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MEDICAL MYTHBUSTERS

A guide to dodging time-honoured medical fallacies

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INTRODUCTION

In recent years, medicine has made huge strides towards becoming a fully evidence-based discipline and seems to still be accelerating towards this goal through large-scale trials and international collaboration by researchers. We smirk at the reasoning used by doctors in previous centuries: that an abnormal uterus was the cause of hysteria, that phlebotomy could cure pneumonia and that trephination could treat epilepsy! Yet somehow in the never-ending search for proof, some areas of medicine are still dominated by facts passed down by senior doctors to junior doctors without any question of their validity; occasionally even when faced with good evidence to the contrary! This short booklet will explore some of the commoner myths pervading the field of anaesthesia and hopefully guide us to improved care for our patients.

RESPITE FOR THE REDHEADS

When I began my time as a junior medical officer in Anaesthetics, I was informed by my senior colleagues that when faced with a red-haired patient, I would need to provide an increased dose of hypnotic agent to ensure that they remained asleep. Like much else I was told, I simply accepted this as helpful advice and laid it down as fact. Why not? There are plenty of examples of pharmacogenetic differences with anaesthetic agents. Red hair is a genetically determined trait. There may well be an association.

The gene for red hair was identified in 1997 and is determined by 2 pairs of recessive genes on chromosome 16 which results in the production of a different melanocortin-1 receptor (MC1R). A second gene, HCL2, on chromosome 4 may also be related. The alteration in structure of the MC1R means alpha-melanocyte stimulating hormone cannot bind the receptor and this results in a switch in melanin synthesis to favour the production of pheomelanin (which causes the production of red hair) rather than eumelanin (which leads to the synthesis of brown or black hair).

The melanocortin receptors are not only involved in cell pigment production, however. They have roles in steroid synthesis, inflammation, immunity and hypothalamic function. Thus, with an altered inflammatory response and hypothalamic function, there exists a definite physiological reason as to why red-haired patients may have altered responses to anaesthesia.

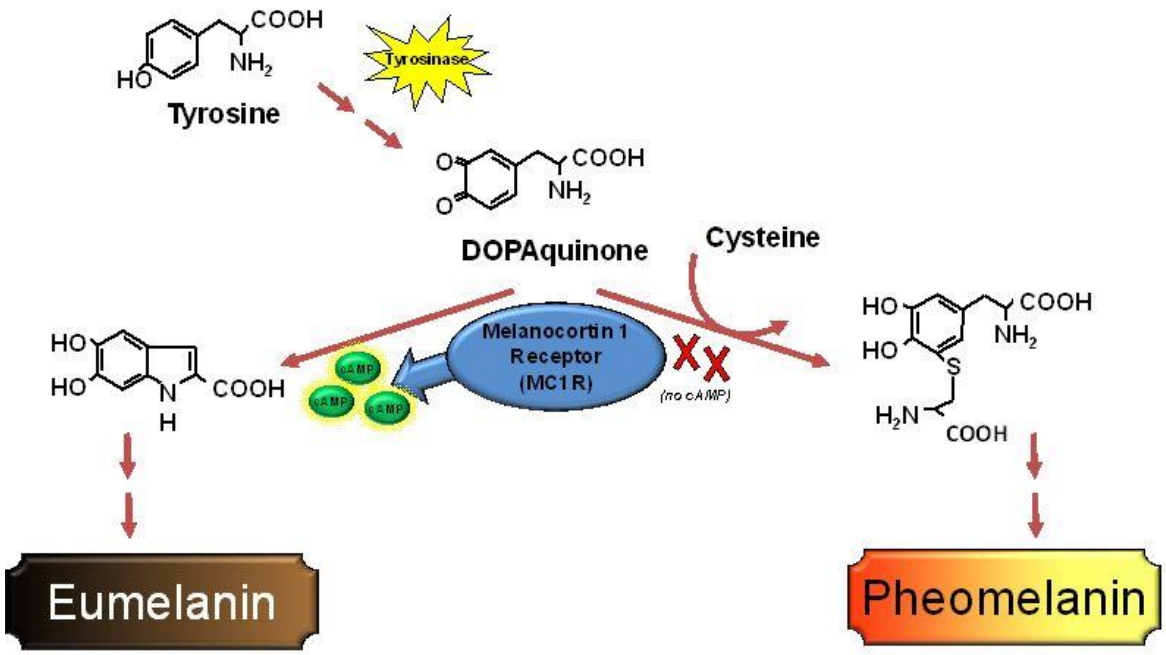


Figure 1 - Variations in MC1R

There is also some evidence to support this. Firstly, Xing et al compared the MAC of 4 different anaesthetic agents in 22 mice with a mutation in the MC1R gene to 18 control mice (1). Response to tail clamping was used to assess MAC requirements. The experiment showed that the mutant mice had a significantly increased anaesthetic requirement compared to the controls, although the magnitude of change was small (5,5% increase; p=0.023).

