07 (95% CI 1.40-3.08, p=0.0007) (Table 6). Further analysis of these patients did not reveal a significant fall in the levels of magnesium pre-and post-operatively in patients who developed complications. However they had significantly lower pre-operative magnesium levels, which persisted post-operatively, compared with those who did not develop post-operative complications (0.83±0.01 mmol/L vs 0.79±0.01 mmol/L, p=0.01) (Table 7). Twenty-one patients with hypomagnesaemia (26.3%) had evidence of post-operative magnesium supplementation (given after the first post-operative reading). 12 of these patients went on to develop post-operative

Table 7: Pre- and post-operative magnesium levels in patients with complications.

	Pre-operative magnesium (mmol/L)	Post-operative magnesium (mmol/L)	p-value
Cardiovascular complication	0.75 ± 0.03	0.76 ± 0.03	p = 0.83
Any complication	0.79 ± 0.01	0.76 ± 0.02	P = 0.16
No complications	0.83 ± 0.01	0.76 ± 0.07	p < 0.001

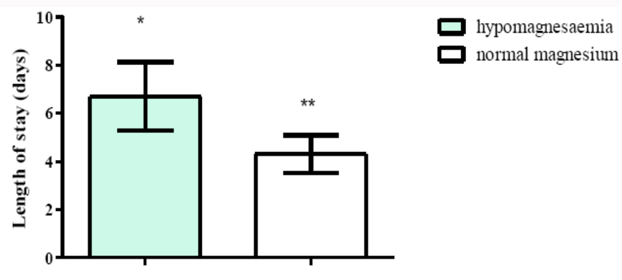
Table 8: Relative risk of complications and magnesium supplementation.

	Mg supplemented (n)	Mg not supplemented (n)	Relative risk (95% CI)
Cardiovascular complication	3	11	0.77 (0.24-2.48) p = 0.75
Non-cardiovascular complication	8	12	1.87 (0.89 – 3.9) p = 0.14
Any complication	12	21	1.61 (0.97-2.66) p = 0.12

complications (3 cardiovascular, 8 non-cardiovascular, 1 both). Magnesium supplementation increased serum magnesium levels from an average 0.80±0.02 mmol/L to 0.95±0.04 mmol/L (p=0.007). However supplementation was not associated with a reduced risk of complications in our population, although there was a small but non-significant trend towards a reduced risk of cardiovascular complications (Table 8). Finally, we collected data on the post-operative length of stay. This ranged from 1 to 43 days, with an average of 5.1±5.7 days. We analysed the association between post-operative length of stay and complications. Patients who developed any complication had an average length of stay of 9.0±1.1 days compared with an average of 3.7±0.2 days in patients who had no complications (p<0.0001). This was also strongly statistically significant when subdivided into patients with cardiovascular complications (LOS 6.5±0.8 days, p<0.0001) and those with other complications (LOS 10.6±1.4 days, p<0.0001). Post-operative hypomagnesaemia was also associated with an increased average length of stay (6.7±6.4 days compared with 4.3±5.3 days in those without hypomagnesaemia). This difference (2.4 days) was statistically significant (two tailed students t-test p=0.0018) (Figure 1).

Discussion

The processes leading to the development of hypomagnesaemia remain poorly understood and require further investigation. Two postulated theories are peri-operative haemodilution [18] and beta-adrenergic-mediated lipolysis and precipitation of insoluble magnesium salts [19,20]. Haemodilution from intravenous fluid administration may play a role, but this does not explain why other ion levels do not decrease by a similar magnitude in the post-operative



*Mean = 6.7 days, 95% CI 5.3–8.1 days

**Mean = 4.3 days, 95% CI 3.5–5.1 days

Figure 1: Post-operative length of stay in patients with hypomagnesaemia and normomagnesaemia.

