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Serum Potassium Levels and Mortality in Acute Myocardial Infarction

Goyal A et al. JAMA. 2012; B157-164

The importance of potassium homeostasis in the post-infarction period has become a cornerstone in modern clinical practice. Several studies have shown that potassium levels of less than 3.5 led to a higher risk of arrhythmia induction. This study investigated what the optimal target potassium level should be, given the lower rates of serious arrhythmias following interventions such as beta-blockade and reperfusion therapy.

This large retrospective observational study looked at 38689 patients admitted to American hospitals with ICD-10 coded Acute Myocardial Infarction and appropriate positive biochemical markers. They documented admission serum potassium and then a mean potassium level based on the average of all post-admission potassium levels. Their results show a U-shaped relationship between in-hospital mortality and mean potassium levels, suggesting an increase in all cause mortality with potassium levels of less than 3.5 and higher than 5.0.

In the group potassium 4.5 to 5.0 mortality was 10%(95% CI, 9.1%-10.9%) compared to mortality rates of 4.8% and 5.0% in the groups of 3.5 to 4.0 and 4.0 to 4.5 respectively (95% CI, 4.4%-5.2% and 4.7%-5.3%). This suggests a twofold increase in mortality if the potassium level is above 4.5. This is contrary to current practice which targets levels between 4.5 and 5.5. The strength of this study is that it utilised all cause mortality as its primary end point rather than focusing on fatal arrhythmia induction as in previous studies.

The problem with observational studies is that an observed relationship between two variables does not confirm causality. 'Normal' potassium levels are considered to be 3-5-4.5; patients with levels outside this may be more unwell and failing to maintain homeostasis. This may result in higher mortality rather than the potassium level itself per se. To fully answer the question posed a randomized trial with patients allocated to target potassium levels would be required. The authors themselves admit this is

unlikely, given the high cost of such trials and the regulatory processes involved.

This study was limited to in-hospital mortality in patients following AMI. The mortality rates seen were not limited to arrhythmias. This raises the question whether potassium levels may have a similar predictive value for mortality in acute medical admissions of different aetiology. For example, studies have suggested that patients with cardiac failure may have higher rates of mortality with potassium levels of <4.0.

Low-Molecular-Weight Heparin and Mortality in Acutely Ill Medical Patients

Kakkar A.K et al. N Engl J Med 2011; **365**: 2463 – 2472 December 29, 2011

The routine use of pharmacological agents in prevention of hospital induced venous thromboembolism (VTE) has been one of the notable intervention success stories of acute medicine. Use of subcutaneous heparin is now almost universal in patients considered high risk and it has identified as a key quality performance indicator. Whilst its use in prevention of VTE is widely accepted to reduce morbidity from acute venous thromboembolism, subsequent improvement in all cause mortality has not been definitively demonstrated.

This interesting multi-national study appears to demonstrate no additional mortality benefit in medical patients. Two studies from over thirty years ago showed the reduction of fatal pulmonary embolism and all cause mortality in post surgical patients treated with subcutaneous heparin, this has not been replicated in medical patients. A meta-analysis of five studies assessing the reduction in fatal PE following pharmacological VTE prophylaxis appeared to conclude there was benefit, but other authors have called the findings into question as the diagnosis of fatal PE was not uniform across the studies included.

This was a randomised, double-blinded, placebo controlled trial. They recruited 8323 patients from 193 centres across India, South America and the Far

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East. They were randomized to treatment with 40mg subcutaneous enoxaparin versus placebo injection with 0.9% saline. Both groups received compression stockings. The primary end point was all cause mortality at 30 days. Secondary end points included 14 and 90 day all cause mortality, mortality from PE and bleeding.

They found no difference in all cause mortality at 14, 30 or 90 days. 4.8 % of patients in the placebo group died at 30 days compared with 4.9% in the enoxaparin group. Only one patient in each group died from pulmonary embolism at 30 days. However 28 patients in each group are classified as having died from 'sudden death', the authors do not comment on whether there was more information available post mortem on these patients.

This is a robust and well-designed study demonstrating mortality outcomes which go against expectations. This doesn't take away from the importance of VTE prophylaxis in preventing the health care burden associated with symptomatic VTE. A note of caution must be exercised in applying data from a different patient group to that of the UK. Patients in the Far East have been reported to have a lower incidence of PE. This may have to do with factors such as lower obesity rates and genetic predisposition.

Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

Enden T CaVenT Study Group. *Lancet*. 2012 Jan 7; **379(9810)**: 31-8. Epub 2011 Dec 13.

Current UK practice in the management of extensive DVT is to offer standard anticoagulation. This leaves patients with a significant risk of post thrombotic syndrome (PTS). Whilst not life threatening PTS does constitute a major burden in terms of ongoing morbidity and is reported in over fifty percent of patients with extensive DVT. Common symptoms include pain and swelling of the affected leg resulting in reduced mobility. NICE guidelines on the treatment of confirmed DVT are currently in development. The SIGN guidance suggests that catheter directed thrombolysis should be considered on an individual patient basis when the DVT is massive and limb threatening or there is incipient venous gangrene.

The aim of this Norwegian study was to assess whether catheter directed thrombolysis (CDT) was effective at preventing PTS without inducing unacceptable bleeding risk. Previous studies looking at systemic thrombolysis concluded that although it was effective at reducing thrombosis load, the incidence of bleeding was unacceptably high.

200 patients were randomised into conventional anticoagulation or conventional anticoagulation plus CDT. The study was not blinded as it was felt unethical to put patients through an invasive procedure for

administration of placebo. CDT involves venous puncture of the popliteal vein followed by localised administration of a thrombolytic agent, in this case alteplase, via an indwelling venous catheter. The mean duration of thrombolysis therapy was 2.4 days. They assessed incidence of PTS using a validated score (The Villalta score) at 6 and 24 months.

