Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study: Improving patient outcome by optimising perioperative fluid therapy

1. Summary of the impact

Original research carried out by The University of Nottingham has shown that both knowledge and practice related to perioperative fluid prescribing was poor, resulting in significant and avoidable postoperative morbidity. We have shown that maintaining patients in as near a state of zero fluid balance as possible reduces hospital stay by 3.4 days and complication rate by 41%. Our work guided the formulation of the British Consensus Guidelines and NICE Guidelines on intravenous fluid therapy for adult surgical patients. It has also reduced the frequency of postoperative fluid overload, and led to improved patient outcome and potential financial benefits of £122m per year for NHS England.

2. Underpinning research

Although fluid and electrolytes are the most frequently prescribed drug in hospitals, prescribing practices were often suboptimal (and still are in a few cases), resulting in avoidable perioperative morbidity and mortality. The work carried out in this field in The University of Nottingham since 1999 (undertaken mainly by Professor Dileep N Lobo, and Professors Simon Allison and Brian Rowlands, who retired in 2004 and 2009, respectively) has influenced national and international guidance, thereby improving care and saving money.

In 1999, the UK National Confidential Enquiry into Perioperative Deaths estimated that 20% of patients had either poor documentation of fluid balance or unrecognised / untreated fluid imbalance [http://www.ncepod.org.uk/pdf/1999/99full.pdf; page 68]. It also reported that a significant number of patients were dying as a result of the infusion of too much or too little fluid by doctors and practitioners who had little knowledge and training on the subject. Furthermore, in 2005, a small study in the Wirral estimated that each year in the UK, around 17% of surgical patients (approximately 42,500 individuals) have complications that can be directly related to mismanagement of fluid therapy [Ann R Coll Surg Engl 2005;87:126-130]. Based on these data, we undertook telephone and postal surveys of junior doctors [Clin Nutr 2001;20:125-30] and consultant surgeons [Ann R Coll Surg Engl 2002;84:156-60]. We found that over 90% of fluid prescription was done by the most junior member of the surgical team, who often prescribed too much fluid and sodium to their patients, and that the seniors did not pay much attention to these prescriptions. The knowledge base was poor and there was a lot of confusion between maintenance, replacement and resuscitation requirements. Both knowledge and practice related to fluid and electrolyte prescribing in the UK was suboptimal and it was clear that a paradigm shift was necessary to improve clinical practice and patient outcomes.

We published a landmark clinical trial in the Lancet [1] (cited >290 times as of July 2013), demonstrating that a cumulative fluid overload of as little as 3 litres in the first 4 postoperative days led to intestinal failure and increased complications when compared with patients in zero fluid balance. These results have since been corroborated by others in several randomised trials (e.g. Ann Surg 2003,238:641-8; Anesthesiol 2005,103:25-32; Ann Surg 2009,250:28-34). Our meta-analysis [2] of these confirmed that patients in a state of fluid imbalance have a 3.4 day longer hospital stay and a 41% greater complication rate than those maintained in a state of fluid balance.

We corroborated these findings in numerous physiological studies, which demonstrated how healthy volunteers handle intravenous fluid loads. These showed that compared with balanced crystalloids, 0.9% saline, even in modest doses, causes a hyperchloraemic acidosis that persists for more than six hours after the infusion [3,4]. We also showed that saline causes increased interstitial fluid overload and oedema compared with balanced crystalloids [5,6], and this finding has been corroborated by others.

This work enabled us to confirm that the hyperchloraemia caused by saline overload can lead to a decrease in renal arterial blood flow and cortical tissue perfusion, a phenomenon we demonstrated in humans for the first time [6]. Subsequently, others have shown that chloride excess can lead to

more patients developing acute kidney injury and needing renal replacement therapy [Ann Surg 2012,255:821-9; JAMA 2012,308:1566-72]. We have also analysed differences in the way the body handles crystalloid and colloid infusions, and have developed a reproducible human model for the study of the responses to fluid infusions.