Liem et al then set about demonstrating this in humans. 20 female volunteers were studied (10 with red hair, 10 with dark hair) by inducing anaesthesia with sevofluorane, maintaining it with desfluorane and then applying a noxious electrical stimulation. The end-tidal desfluorane for each volunteer was then adjusted to establish the threshold for “non-movement” to the stimulus. The red-haired women had an increased requirement for desfluorane compared to the dark-haired ones (6.2 vol% vs 5.2 vol% p=0.0004). (2)

As a result of these trials, the folklore was confirmed and cemented into our knowledge base. However, in 2012, Myles’s Australian research team undertook a much larger trial to retest the hypothesis. 468 patients aged 18-70 were enrolled into a prospective cohort study between 2003 and 2007. General anaesthesia was induced with propofol (or thiopentone in 2 cases) and maintained with isofluorane, sevofluorane or desfluorane, with or without nitrous oxide. End-tidal volatile concentration was adjusted for age and monitored, and then repeated BIS readings were documented every 5-10 minutes. The average BIS score was equivalent in the 2 group’s intra-op, at skin closure and at eye opening. Also, the MAC requirement (age-adjusted) was equivalent (1.28 vs 1.31 vol% p=0.46). The speed of recovery after anaesthesia was also equal in the groups. There were no differences in post-operative morphine administration, pain scores or overall quality of recovery measured by a 40-item score sheet. (3) There were several limitations to the trial. Firstly, the primary outcome was speed of recovery from anaesthesia, not MAC requirement; BIS levels represented only a secondary outcome. Also, the MC1R gene was not tested for in the red-haired patients, but rather assumed. This confounder is minimised by a separate study showing a 96% correlation between those with self-reported red hair and the MC1R

gene.(4)Myles et al also did not blind any of the anaesthetists involved and included no description of investigator blinding. Since this trial, BIS monitors have had their accuracy called into question, which in turn affects the accuracy of this secondary outcome. However, the trial contains a much larger number of patients than the previous one and involves a superior study design with real-world clinical scenarios rather than laboratory testing. Even if one was to discount the BIS reading, there was still no evidence of an increased MAC requirement or a quicker time to recovery.

It is difficult to form a resolute conclusion based on one cohort study. However this trial currently constitutes the best quality evidence we have in this field of research – far superior than an n=20 human trial and a rat study. While this remains an area which would benefit from a large, well conducted trial, the absence of a significant difference in any of the end points in Myles's trial certainly provides impetus for us to reject the tenuous myth that red haired patients have an increased requirement for anaesthesia.

NITROUS OXIDE BACK TO THE FUTURE

Not too long ago, nitrous oxide was a forbidden substance in anaesthesia. It appeared to have been banished to the realms of medical history by a multitude of studies suggesting everything from a potent emetogenic effect to immune suppression, pulmonary hypertension, peri-op myocardial infarction, an increased peri-op mortality and even ozone depletion. However on the back of more recent studies, most notably the ENIGMA II trial, the medical pendulum appears to be swinging swiftly in the opposite direction once again. It appears, therefore, to be a suitable time to explore another medical "fact": Is nitrous oxide contra-indicated in laparoscopic surgery?

There has been a huge increase in day-case surgery in the past few years, and an equally massive rise in laparoscopic work. Taken at face value, nitrous oxide appears to have numerous benefits in this setting. It is known to be associated with faster emergence, facilitating rapid turnaround and more rapid discharge from post-anaesthesia care units.(5) Also, contrary to what was previously thought, it appears to be roughly half as emetogenic as the other volatile agents. It has potent analgesic properties, which may facilitate surgery taking place without an opioid. This may reduce time to establish normal bowel function post-operatively and may speed up time to hospital discharge. However its use in laparoscopic surgery is still largely hamstrung by the perceived risk of bowel distension and the fears of worsening operating conditions for our surgical colleagues.

It is taught that nitrous oxide is contra-indicated in any surgery involving a sealed-off, air-filled cavity such as in middle ear surgery, the injection of air bubbles in ophthalmic surgery and in patients with un-drained pneumothoraces (not that any anaesthesia is particularly beneficial to this last category!). The physiological basis for this concern comes from nitrous oxide's increased solubility compared to nitrogen. Nitrogen has a blood: gas partition coefficient of 0.015, while that of nitrous oxide is roughly 34 times higher. This results in more nitrous oxide molecules leaving the solution and filling gas-filled spaces than nitrogen molecules leaving the spaces and going into solution.

