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Perioperative fluid management: science, art or random chaos?

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As anaesthetists, we like to believe that the i.v. fluid we administer during surgery is based on a careful consideration of the contemporaneous clinical situation in the particular individual under our care. We estimate deficits; we use clinical assessment and haemodynamic monitoring to characterize circulating blood volume, and we respond to changes with fluid challenges and vasopressors.

A recently proposed framework within which to consider fluid therapy for acutely ill patients (including those where the 'acute illness' is the stress of major surgical resections) emphasizes that fluid needs differ depending on which of the following four phases is relevant at the time: (i) salvage (resuscitation); (ii) optimization; (iii) stabilization; or (iv) de-escalation.[1]

In haemodynamic situations that are likely to incorporate resuscitation and optimization phases (such as trauma or sepsis), the individual requirements may vary greatly. Contemporary surgery, often with minimal access or laparoscopically assisted, probably triggers much less physiological stress response fluid shift than surgery of 15 yr ago.[2] The notion that major surgery triggers 'a loss of fluid to third space'[3] holds no foundation. Systematic review shows that the evidence for a disparate reduction of the extracellular fluid volume following trauma or surgery is weak and that this long held belief is probably a result of flawed methodology.[4]

Thus, with modern elective resection techniques, physiological disruption is minimized and fluid shifts are rare. Fluid therapy in this setting is predominantly for optimization and stabilization. If we are as good as we think we are at perioperative fluid therapy, then in such patients we would expect to see consistency in the volume we give; individual providers might differ somewhat in how they interpret the haemodynamic variables, but in general, for any particular operation we should see a fairly narrow range of i.v. fluid volumes used.

Well, apparently not! A retrospective observational study in this issue of the *BJA* reports intraoperative fluid therapy practices at two US academic hospitals.[5] In a database of 5912 patients having common types of abdominal surgery, the authors found great variability in the amounts of crystalloid administered. The average corrected infusion rate across all providers at both hospitals was 7.1 (SD 4.9) ml kg^{-1} h^{-1}. A sophisticated linear regression was then used to identify explanatory factors for the volumes given. In the final model, the most important predictor by far was the provider of anaesthesia. Other variables included in the analysis were many of the end points that we surmise perioperative physicians might be using to judge fluid therapy, and these hardly seemed to matter. Factors such as minimum or median mean arterial pressure and median heart rate during surgery, estimated blood loss, surgical approach, and surgical type had either relatively weak or no effects in the final model in comparison to who was giving the fluid. The summary message is that fluid administration was largely according to the individual provider's 'habit', or that there was great inconsistency in the way that providers interpret and respond to haemodynamic and clinical signals during surgery.

In some instances, there was even wide intraprovider variability. A modified corrected coefficient of variation (cCOV) was used to express the range seen across institutions, procedures, and providers. This was calculated by dividing the sample SD (say, of all the cases of a particular provider) by the mean of the entire cohort (7.1 ml kg^{-1} h^{-1}). The lowest provider cCOV was 26% (consistent fluid administration across many cases) and the highest 141% (very inconsistent). In an applied example, the authors showed how a patient weighing 75 kg undergoing a 4 h procedure with minimal blood loss could receive anything between 700 and 5400 ml of crystalloid during surgery, depending on their anaesthesia provider.

Critics might say this is because of individual variability of the cases, many details of which may be invisible at registry level; however, the authors have taken great care to identify in their data set only those patients undergoing uncomplicated abdominal surgery under general anaesthetic, the underlying philosophy being to eliminate as much as possible the interpatient differences in the pathophysiological and surgical insult. A carefully restricted list of procedures was used; complex cases were excluded, as were urgent or emergency operations, and any with >500 ml estimated intraoperative haemorrhage or where blood product transfusion was required.

To reduce artificial bias further, the authors also disregarded procedures of <60 min duration, which might increase the overall milligram per kilogram per hour figure as a result of 'frontloading', patients looked after by student nurse anaesthetists, and all episodes by providers or surgeons with fewer than six patients in the registry.

This well-reasoned approach to the analysis resulted in a relatively homogeneous cohort. Nevertheless, the distribution of perioperative fluid volumes given was very wide.