3. References to the research

1. **Lobo DN**, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet. 2002 May 25;359(9320):1812-1818.
http://dx.doi.org/10.1016/S0140-6736(02)08711-1

2. Varadhan KK, **Lobo DN**. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010 Nov;69(4):488-498.
http://dx.doi.org/10.1017/S0029665110001734
Epub 2010 Jun 2. Erratum in: Proc Nutr Soc. 2010 Nov;69(4):660.
http://dx.doi.org/10.1017/S0029665110002028

3. **Lobo DN**, Dube MG, Neal KR, et al. Problems with solutions: drowning in the brine of an inadequate knowledge base. Clin Nutr. 2001 Apr;20(2):125-130.
http://dx.doi.org/10.1054/clnu.2000.0154

4. Reid F, **Lobo DN**, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond). 2003 Jan;104(1):17-24.
http://www.clinsci.org/cs/104/0017/1040017.pdf

5. **Lobo DN**, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. Crit Care Med. 2010 Feb;38(2):464-470. (PDF available on request.)
http://dx.doi.org/10.1097/CCM.0b013e3181bc80f1

6. Chowdhury AH, Cox EF, Francis ST, **Lobo DN**. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012 Jul;256(1):18-24. (PDF available on request.)
http://dx.doi.org/10.1097/SLA.0b013e318256be72

Grants (all awarded to Dileep N Lobo):

- 1999-2001. £76,000 from the Special Trustees of Nottingham University Hospitals: Physiological aspects of fluid and electrolyte balance.
- 1999. €15,000 from ESPEN (European Society for Enteral and Parenteral Nutrition): The effects of salt and water overload on gastrointestinal function in the postoperative period.
- 1999. £2,000 from Nutricia Clinical Care: Mechanisms of hypoalbuminaemia.
- 2010. £48,000 from Baxter Health Care: The effects of crystalloid and colloid infusions on renal and superior mesenteric blood flow.
- 2012-2013. £78,000 from the European Hydration Institute: The effect of hydration status at admission on clinical outcomes.

4. Details of the impact

Our work has led to a paradigm shift in the thinking about and management of perioperative fluid therapy. Initially raising awareness within the professional community, it also informed the development and adoption of clinical guidelines to change clinical practice, resulting in improved surgical outcomes, both nationally and internationally.

Increasing awareness

Our surveys of junior doctors and consultant surgeons led to an increased awareness of the importance of handling fluid prescriptions. Since 2003, as a result of our surveys, there have been several conferences debating this subject and Professor Lobo has been invited to give over 70 lectures (45 since 2008) at prestigious international meetings and to international societies in six continents. He has also written 4 book chapters on the subject (2 since 2008), as well as a complete book which is now recommended reading for science and medical students in several Universities in the UK and worldwide (e.g. University of Nottingham, University of Leeds and University College, London; and Universities in Sweden, Madrid and New Zealand) [a,b]. It is also recommended reading for members of the European Society for Clinical Nutrition and Metabolism (ESPEN), and was distributed to all 2,500 delegates at the 2013 Conference of the Society. The book has been made freely available with the help of an educational grant from BBraun.

Universities have now included a fluid therapy module in undergraduate courses, and fluid therapy forms an important part of postgraduate surgical examinations [c]. In 2008, Professor Lobo developed an international educational course on fluid prescription for health care professionals, with the help of Baxter Healthcare [d]. To date, the course has trained over 1,000 surgeons, anaesthetists, nurses and Operating Department Personnel in the UK and Europe, and has received excellent feedback [d]. Professor Lobo also teaches the fluid therapy module of the Perioperative Care section of the Life Long Learning Course run by ESPEN, for which the book is also recommended reading.

Informing clinical guidelines

Our findings have been incorporated into national and international guidelines [e-h] that serve to inform optimal perioperative fluid therapy. Our work was instrumental in the set-up of the GIFTASUP and NICE fluid therapy guideline groups, and also in the formulation of the resultant guidelines [e,f]. Our research is also quoted extensively in four sets of clinical guidelines from the Enhanced Recovery After Surgery (ERAS) Group [g] and in the NHS Diabetes guidelines [h]. Guidelines incorporating the findings of our research have been endorsed and publicised by major professional bodies (e.g. BAPEN, ESPEN, AAGBI, ASGBI, Renal Association), nationally and internationally. Professor Lobo has also advised the Renal Association and the Royal College of Physicians of Edinburgh regarding fluid therapy in acute kidney injury.