Numerous studies in various settings have confirmed that the phenomenon is not simply confined to the realms of physiology either. In an article published as early as 1965, Eger and Saidman demonstrated an increase in stomach, colonic and small intestinal volumes in dogs anaesthetised with halothane and nitrous oxide compared with the control group dogs where halothane and oxygen was used.(6)

Akca et al (7)conducted a study in open colonic surgical patients where 344 patients were randomised into a nitrous oxide group or a nitrogen/air group. The surgeons (who were blinded to the patients' group allocations) were then asked to comment on whether the bowel distension should be classed as "none, mild, moderate or severe". There were no significant differences between the 2 groups in terms of each individual class of distension assessment. A post-hoc combination of moderate and severe classes, however, showed 23% of nitrous oxide patients to be moderate or severe compared to 9% of nitrogen/air patients and this observation did reach statistical significance ($p<0.001$).

Criterion	Nitrous Oxide (n=175)	Air (n=169)	p
PONV	75 (43%)	71 (42%	0.874
Bowel Distension			
None	92 (53%)	120 (71%)	
Mild	42 (24%)	34 (20%)	
Moderate	30 (17%)	12 (7%)	} <0.001
Severe	11 (6%)	3 (2%)	

Table 1 - Akca et al showing increased bowel distension with use of nitrous oxide

The discussion in this study then states “avoiding nitrous oxide administration during prolonged bowel operations will minimize bowel distension, and thus, facilitate surgery”. However analysis of the results of the study shows this was not in fact what was proven. The trial showed that there was a statistically significant increase in the combined outcome of moderate and severe bowel distension with nitrous oxide use compared to no nitrous oxide. The question of whether or not the surgery was facilitated by avoidance of nitrous oxide was not investigated. Furthermore, at no point did the investigators have to break protocol to improve the surgical conditions and in fact the time taken to complete the procedure was equal in both groups (3hrs for nitrous vs 3.4hrs for air p=0.017). Strengths of the study were its large size relative to the other research done in this field, and the fact that investigators went to appropriate lengths to ensure randomization as well as blinding of surgeons. A weakness was the subjectivity of the assessment as well as the fact that the clinically important variable (ease of surgery) was not tested.

Krogh et al (8) performed a similar study in 150 elective colonic surgery patients. Patients were randomly allocated into nitrous oxide and air groups and again, blinded surgeons were asked to rate the degree of bowel distension at 3 points during the operation. The rest of the anaesthetic was standardised by the trial protocol. The results showed that at no point in the operation was there a statistically significant difference between the groups in terms of bowel distension. Also the secondary outcomes of post-operative nausea, post-operative pain, recovery of bowel function and surgical complications (anastamotic leakage, ileus) were equivalent in the two groups. The trial has some limitations. There was no description of randomisation technique (the write-up only mentions that the patients were randomised) and there was no blinding of the anaesthetist or the investigator. Also, on a more clinical note, the patients all received bowel preparation pre-operatively and had gastric contents suctioned via nasogastric tube before commencement of surgery: neither of these is in line with current best practice and thus they may act as confounders if we are to apply this trial to our daily practice – less gas present in the intestinal lumen at the start of the case would mean less nitrogen to replace and thus less distension when nitrous oxide was commenced.

Taylor et al (9) conducted a double-blind randomised control trial investigating the use of nitrous oxide in laparoscopic cholecystectomy patients. 50 patients were randomised to one of 2 groups: 70% Nitrous oxide/oxygen and oxygen/air. At every 15 minutes intra-operatively, the surgeon was asked to estimate the degree of bowel distension as well as the difficulty of the operation on a scale from 5 (very good conditions) to 1 (extremely poor conditions). The results showed no difference in surgical assessment of bowel distension between the two groups. Also, there was no difference in operating conditions, and overall, surgeons were only able to correctly guess the patient’s assigned group in 44% of cases. There was no difference between the groups in terms of which patients were converted to open procedures and there was no difference in number of operations where the surgeon requested that nitrous oxide be switched off because of difficulties in operative field

visualization (1 in each group). Oddly, in this trial, although the numbers appear visually similar in each group and although the text makes note that there were no differences, no confidence intervals or *p* values are provided in the article or supporting figures. Also, a limiting factor here is the small sample size. The double blind nature of the trial as well as the good randomisation procedure adds extra weight to the findings, however.

A second, similar study in laparoscopic cholecystectomy patients was performed by Abballe et al. (10) Here, 44 patients were randomly assigned to one of the groups of nitrous oxide vs no nitrous oxide. Again, the primary outcomes were bowel distension and technical difficulty, and again, no difference between the groups was found.