period. The beta-adrenergic-mediated response to stress causes lipolysis and the precipitation of insoluble magnesium. The resultant fall in intracellular magnesium leads to a transfer of extracellular magnesium into the cell [15]. This theory is supported by a study reporting an inverse relationship between post-operative serum magnesium and inflammatory markers (C reactive protein) in elective cardiac surgery [4]. Hypomagnesaemia is common in our population after elective vascular surgical procedures. The incidence varied by the type of procedure, with the more invasive procedures (open aneurysm repair, lower limb bypass) having a higher incidence of post-operative hypomagnesaemia than less invasive procedures (EVAR and carotid endarterectomy). Post-operative hypomagnesaemia was associated with a doubled risk of cardiovascular and other complications, as well as an increased length of stay in hospital by a mean of 2 days. This finding is similar with other studies, primarily in patients undergoing cardiac surgery showing a relationship between post-operative hypomagnesaemia and major adverse cardiac events [9,13,21,22]. The role of magnesium supplementation in reducing the incidence of dysrhythmias after major cardiac surgery is debated [21-23]. Aglio et al. [24] studied 101 patients undergoing primarily coronary artery revascularization and valve replacement, and reported an incidence of post-operative hypomagnesaemia of 71.0% (compared with 19.2% pre-operatively). The incidence of atrial dysrrhythmias and requirement for prolonged ventilatory support was significantly increased in the hypomagnesaemic patients. Analysis of several studies failed to conclusively show significant efficacy of magnesium therapy in prevention of dysrhythmias after cardiac surgery [24-26] or in patients with acute coronary syndromes [25,26]. Kohno et al. [21] report a reduction in post-operative atrial fibrillation with a three day magnesium infusion (from 35% to 16%), however a systematic review by Alghamdi et al. [22] failed to show a conclusive benefit from magnesium administration. The inconclusive findings of these trials may be partly due to limitations in methodology, but most probably reflect the poor correlation between serum and intracellular magnesium levels [19]. Due to small sample size we were not able to show a significant reduction in adverse events in our population, although there was a small but non-significant trend towards a reduction in cardiovascular complications. In addition, the patients received supplementation only after low levels of magnesium were recorded. Pre-emptive magnesium supplementation prior to a predicted fall in magnesium levels could possibly lead to improved outcomes in these patients. Our study had a number of limitations. First, we do not have data on these patients' comorbidities and underlying coronary artery disease which would further predispose them to adverse events [14,15]. However, we have removed a major confounder by focusing on patients who underwent elective procedures, and thus had pre-operative assessment, risk management and optimization for surgery. In addition, these patients with peripheral vascular disease often have silent coronary and cerebrovascular disease which is not always accounted for. Also, serum magnesium levels are associated with serum calcium and potassium levels, data of which was not obtained during this study. Due to the heterogeneity of the procedures under consideration, patient numbers for subgroup analysis were small. In addition, as this was an observational study, only a small number of patients received supplementation. Nevertheless, we were able to draw meaningful conclusions which will influence future practice in our unit.

Conclusion

Our observational study shows a significant reduction in serum magnesium levels following major elective vascular surgery, with associated doubling of the risk of both cardiovascular and non-cardiovascular complications. In our small sample of patients who received magnesium supplementation, this did not appear to have a significant impact on the incidence of post-operative complications. A further prospective study comparing magnesium levels with those of other electrolytes (notably calcium and potassium), and analysing outcomes in a larger cohort of patients who receive pre-emptive magnesium supplementation (pre- or peri-operatively) will provide greater insight.