Changing clinical practice

Demonstration of the adverse effects of large volumes of 0.9% saline has led to balanced crystalloids being preferred to 0.9% saline [e]. This is a major achievement, considering that until recently the yearly consumption of 0.9% saline was 10 million litres in the UK and 200 million litres in the USA [Clin Nutr 2008,27:179-88; Ann Surg 2012,256:18-24]. Now, largely because of the increased awareness of saline-induced hyperchloraemic acidosis, as demonstrated by our research and subsequent incorporation into guidelines, balanced fluids rather than 0.9% saline are the crystalloids of choice in most hospitals in the UK and Europe.

Patients are less likely to be fluid overloaded now than they were at the beginning of the 21st century. Patients who are now maintained in a state of fluid balance have an average of a 3.4 day shorter stay in hospital, and a 41% reduction in relative risk of postoperative complications. This has led to improved quality of life for patients and projected financial benefits to healthcare systems in the UK, Europe and Worldwide. Based on the fact that each year around 182,000 major abdominal operations are performed in England, it has been calculated that this would equate to a total annual saving of £122 million for NHS England [i].

Impact on industry

Professor Lobo has advised industry (Baxter Healthcare and BBraun) on intravenous fluids and subsequently established research collaborations with these companies [d]. This collaboration has led to both companies investing more in research on balanced crystalloids and how optimal fluid therapy can influence patient outcomes [d]. We are currently collaborating with BBraun on work on fluid physiology in healthy volunteers, and planning a 3 year programme grant on fluid therapy in surgical patients with Baxter Healthcare.

5. Sources to corroborate the impact

[a] Letter from Dr G Grimble, Prinicipal Teaching Fellow, University College London.

[b] Letter from Professor O Ljungqvist, Professor of Surgery, Orebro University Hospital, Sweden.

[c] Intercollegiate surgical curriculum programme; Module 5 'Peri-operative care of the surgical patient' – 'To assess, plan and manage post-operative fluid balance': https://www.iscp.ac.uk/surgical/SpecialtySyllabus.aspx?enc=j4VfyFXq6Hwh0loAlHujtkC075cafAX8g/MdvMtfyBw

[d] Letter from Carol R. Schermer, Medical Director, Baxter Healthcare.

[e] Powell-Tuck J, Gosling P, **Lobo DN**, *et al.* British consensus guidelines on intravenous fluid therapy for adult surgical patients. GIFTASUP. 2008 British Association for Parenteral and Enteral Nutrition: http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf

[f] National Clinical Guidance Centre. Intravenous fluid therapy: Intravenous fluid therapy in adults in hospital. Draft for consultation. Commissioned by the National Institute for Health and Care Excellence. May 2013: http://www.nice.org.uk/nicemedia/live/13298/63879/63879.pdf (see section 7)

[g] Enhanced Recovery After Surgery (ERAS®) Society recommendations:
Lassen K, Soop M, Nygren J, et al; Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery. Arch Surg. 2009 Oct;144(10):961-969: http://dx.doi.org/10.1001/archsurg.2009.170

Other ERAS guidelines for:
- pancreaticoduodenectomy: http://dx.doi.org/10.1007/s00268-012-1771-1
- elective rectal/pelvic surgery: http://dx.doi.org/10.1007/s00268-012-1787-6
- elective colonic surgery: http://dx.doi.org/10.1007/s00268-012-1772-0

[h] Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, Hilton L, Jairam C, Leyden K, Lipp A, **Lobo D**, Sinclair-Hammersley M, Rayman G; Joint British Diabetes Societies. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. *Diabet Med* 2012; 29: 420-433: http://dx.doi.org/10.1111/j.1464-5491.2012.03582.x

[i] Economic analysis by Professor R Elliott, Lord Trent Professor of Medicines and Health, The University of Nottingham.