Aline Boulanger and Jean-Francois Hardy (11) actually measured the circumferences of the terminal ileum and transverse colon in addition to asking for a subjective assessment by the surgeons as to how difficult it was to close the abdomen. They investigated 20 patients randomised to either air or 60% nitrous oxide undergoing elective open abdominal surgeries. There was no difference in subjective assessment, however the investigators showed a 45% increase in circumference on the terminal ileum. This increase from 4.5 – 5.8cm was statistically significant ($p<0.05$) without being clinically significant (no difference in ease of operation).

Thus the overall trend in the evidence strongly refutes the claim that nitrous oxide cannot be used in laparoscopic surgery. While the gas may cause bowel distension, especially in longer procedures, the distension is not clinically relevant to either the patient (no increased need to convert to an open procedure) or the surgeon (no increase in difficulty performing operation) and thus it seems the myth, not the gas should be confined to medical history: nitrous oxide is not contra-indicated in laparoscopic surgery.

COUNTING THE COST OF ADRENALINE IN DIGITAL NERVE BLOCKS

I don't think there is an intern who has passed through their anaesthetic rotation without being told at least 8 times that they should never use adrenaline in a local anaesthetic solution when performing a digital nerve block. It is something that it truly entrenched in all medical teaching – "it's a safely thing. It's pass/fail". Have we actually got any evidence for this however?

Certainly when dealing with other nerve blocks or local wound infiltration, there is a benefit to adding adrenaline to lignocaine (in particular). It results in prolonged analgesia of up to 8 hours (compared to 1 hour with no adrenaline) and also decreases the risk (albeit a very small one) of intravascular bupivucaine injection if this agent is chosen to prolong the duration of action instead. Several authors comment that owing to the vasoconstrictive effect, a limb tourniquet is required less often, therefore minimising the complications associated with this.

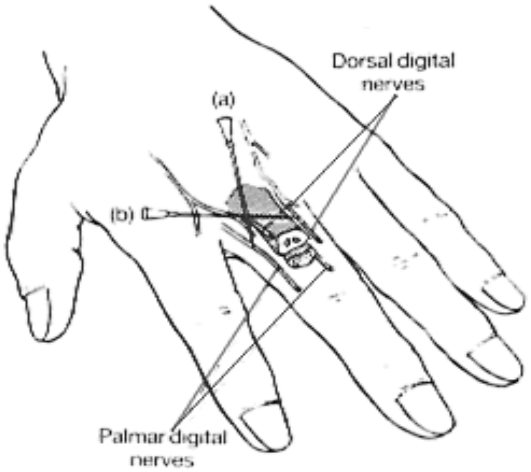


Figure 2 - Digital Nerve Block

It is difficult to establish where the original description of the problem of digital ischaemia was published. 2 single case reports from the 1940's describe ischaemia and necrosis of digits that occurred after the administration of local anaesthetic and adrenaline. Lignocaine was not used in either case, the volume of injectate and concentration of adrenaline was not recorded, and there were several other possible causes for the ischaemia that were not considered by the authors. Nevertheless, digital necrosis after "ring" block represents a dire consequence of a very minor procedure and thus doctors heeded the warning sounded by the case reports and began completely avoiding adrenaline in any distal nerve block: the adage "Fingers, nose, penis, and toes" used to remind medical students of the dangerous areas! The textbook "Surgery of the Hand" by Bunnell (first published in 1956) is credited with popularizing the notion by stating "adrenaline should never be injected into a digit, because from this gangrene has often resulted". (12)

So prevalent was the belief, that when Latimer and Kay (13) decided to experiment with using adrenaline-containing local anaesthetic solutions in digital nerve blocks in 1991, they felt required to use themselves as test subjects. With some caution, Kay began by selecting his third toe "for understandable reasons" and injecting bupivucaine with 1:200 000 adrenaline. For those still wondering, he did not sacrifice any digits in the pursuit of knowledge!

It still took until 1998 for a trial exploring the use of adrenaline-containing local anaesthetics to be published. Sylaidis and Logan (14) published an article in the Journal of Hand Surgery of Britain & European Volume. In this prospective trial, 100 patients had digital nerve blocks performed using 2% lignocaine and 1:80 000 adrenaline (2ml was injected on each side of the finger). Brachial artery systolic blood pressures were measured along with digital systolic pressures and finger temperatures and 10 of the patients had blood velocity measured with a Duplex Doppler. The pre-block average brachial artery systolic pressure was 132mmHg while the pre-block digital systolic pressure was 123mmHg, resulting in a mean brachial-digital index of 0.93. After performance of the block, brachial pressures dropped to 126mmHg, digital pressures to 94mmHg and the index to 0.75. There was unfortunately no control group included in the study. Finger temperature showed a non-significant increase in temperature. Doppler imaging showed a decrease in blood flow in the first 5-10minutes but then an increase back to baseline thereafter. There were no colour changes noted. None of the patients had features of ischaemia. The trial is limited by its observational nature and the absence of a control group, randomization or blinding. However, it provided enough evidence to embark on better designed studies.