This paper makes for quite uncomfortable reading.

But these data don't apply to me

Can we claim that US perioperative clinical practice differs too much from ours for the headline observations from this study

to be relevant to European practice? The model of anaesthesia care is somewhat different; in these hospitals, a licenced 'attending' anaesthesiologist supervises anaesthesia provision by either a certified registered nurse anaesthestist ('CRNA'; who comprised just under half of the in-room providers in this study) or medically trained residents (the remainder). No patients who received fluid therapy from a student registered nurse anaesthestist were included, on the basis that only one of the two institutions had them. In the UK, intraoperative cardiac output monitoring to guide stroke volume optimization during many elective major surgeries is recommended by the National Institute for Health and Care Excellence (NICE)[6] and advocated as a means to achieve bespoke fluid therapy for the individual, but this has gained little traction in America as yet. The authors of this paper specifically mention that goal-directed fluid therapy was not practised. Also omitted is information about perioperative vasoactive drug use. Vasopressors may be used as part of 'balanced' haemodynamic therapy during surgery and are likely to have an impact on the fluid volumes used.

But there are broad similarities between the health-care models in the two continents. With the advent of the 'perioperative surgical home' in the USA, elective surgical services increasingly resemble Europe's enhanced recovery.[7] If anything, outcomes from leading US hospitals are often better than ours for similar procedures.[8]

Is the variability unique to the two institutions in this study? No! Registry data for a period of 5 yr from more than half a million patients having colonic or arthroplasty surgery confined to nine ICD-9 procedure codes across 524 US hospitals shows that fluid usage complies to a U-shaped curve, with a median of around 3 litres crystalloid per procedure; however, the interquartile range of intraoperative fluid administration ranges from 1.3 to 5.0 litres, and varies by institution. A quarter of colonic surgery patients received >5 litres on the day of surgery and 11 litres postoperatively.[9]

In the UK, it is likely that there is similar variability in 'standard care' across providers and institutions. This is certainly apparent in UK perioperative fluid therapy studies. Recommended control group baseline fluid regimens in recent prominent trials have ranged from dextrose water 5% (1 ml kg^{-1} h^{-1})[10] to isotonic crystalloid (10 ml kg^{-1} h^{-1}).[11] Consensus guidelines from England's Enhanced Recovery Partnership Programme recommend that maintenance fluid during surgery should be limited to <2 ml kg^{-1} h^{-1}, with further fluid challenges guided by stroke volume monitoring;[12] several state-of-the-art recent fluid therapy studies[13] have used no baseline crystalloid at all. It seems unlikely that both ends of this spectrum of current common clinical practice are correct (Fig. 1).

Fig 1 Hourly water and solute load of two i.v. fluid maintenance regimens commonly used in clinical practice. For a 70 kg patient, dextrose water 5% administered at 1.5 ml kg^{-1} h^{-1} (lower left) contains the equivalent of two 50 ml syringes of water and 5 g dextrose (approximate sugar content of a small handful of raisins). In contrast, 10 ml kg^{-1} h^{-1} is the equivalent of fourteen 50 ml syringes of water and the salt content of ten 32.5 g bags of crisps. (Image courtesy of Department of Medical Photography, Derriford Hospital.)

Does all this variability have any consequences?

We cannot answer that from the data in the paper. No clinical outcomes are reported.

However, experience from enhanced recovery (ER)/'perioperative surgical home' programmes is likely to be relevant.[14] Great improvements in perioperative outcome can be achieved through adherence to simple management processes, seeking to iron out inconsistency in practice. The more elements achieved, the better the outcome. For elective abdominal surgery, of around 20 elements, avoidance of fluid overload is one of the key two (the other is provision of preoperative carbohydrate drinks).[15] The amount of i.v. fluid given is inversely proportional to postoperative complications. In a prospective cohort study of 953 colorectal cancer patients, for every 1 litre excess fluid given on the day of surgery, a 32% increase was seen in measured postoperative complications. This theme is echoed in the UK ER literature. Deviation from an ER pathway is associated with an increase in length of stay; continued i.v. fluid administration past the first postoperative day is strongly associated with delayed discharge (OR=4.80, 95% confidence interval 3.02–7.75).[16] It is important not to be disingenuous about this association. An obvious argument is that 'excess' postoperative fluid is a marker of mischief, rather than its cause; for example, the drip stays up on the patient with an intestinal ileus who is vomiting and apparently unable to drink. But it is likely that also included in the delayed discharge group are many patients who receive excess i.v. fluid simply because it is 'standard practice.'