References

1. Iseri LT, Allen BJ, Ginkel ML, Brodsky MA. Ionic biology and ionic medicine in cardiac arrhythmias with particular reference to magnesium. Am Heart J. 1992; 123: 1404-1409.
2. Dyckner T. Serum magnesium in acute myocardial infarction. Relation to arrhythmias. Acta Med Scand. 1980; 207: 59-66.
3. Hollifield JW. Magnesium depletion, diuretics, and arrhythmias. Am J Med. 1987; 82: 30-37.
4. Švagždiene M, Širvinskas E, Baranauskiene D, Adukauskiene D. Correlation of magnesium deficiency with C-reactive protein in elective cardiac surgery with cardiopulmonary bypass for ischemic heart disease. Medicina (Kaunas). 2015; 51:100-1066.
5. Whang R, Hampton EM, Whang DD. Magnesium homeostasis and clinical disorders of magnesium deficiency. Ann Pharmacother. 1994; 28: 220-226.
6. Chen M, Sun R, Hu B. [The influence of serum magnesium level on the prognosis of critically ill patients]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015; 27: 213-217.
7. Djagbletey R, Boni F, Phillips B, Adu-Gyamfi Y, Aniteye E, Owoo C, et al. Prevalence and predictive factors of preoperative hypomagnesaemia among adult patients in a large tertiary hospital in Ghana. BMC Anaesthesiol. 2015; 15: 132.
8. Agus ZS. Mechanisms and causes of hypomagnesemia. Curr Opin Nephrol Hypertens. 2016; 25: 301-307.
9. Satur CM. Magnesium and cardiac surgery. Ann R Coll Surg Engl. 1997; 79: 349-354.
10. Polderman KH, Girbes AR. Severe electrolyte disorders following cardiac surgery: a prospective controlled observational study. Crit Care. 2004; 8: R459-66.
11. Famularo G, Gasbarrone L, Minisola G. Hypomagnesemia and proton-pump inhibitors. Expert Opin Drug Saf. 2013; 12: 709-716.
12. Parra L, Fita G, Gomar C, Rovira I, Marin JL. Plasma magnesium in patients submitted to cardiac surgery and its perioperative morbidity. J Cardiovasc Surg (Torino). 2001; 42: 37-42.
13. Sheybani A, Geraci SA. When should serum magnesium be measured prior to non-cardiac surgery? J Miss State Med Assoc. 2008; 49: 295-298.
14. Sprung J, Abdelmalak B, Gottlieb A, Mayhew C, Hammel J, Levy PJ, et al. Analysis of risk factors for myocardial infarction and cardiac mortality after major vascular surgery. Anesthesiology. 2000; 93: 129-140.
15. Mamode N, Scott RN, McLaughlin SC, McLelland A, Pollock JG. Perioperative myocardial infarction in peripheral vascular surgery. BMJ. 1996; 312: 1396-1397.
16. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg. 1984; 199: 223-233.
17. Jolly K, Faulconer R, McEwan R, Becker H, Garnham A. The incidence of

hypomagnesaemia following abdominal aortic aneurysm surgery. Ann R Coll Surg Eng. 2015; 97: 379-381.

18. Sasaki R, Hirota K, Masuda A. Prediction of degree of hypomagnesaemia during general anaesthesia. Anaesthesia. 2000; 55: 1137-1138.

19. Archbold RA, Zaman AG. Magnesium for atrial fibrillation after coronary artery bypass graft surgery: its role in aetiology and prevention. Crit Care Resusc. 2000; 2: 260-268.

20. Zwerling HK. Does exogenous magnesium suppress myocardial irritability and tachyarrhythmias in the nondigitalized patient? Am Heart J. 1987; 113: 1046-1053.

21. Kohno H, Koyanagi T, Kasegawa H, Miyazaki M. Three-day magnesium administration prevents atrial fibrillation after coronary artery bypass grafting. Ann Thorac Surg. 2005; 79: 117-126.

22. Alghamdi AA, Al-Radi OO, Latter DA. Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. J Card Surg. 2005; 20: 293-299.

23. Klinger RY, Thunberg CA, White WD, Fontes M, Waldron NH, Piccini JP, et al. Intraoperative Magnesium Administration Does Not Reduce Postoperative Atrial Fibrillation After Cardiac Surgery. Anesth Analg. 2015; 121: 861-867.

24. Aglio LS, Stanford GG, Maddi R, Boyd JL 3rd, Nussbaum S, Chernow B. Hypomagnesemia is common following cardiac surgery. J Cardiothorac Vasc Anesth. 1991; 5: 201-208.

25. Santoro GM, Antoniucci D, Bolognese L, Valenti R, Buonamici P, Trapani M, et al. A randomized study of intravenous magnesium in acute myocardial infarction treated with direct coronary angioplasty. Am Heart J. 2000; 140: 891-897.

26. Rasmussen HS, McNair P, Norregard P, Backer V, Lindeneg O, Balslev S. Intravenous magnesium in acute myocardial infarction. Lancet. 1986; 1: 234-236.