Denkler (15) conducted a comprehensive literature review of all documented cases of digital ischaemia after nerve blockade. He looked through Index Medicus from 1880 to 1966 and performed a computer scan of the National Library of Medicine database from 1966 to 2000 and then analysed all reports of digital ischaemia. A total of 48 cases of ischaemia had been reported worldwide and in only 21 of these was adrenaline used as an additive. Most of the case reports were from over 70 years ago and involved older local anaesthetic solutions (cocaine, eukain) and in only 4 of the 21 reports was the concentration of adrenaline reported. Denkler also commented on other factors which were possibly causative (excessive volume of local anaesthetic, poor surgical technique, infection, inappropriate use of tourniquet).There were no cases of gangrene reported with the commercially available, pre-mixed lignocaine/adrenaline solution. Thus, it was unsurprising that the author commented that the review “failed to provide consistent evidence that our current preparations of local anesthesia with epinephrine cause digital necrosis” Krunic et al embarked on a similar literature review in 2004 and failed to find any further cases of ischaemia. The authors of this review went on to provide evidence that any prolonged ischaemia can be reversed by the local administration of the alpha blocker phentolamine, thus further improving the safety margin of adrenaline. (16)

Chowdhry et al performed a retrospective observational trial of 1111 patients who underwent digital nerve blocks.(17) 500 of these were done without adrenaline and 611 were done with 1% lignocaine and adrenaline 1:100 000. The blocks were performed using an average volume of 4.33ml and a maximum volume of 10ml. None of the patients in either group exhibited features of ischaemia either immediately or at a follow-up visit (88.75% follow-up). The trial was both retrospective and observational and this limits its impact on changing clinical practice. Also, patients with pre-existing injuries which compromised the digital vasculature and patients with peripheral vascular disease were excluded from the trial. Nonetheless, the trial served to show again that the use of a dilute adrenaline solution in combination with a modern local anaesthetic does not result in any ischaemia.

In 2015, Llicki performed a literature review of available evidence concerning the use of adrenaline in digital nerve blocks. (18) The aim of the review was to determine if digital nerve blocks with adrenaline are safe in patients with and without peripheral vascular disease (or poor peripheral circulation). A total of 39 articles were analysed after a search of Pubmed, the Cochrane Library and World of Science. Overall, 2797 digital nerve blocks with local anaesthetic and adrenaline were performed, yet there were no cases of digital gangrene

which could be directly attributed to the use of adrenaline. Only 2 of the studies examined in the review investigated patients with peripheral vascular disease, but there were no reported ischaemic complications in either study. The review's strengths were the extensive nature of the literature search and the fact that several different types of study were included, making it very unlikely that any cases of ischaemia were missed. The weaknesses were the relative paucity of well-designed randomized control trials directly aiming to confirm safety, and the reliance therefore on observational and often unblinded studies. Also, there were only 2 studies investigating peripheral vascular disease patients, resulting in an inadequate number of patients being studied. Interestingly, the review also included 2 studies which investigated patients who had had an accidental digital injection with adrenaline 1:1000 (kept as an "Epi Pen" by those at risk for anaphylactic reactions). Only a small number of these patients experienced ischaemic symptoms despite the highly concentrated adrenaline mixture, and only 23% (in one study) and 46% (in the other) required the adrenaline's effect to be reversed (with phentolamine). There were no cases of necrosis in either study. This aspect of the review highlights the relative safely margin clinicians have when injecting a solution of adrenaline which is 10-20 times as dilute. The author concludes that adrenaline is safe to use in digital nerve blocks in patients without vascular disease but reports that there is insufficient evidence to confirm safety in vasculopaths.

In 2015, the Cochrane Group commissioned a review of available randomized control trials and looked at three primary outcomes: adverse reactions such as ischaemia, cost analysis and duration of anaesthesia. The secondary outcomes were duration of pain relief and bleeding during surgery. (19) Despite an extensive literature search, however, only 6 studies were eligible for review, with a further 2 being removed because they involved volunteers and not patients. Thus the total number of patients investigated in a randomized manner totaled a meager 167. Only 1 of the 4 studies reported concealment of allocation and only 1 reported blinding the participants and personnel. Overall, the duration of anaesthesia was significantly longer with adrenaline + lignocaine than with lignocaine alone (Mean difference in duration 3.20 hours, 95% CI 2.48 to 3.92). There were no patients with digital ischaemia in either group and a cost analysis was not done in any study. 2 of the studies measured intra-operative bleeding and when grouped together (103 patients in total), the trials showed a risk ratio of 0.35 (95% CI 0.19 to 0.65).Unsurprisingly, however, the authors of the review commented that owing to the trials being of poor methodological quality and low participant number, the review was "not robust enough for review authors [to] recommend or refute the use of adrenaline with lidocaine during surgeries on toes and fingers."