Developing consistency

Is consistency achievable across a multitude of clinicians? Certainly! A recent trial of fluid and salt restriction *vs* a liberal controlled perioperative fluid regimen in 240 patients undergoing elective abdominal surgery managed to deliver intraoperative median fluid volumes of around 1 or 2 litres, respectively, with interquartile ranges of <500 ml either way.[17]

It is interesting that in the paper by Lilot and colleagues,[5] the mean fluid administration rate for ASA I patients was 9.9 (SD 6.2) ml kg^{-1} h^{-1} with a cCOV of 87%, whereas for ASA III patients it was 6.9 (SD 4.7) ml kg^{-1} h^{-1}, a cCOV of 66%. Is this indicative of closer attention being paid to patients who are perceived as sicker?

For colorectal surgery carried out within an ER model of minimal physiological upset, a 'zero balance' approach appears to be as effective as 'stroke volume optimization' in terms of achieving good clinical outcomes. This means bringing patients to theatre in a euvolaemic state, then paying meticulous attention to detail in fluid administration.[18] Let's be clear; this is not evidence that stroke volume optimization does not work. 'Zero balance' is not easy to do, and in all likelihood it bears little resemblance to current standard practice in most hospitals.

Does it take something unique or special to reduce inter and intraprovider variability in this manner? Experienced anaesthetists claim that there is no substitute for their clinical judgement. There is some evidence for this. Two recent large multicentre effectiveness randomized controlled trials of early goal-directed therapy for patients admitted to the emergency department with

severe sepsis have returned the same result; that strictly protocolized management targeted at defined haemodynamic milestones is no better than judicious sustained care delivered by experienced clinicians.[19] However, the end points that senior clinicians use to realize such results may be subtle, whereas care on the front line is often delivered by relatively junior doctors or by nursing staff following a protocol. Additional information provided by minimally invasive advanced haemodynamic monitors could be a useful adjunct to assist understanding of the volaemic status of individual patients, effectively allowing inexperienced staff to emulate the artistry of the masters through painting by numbers.

What does good perioperative fluid practice look like?

British Consensus Guidelines for Intravenous Fluid Therapy in Adult Surgical Patients[20] recommend that whenever we give fluid (and salt) for correction of a volume deficit during major surgery it should be directed towards a particular goal. Goals may (or may not) be a nominal cardiac stroke volume or related index of blood flow.

The consensus statement from the Department of Health's Enhanced Recovery Partnership Programs (ERPP) on perioperative fluid therapy makes a similar recommendation regarding goal-directed therapy.[12] Whatever the goals and however they are attained, it is important that providers remain focused on them throughout the operation.

An underappreciated facet of perioperative care is that much of the i.v. fluid that patients receive during a surgical admission is delivered postoperatively. In contrast to the intraoperative setting, many hospitals leave delivery of this to nurses and surgical juniors. In December 2013, NICE published 'clinical guideline 174', entitled 'Intravenous fluid therapy in adults in Hospital.'[21] The introduction says:

> . . . the recommendations do not apply . . . to patients needing inotropes and those on intensive monitoring, and so they have less relevance to intensive care settings and patients during surgical anaesthesia . . .

NICE 174 are thus broadly intended for non-expert first responders, such as trainee doctors on call out of hours. That should not mean we, as perioperative physicians, can ignore them. We need to be accountable for this territory. As self-proclaimed experts in perioperative care, it is our responsibility to prescribe an appropriate fluid in an appropriate volume for postoperative care and to participate in consistent education of those entrusted with front-line delivery of this. In the modern multidisciplinary era, much postoperative care is directly delivered by nursing staff, who are very capable of following algorithms to achieve good clinical outcomes.[22]

NICE 174, GIFTASUP and the ERPP consensus statements are highly relevant to perioperative fluid therapy, although all three have been controversial[23] as a result of perceived alignment with particular advanced haemodynamic monitors or fluids. Whilst some recommendations are limited by the absence of conclusive evidence,[24] according to our reading, the important common elements in the consensus statements are as follows: (i) fluid management is important and when done badly causes very significant harm.