They report a 14% risk reduction of post thrombotic syndrome in the CDT group. The recorded occurrence was 41.1% compared to 55.6% in the group treated with anticoagulation alone. While this represents a statistically significant reduction, the risk of PTS remains high regardless of intervention. Other groups studying PTS found lower rates post CDT. Possible reasons for this could be that they had a higher incidence of pelvic thrombosis (indicating more extensive DVT) in the CDT group than the anticoagulation group alone (46% vs 36%). Pelvic thrombosis is a strong predictor of subsequent PTS.

An additional important factor was that venous stenting, which is common practice in American percutaneous thrombolysis, was left to individual investigators discretion. Only 15 patients received venous stenting in this trial. Previous studies have shown that 80% of patients with ileo-femoral DVT have an underlying venous stenosis proximally, which has to be treated to restore good venous outflow after thrombolysis. This low incidence of stenting may have reduced the overall impact of CDT.

An incidence of significant post procedure bleeding of 9% was reported, which is compatible with previous studies. No patients had intracranial or fatal haemorrhage. Most of the bleeding complications were related to the puncture site due to multiple attempts to gain venous access, highlighting the need for operator experience with this technique.

A larger multicentre study in America is currently recruiting with the aim to assess catheter directed thrombolysis in nearly 700 patients (ATTRACT); the results are expected in 2015. If this study confirms that CDT is a safe approach to the treatment of massive DVT it is possible the UK will need to develop interventional radiology services to meet this need.

Host and Pathogen Factors for *Clostridium difficile* Infection and Colonization

Loo V.G. et al. *N Engl J Med* 2011; **365**: 1693 – 1703 November 3, 2011

Clostridium difficile has a huge impact on our approach to healthcare associated infections; it is the leading cause of healthcare associated infectious diarrhoea. Pressure from the Department of Health to reduce infection rates has seen a radical shift in the way antibiotics are prescribed. Stringent infection control policies and mandatory reporting of cases has brought this subject to the forefront of healthcare policy.

This study from Canada was carried out in 2006, a time at which there was already heightened awareness in the UK. A total of 4143 patients were included in the

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study; 117 (2.8%) had symptomatic *C.difficile* (CD) infection consistent with previously published infection prevalence. It was a large well designed study attempting to tease out relative impact of host and pathogen factors on risk of CD colonisation and infection in an unselected population.

This study provides information about absolute risk increases for factors implicated in CD infection that had been identified in previous studies. Advancing age (odds ratio OR 1.02 per increase of one year), use of antibiotics (OR 5.25) and proton pump inhibitors (PPIs) (OR 2.64) were all independent risk factors for developing CD infection. Interestingly 26.7% of CD infections occurring within 72 hours of admission had no history of hospital care within the past 12 months suggesting true community acquired infections.

Hospitalisation in the past 2 months, PPIs and H2 blockers, chemotherapy and serum antibodies were associated with a higher prevalence of CD colonisation, defined as a positive stool culture for CD in the absence of diarrhoea. These agents disrupt gut microbiota and may predispose to CD colonisation. Approximately half the patients were colonised on admission to hospital whilst the other half developed colonisation after more than 72 hours in hospital. There is some limited evidence that colonisation with CD regardless of strain offers protection against the development of symptomatic infection.

In terms of pathogen factors; the study confirmed that the NAP1 strain (associated with epidemic outbreaks of CD) was more prevalent in infected patients. Other strains were more prevalent in colonised patients. It is postulated that NAP1 is more virulent due to genetic deletions resulting in increased toxin production.

One of the limits of the study was the relatively low participation rate (57%) and the fact that large numbers of patients could not be included due to incomplete laboratory studies; therefore when the data was analysed the number in each subgroup is relatively small. This study highlights the relative importance of different risk factors for CD infection.

Effect of intravenous β -2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial

Gao Smith F et al BALTI-2 study investigators Lancet. 2012 Jan 21; **379(9812)**: 229-35.

Acute respiratory distress syndrome (ARDS) is a condition with a high mortality rate (40-60%) for which effective interventions are constantly being sought. This study is the follow up from the earlier promising BALTI study which showed that intravenous β -2 agonist showed improvement in ARDS severity markers such as plateau pressure and extravascular lung water in ventilated patients.

The initial BALTI trial was a single centre study of 40 patients and hence was not powered to look at mortality data. Following on from this a larger multi-centre study aiming to recruit over 300 patients was initiated. The study was stopped early as interim analysis from 273 patients showed convincing evidence that the 28 day mortality in the salbutamol arm exceeded that in the placebo and that the two mortality curves appeared to be continuing to diverge. Intravenous salbutamol resulted in a 10.9% (95% CI 1.0-20.4) absolute increase in 28-day mortality.

This was an unexpected finding. On further analysis the risk of tachycardia, new arrhythmia and significant lactic acidosis was markedly higher in the treatment group compared with placebo. The dose of salbutamol they used was 15 μ g/kg after an earlier dose-ranging study showed this to be the maximum dose in critically unwell patients without a significant increase in arrhythmias. The authors accept that this is at the higher end of the manufacturer's recommended dosing regimen; hence the beneficial effects might have been outweighed by the increase in adverse incidents seen. The exact mechanism by which salbutamol causes harm is not clear, stimulation of adrenergic drive causing cardiovascular effects such as tachyarrhythmias may well be important.

A cautionary tale highlighting the need to use data from properly conducted randomized control trials before leaping on a treatment that seems promising from small studies which are often not powered to detect significant adverse effects.