We can see that this is a fertile area for good quality randomized control trials. There is enough evidence that adrenaline use is not harmful that ethics boards should not need to consider the Helsinki Declaration too carefully in reviewing any proposed research. In fact, in the author's opinion, we have already moved past the point of equipoise and lifted the 70 year old ban on adrenaline in peripheral nerve blocks. Admittedly the evidence for the use of adrenaline is largely in the form of non-randomised, non-blinded trials, but the evidence against it is overwhelmingly inferior.

POTASSIUM PROBLEMS

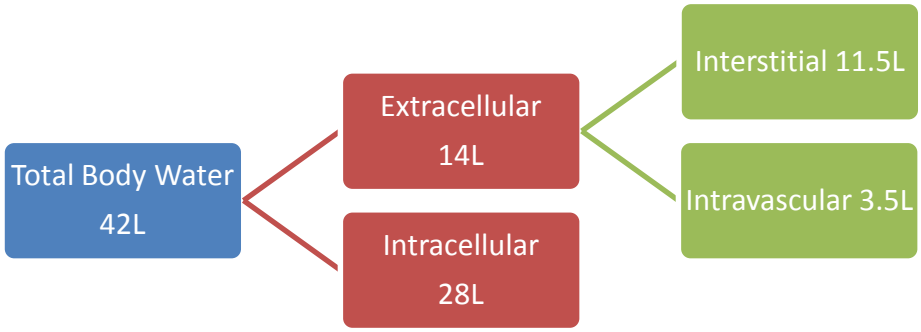
Anaesthetists and Critical care physicians are often faced with patients with hyperkalaemia and the problem is especially common in those with acute kidney injury. In any patient starting out with a high serum potassium, and even in those at risk of developing a high serum potassium, it is often touted that we should avoid all potassium-containing fluids. While this may be sensible in the ICU with a patient on maintenance fluids such as Electrolyte number 2 (E2) or Maintelyte (which each contain 25mmol of potassium per litre), Does the 4mmol of potassium in Ringer's Lactate (or 5.4mmol in modified ringer's lactate) make any difference to serum potassium levels? It would logically follow that adding potassium to a patient who is failing to excrete it would cause a worsening of hyperkalaemia.

Well, this may in fact not be as clear if we were to take a closer look at the physiology behind inter-compartmental fluid and electrolyte shifts. Potassium is the predominant intracellular cation, with typical intracellular levels of 140mmol/L. In the extracellular compartments it is present in much lower (4mmol/L) concentrations.

Electrolyte (mmol/l)	Intracellular	Extracellular Interstitial	Extracellular Intravascular
Sodium	10	142	145
Potassium	140	4	4
Calcium	<1	3	3
Magnesium	50	2	2
Chloride	4	110	105
Bicarbonate	10	28	24
Phosphorus	75	2	2
Protein (g/dL)	16	2	7

(20)

If one takes the different compartment volumes into account, the total body potassium quantity of a 70kg male approximates 3976mmol.



70kg x 0.6L/kg = 42L

28L x 140mmol/L = 3920mmol
14L x 4mmol/L = 56mmol

3920 + 56 = 3976mmol

Infusing a litre of Ringer's Lactate will increase total body potassium by 4mmol (constituting a rise in total body potassium of just over 0.1%) but will add 1 litre to total body water (an increase of 2.3%). The net effect on potassium after inter-compartmental equilibration is thus a dilutional one. As can be seen however, these are very simplistic calculations, based on a purely physiological model which does not take into account variability in renal concentrating and excreting ability in patients with kidney pathology. As such, we cannot simply apply this model to real-world patient management without first confirming its accuracy.

Why can't we simply use 0.9% Saline and forget about ringer's lactate altogether? "Normal" saline is a widely available resuscitation fluid which has been used for decades in a variety of clinical settings. Unfortunately its use has been associated with several complications and the recent past has seen an explosion of literature condemning its routine use. It is becoming increasingly well known that it is neither normal nor physiological as its nickname may imply. It is associated with nausea and abdominal discomfort and distension. It results in decreased renal perfusion and a decreased time to micturition,(21) a phenomenon likely caused by increased renovascular resistance owing to chloride accumulation in the macula densa cells and an alteration in the tubuloglomerular feedback mechanism.(22) Furthermore, a meta-analysis by Krajewski et al found a statistically significant increase in the incidence of acute kidney injury in peri-operative and critical care patients who were resuscitated with a high-chloride solution (concentration >111mmol/L) compared with a low-chloride one (RR 1.64, 95% CI 1.27-2.1, p <0.001). (23) Finally, the disproportionally high chloride composition (154mmol/l) in 0.9% saline alters the strong ion difference, causing a metabolic acidosis if given in sufficient quantities. This, in turn, causes a shift of potassium ions towards the extracellular compartments, increasing serum levels.