(ii) Outcomes are better when algorithms, guidelines and regular audit are used to guide care.

Best-practice algorithms are elusive. There is some primary and systematic review literature in favour of a more restrictive approach to perioperative fluid therapy,[25 26] in keeping with the current view that third space loss does not occur, but the 'definitive' large multicentre trial, RELIEF, currently recruiting, is unlikely to report results before 2017 [http://www.relief.org.au/ (accessed 18 November 2014)]. This will be the largest perioperative fluid study to date, a randomized controlled trial of liberal *vs* restrictive fluid therapy in >2800 patients undergoing elective intra-abdominal surgery. Many UK hospitals have declined involvement on the basis that they consider the question resolved in favour of restrictive and consider themselves to practice this already.

But do you really know how much fluid you give? It is not clear that all these hospitals collect data on their fluid practice. It is striking that in a prominent goal-directed therapy study, isotonic crystalloid maintenance at 10 ml kg^{-1} was advised, perhaps already an excessively liberal baseline regimen, yet attending anaesthetists gave on average 17 ml kg^{-1} h^{-1} to the elective colorectal surgery patients enrolled in the trial.[11]

The perpetual cycle of quality improvement relies on embedded collection and continuous feedback of reliable data. This allows services to know how they are really performing (rather than how they think they are).

(iii) It is of practical use to distinguish '**R**'esuscitation from '**R**'eplacement from '**R**'egular maintenance in deciding the volume and type of fluid to use. Definitions are difficult, there being considerable overlap between the four phases of fluid therapy relevant to acute patients as mentioned above. Clinical application may be even more difficult because we do not know what the best end points and algorithms are.

Resuscitation is restoration of circulating volume to above a critical perfusion threshold[27] and is achieved with isotonic colloid, crystalloid, or where appropriate, blood and blood products.

Replacement is likewise targeted, bespoke, and difficult. We believe that careful measurement and replacement of losses with fluid of a similar composition makes biological sense. Advanced haemodynamic monitoring may assist in achieving this aim.

However, we wish to conclude this commentary by focusing on maintenance fluid therapy, particularly after surgery.

What should we hang after surgery?

We currently 'hang salt by default.' This is irrational. Consider our model of electrolyte and fluid homeostasis in the human organism after a physiological stress, such as major surgery. The body is avidly holding on to salt and water.[28] Does it make sense to infuse yet more?

If patients receive consistently judged intraoperative fluid therapy and arrive at the end of surgery euvolaemic, it seems appropriate to provide ~1 ml kg^{-1} h^{-1} or less afterwards. And why should we not hang dextrose water 5% as our baseline maintenance, reserving isotonic crystalloids for replacement of losses?

Lactated Ringer solution and normal saline are not maintenance solutions, because their sodium content is much too high for this purpose. A single litre bag of Hartmann's solution contains around twice the recommended daily intake of sodium chloride. Accordingly, three bags of this stuff hung as daily maintenance creates a large salt load. On a cautionary note, we emphasize that no more than 2 litres per day of dextrose water 5% should be infused and that i.v. maintenance should be taken down as soon as patients are drinking freely.[29] If a patient remains nil by mouth for an extended period for clinical reasons then electrolytes should be checked; in this situation, dextrose saline with potassium is a reasonable choice if plasma sodium is normal and 'routine maintenance' is the aim.

Can we as a clinical community agree? I.V. fluids should be administered with the same rigour as with any other drug. We have been researching perioperative fluid therapy for a very long time, yet because of inconsistent trial design we are no closer to the truth. In the absence of clearer evidence, in our view fluid management according to the standard practice group in the OPTIMISE trial is a reasonable approach to adopt for current best practice.[10] It may be true that aspects of expert consensus guidelines are controversial,[24] but surely treatment according to individual provider habit is even harder to justify? An acceptable alternative is that hospitals produce their own local perioperative fluid guidelines based on reliable local audit. But continued apathy is not the answer.