Despite all of these concerns, protocols from several units around the world (24-27), including Inkosi Albert Luthuli Central Hospital, advise that normal saline is still the first-line fluid for use during renal transplant surgery. It there any literature backing up the anaesthetic fear of ringer's lactate causing hyperkalaemia?

Fortunately there have been numerous trials comparing Modified Ringer's Lactate with 0.9% Saline during kidney transplants. O'Malley and colleagues published a double blind randomised control trial in 2005 to compare these two fluids in renal transplant patients.(28) The primary objective was to assess differences in serum creatinine on day 3 post-op, and the secondary ones included the change in serum potassium and acid-base status. The proposed sample size was 100 patients, but after the planned interim safety analysis (done after enrolment of 51 patients), there were significant differences between the groups in terms of the "safety data" concerning serum potassium and acid-base balance and the trial was stopped early. As a result, data from only 25 patients in the ringer's lactate (RL) and 26 patients in the normal saline (N/S) groups were analysed. There were no significant differences between the groups with regard to post-operative creatinine levels or graft loss. 5 of the normal saline patients experienced a peak serum concentration of potassium over 6mmol/L and none of the ringer's lactate patients had this complication (p = 0.05). All 5 of these patients were treated for hyperkalaemia. Peak serum potassium of the groups as a whole, however, was not different (5.1 ± 0.6 mmol/L in N/S vs 5.1 ± 1.1 mmol/L in RL). 8 of the N/S patients were treated for metabolic acidosis using sodium bicarbonate (mean pH 7.2 ± 0.09), while none of the RL patients required treatment. Mean pH for the rest of the N/S patients was 7.28 ± 0.06 while mean pH for the RL group was 7.33 ± 0.07. The study was pragmatic in that all other aspects of patient management (including fluid volume) remained at the discretion of the treating physician. The patients were well randomised and blinding was ensured throughout the trial. However, the trial's power was greatly reduced

by its early termination. The results were also displayed in a confusing manner and it appears that the significant differences between the groups were only found on post-hoc analysis.

Khajavi et al (29) conducted a similar double blind randomised control trial on renal transplant patients. Here, 52 patients were enrolled in the study and divided into the same RL and N/S groups. Unlike O'Malley's trial, all phases of the anaesthetic and surgery were strictly controlled by the trial protocol; however the findings were very similar. The primary outcomes in this trial related to the safety of RL in renal transplant patients. These were the serum potassium level and pH at the completion of surgery. The N/S patients experienced a significant decrease in pH compared with their RL counterparts (7.29 ± 0.08 vs 7.34 ± 0.05; $p = 0.007$) and had a significant increase in serum potassium (4.88 ± 0.7 vs 4.03 ± 0.8 meq/L; $p < 0.001$). There was no significant difference in creatinine level on day 3 post-op (used as a surrogate for early graft function). The strengths of this trial were its double-blind nature and the good randomization of participants, but it was limited by the small sample size. Also, while the differences in potassium and pH were statistically significant, they were not clinically significant except for in 2 cases where the treating physician decided to administer sodium bicarbonate to correct the serum acidosis.

Modi et al (30) conducted a double-blind randomised control trial of 74 patients undergoing renal transplant. Patients were assigned to receive either RL or N/S in quantities titrated to maintain an intra-operative CVP of 12-15mmHg. The rest of the anaesthetic was standardised and arterial blood gas samples were sent for analysis at hourly intervals. There was a significant fall in base excess in the N/S group (-2.73 to -4.97) while the base excess in the RL group remained unchanged. Compared to the RL patients, the N/S participants had a significant decrease in plasma bicarbonate levels (19.47 ± 3.02 vs 21.62 ± 3.56 $p < 0.05$) as well as a significant rise in plasma potassium levels (4.31 ± 0.59mmol/L vs 3.99 ± 0.71mmol/L $p<0.05$). This trial was again well conducted, well randomised (computer randomisation), and double-blinded, with study fluids arriving from the pharmacy modified by opaque paper covering their labels. The similarity of the results with the previous studies also adds further weight to the concept that ringer's lactate is not only safe to administer in renal transplant patients, but is superior to N/S.

Potura et al (31) conducted a larger study in 150 patients scheduled for renal transplantation and compared N/S with Elomel Isoton ©, a fluid very similar in make-up to ringer's lactate (containing Na 140 mmol/L, Cl 108 mmol/L, K 5 mmol/L, Ca 2,5 mmol/L, Mg 1,5 mmol/L, Acetate 45 mmol/L). Patients were randomised using a computer and sealed envelopes but there was no description of blinding included in the write-up. Patients received 4ml/kg/hr of fluid intra-op and 2ml/kg/hr in the recovery area. Venous blood gases were done every 30 minutes intra-op in order to establish the primary outcome: whether the use of a balanced salt solution increases the risk of peri-operative hyperkalaemia (defined as a serum potassium >5.9mmol/L) compared to a potassium free fluid. In contrast to the previous trials, there was no statistically significant difference between the groups in terms of hyperkalaemia (13 N/S patients experiencing hyperkalaemia vs 15 Isoton © patients ($p = 0.68$)). There was no significant difference in potassium fluctuation intra-op. A possible reason for the difference in outcome between the trials is the hugely reduced volume of fluid administered in this trial (1500ml and 2000ml in the groups here vs 6100ml and 5600ml in the 2 groups in O'Malley's trial and 5100ml and 5250ml in Modi's trial). Potura's trial was well conducted and is currently the biggest trial in this research area, but without a description of blinding technique, one can only assume it was unblinded, which detracts somewhat from the Jadad score and thus the trial's impact.

So is there enough evidence to suggest changing our fluid choice to ringer's lactate? This question remains unanswered for the time being – in the trials above, the hard end-points of acute kidney injury or graft failure remain unchanged by choice of fluid. However the intra-operative administration of ringer's lactate certainly does not cause an increase in serum potassium, thus this myth has been firmly debunked. Also, its use results in less metabolic acidosis and less abdominal distension and discomfort as well as less nausea and so at the very least, renal transplant protocols should not recommend the routine use of un-physiological saline.

Can these conclusions be carried over to other clinical scenarios with a similar concern about iatrogenic hyperkalaemia? The current advice given to Kwa-Zulu Natal paramedics extracting and transporting massive soft tissue injury patients is that they should use normal saline and not ringer's lactate in order to prevent hyperkalaemia, as these patients are susceptible to rhabdomyolysis and crush syndrome. Can we extrapolate the results obtained from the trials in renal transplant patients? Fortunately, we actually don't have to. Cho et al (32) performed a prospective study on patients with biochemical evidence of rhabdomyolysis and randomised them to receive either Ringer's Lactate or 0.9% saline at 400ml/hr for 12 hours. Patients were blinded to fluid choice but investigators weren't. After the study period, serum pH was significantly higher in the RL group than the N/S one (7.44 vs 7.36 $p< 0.001$) but there was no statistically significant difference in potassium between the groups. The trial was limited by a small number of participants (28 in total), resulting in some trends not reaching statistical significance. Blinding was also suboptimal. Furthermore, it can be argued that the trial is not clinically relevant, as fluid loading alone does not represent the current trend in management of crush syndrome patients; early dialysis is now widely recommended in severe cases. However as mentioned, pre-hospital staff still need to decide on the first-line choice of fluid and also there are many rural hospitals in South Africa without access to dialysis for these commonly-encountered patients. Additionally, this trial again debunked the concern about hyperkalaemia resulting from the use of ringer's lactate.

As has now been shown in two different settings, giving ringer's lactate to patients at risk for acute kidney injury and with established kidney disease does not result in hyperkalaemia. In fact, in the majority of trials, ringers lactate performs better than normal saline with regards both serum potassium levels and serum pH. In the meta-analysis by Krajewski, even the significant outcome of acute kidney injury was higher in the normal saline group, albeit without any significant difference in patient mortality. Therefore the ban on ringer's lactate in patients at risk for hyperkalaemia has surely been lifted – perhaps it has even now been moved to encircle the previously "safe" 0.9% saline.

CONCLUSION

Countless medical students have begun their undergraduate training with advice from their Dean that “Half of what we teach you now will be found to be incorrect by the time you finish your medical training; the problem is we don’t know which half that is yet!” As our understanding of physiology and pharmacology advances and as evidence-based medicine begins to govern more and more decisions, many seemingly unmovable medical truths are inevitably shaken and brought crumbling down.

It is admittedly difficult to push aside facts that have become entrenched in our medical knowledgebase - it may even make one angry or confused - but it is entirely necessary in order to continue moving forward in scientific endeavour. In order to ensure the best possible care for our patients, we need to analyse all medical facts and carefully consider every decision we make. So I challenge you to continue to think about every aspect of your medical knowledge, with all the aptitude of a truly first-rate mind.

*“The third-rate mind is only happy when it is thinking with the majority. The second-rate mind is only happy when it is thinking with the minority. The first-rate mind is only happy when it is thinking." — **A.A. Milne***

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