Declaration of interest

G.M. is the UK national co-ordinator of the RELIEF fluid therapy study. M.G.M. is: expert advisor to NICE Guidance 174; co-author of GIFTASUP guidelines; National Clinical Advisor to Enhanced Recovery Partnership UK Department of Health May 2009 to March 2013; Consultant for Edwards Lifesciences and Deltex; has received honoraria/expenses from Baxter, BBraun and Fresenius-Kabi; and is Editor-in-Chief of *Perioperative Medicine*, on the Editorial Board of *BJA*, a Council Member of the Royal College of Anaesthetists and Chair, DMEC for the RELIEF trial.

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Experimental behaviour testing: pain

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Behavioural testing is a widely used method in pain research in animals, particularly in rodents. With a wide range of tests available, it is easy to tailor experiments to examine specific brain or spinal cord areas, such as the dorsal horn. This editorial outlines some of the more commonly used tests and gives examples of how they can be used to further our knowledge of neurological processes in disease conditions such as neuropathic pain or to assess the efficacy of therapeutic strategies.

Pain sensation starts in receptors in the skin and viscera which project up to the spinal cord. The majority of sensory inputs to the spinal cord terminate in the dorsal horn, where afferents carrying the signal from the periphery converge onto interneurones or projection neurones. Some inhibitory or excitatory modulation can occur in the spinal cord via the interneurons before the signal continues to the brain.[1] Sometimes, before the signal reaches the brain, efferent fibres from the spinal cord also project to the muscles surrounding the initial stimulation to elicit a reflex, such as withdrawal to protect the body from the noxious stimulus.[2] The various pathways involved in carrying and modulating pain sensations from periphery to the brain involve complex circuitry and the majority of neurotransmitter types found in the higher centres of the central nervous system are present in the dorsal horn.[3] In the spinal cord, the majority of interneurons either release glutamate or GABA (often in conjunction with glycine).[4] Glutamate is an excitatory neurotransmitter, so activates the next cell in the pathway, while GABA and glycine are inhibitory, so reduce the effect of the next neurone along. Using these two neurotransmitters, incoming signals can be modulated, that is, strengthened or dampened down, before reaching the brain. The hierarchical organization of the nervous system, highlighting the sites of action of the more commonly used pain models and nociceptive tests, are illustrated in Figure 1.

Models of pain induction

Different pain tests can be classified as thermal, mechanical, or chemical and can test for periods as short as a few seconds (acute), up to a few months (chronic) depending on the stimulus used.[5]

Formalin injection

Formalin injection is a commonly used acute nociceptive model which elicits a two-part response; an initial peripheral pain, driven by TRPA1 receptor and C-fibre activation, and a later response involving inflammation and central sensitization of the dorsal horn.[6 7]

Nerve ligation

Nerve ligation is a commonly used method of chronic pain, involving surgery to tie off one of a number of spinal nerves or peripheral nerves to induce a neuropathic pain phenotype.[8–10] Ligation of spinal nerves S5, often combined with ligation of S6, results in a consistent phenotype of heat hyperalgesia, and allodynia induced by cold or mechanical stimuli. Inadvertent damage to surrounding nerves will result in visible defects such as paralysis of hindlimbs for damage to S4, a simple safeguard against inadvertently ligating the incorrect nerve.[9]

Heat injury

Heat-induced injuries can be induced by a number of methods. Most common models involve immersion of limbs or small portions of skin to water ranging from 60°C to 100°C.[11] This gives a reliable burn injury which can be studied for histological and behavioural outcomes. By varying temperature and time immersed, severity of the burn injury can be easily controlled. Other models involve injection of drugs such as capsaisin which, while not causing a burn themselves, elicit a burning sensation and hyperalgesia to heat.[12] These capsaicin models have also been applied to human studies.[13]

Testing pain-related behaviour

The type of behavioural test used will naturally depend on the pain model being studied. For example, tests may not be useful in models where the animal remains anaesthetized throughout, and complex behavioural test involving learning and memory may be too stressful for an animal in high levels of pain, for example, after a burn injury over a large area of the body. In this