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- β -Blockers and cardiac protection: 5 yr on from POISE
- Fluid management in association with neonatal surgery: even tiny guys need their salt
- Flexion-rotation manoeuvre increases dimension of the acoustic target window for paramedian thoracic epidural access
- Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery surgery in patients with moderate vs deep neuromuscular block

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BJA**EXCERPTS****SOUTH AFRICAN EDITION****Comment**

This edition of BJA(SA) contains a number of articles that are of considerable relevance to clinical practice. An excellent editorial from two well-known experts in the field reviews the current status of the use of beta-blockers in the perioperative period. The editorial ends with a series of practice pointers that can usefully be used to guide clinicians faced with the decision of whether or not to introduce beta-blockade in the immediate perioperative period¹. It should be noted that the conclusions are not quite as clear-cut as the original POISE study might have suggested and that the use of differing timings, as well as alternative beta-blocking agents may alter clinical practice in this area. What is clear is that the era of almost uniformly administered perioperative beta-blockade for patients at risk of myocardial ischaemic injury is over.

Another practice-changing intervention that has evolved over the last few years is the revision of fluid composition in paediatrics. An editorial reviews a publication in BJA (not included) dealing with fluid and sodium loads in the perioperative phase². For many years it was taught that low-sodium containing solutions were appropriate for perioperative paediatric fluid therapy, based on the original studies that were conducted on non-surgical patients. The recognition of hyponatraemia as a major post-operative complication in paediatrics has resulted in a change in emphasis towards crystalloid solutions that contain concentrations of sodium that resemble those in the plasma. It is of interest that the preoperative management of these patients does not appear to pose a risk of hyponatraemia and it is only once the surgical stress occurs that the rise in ADH and other physiological responses to trauma poses the risk that hyponatraemic solutions may result in a potentially lethal reduction in serum sodium in the post-operative period. The perioperative use of solutions containing normal plasma concentrations of sodium in paediatrics should not be routine.

Arbitrary decisions on coagulation management have frequently been controversial, no more so than in the complex field of liver transplantation. Thrombelastography has, for many years, been the mainstay of coagulation management during this procedure and the greater sophistication offered by the ROTEM device may enhance the ability of anaesthetists to make high-quality decisions. The article by Song et al³ examines the utility of very early results from the ROTEM and concludes that excellent data of good clinical relevance can be obtained within the first five minutes of the test allowing early and precise regulation management.

Finally, an interesting ultrasound article has examined positioning of patients for the placement of low-thoracic epidural catheters⁴. The innovation of a rightward twist of the spine in addition to good flexion appears to offer the best potential access to the thoracic epidural space as judged in this ultrasound study. Whether or not this will apply to upper thoracic anatomy remains to be evaluated, but this approach appears to be one well worth considering where thoracic epidural catheters are to be placed.

1 Foex P, Sear JW. II. β -Blockers and cardiac protection: 5 yr on from POISE. *British Journal of Anaesthesia* 2014; 112: 206-10

2 Lönnqvist P-A. III. Fluid management in association with neonatal surgery: even tiny guys need their salt. *British Journal of Anaesthesia* 2014; 112: 404-6

3 Song J-G, Jeong S-M, Jun I-G, Lee H-M, Hwang G-S. Five-minute parameter of thromboelastometry is sufficient to detect thrombocytopenia and hypofibrinogenaemia in patients undergoing liver transplantation. *British Journal of Anaesthesia* 2014; 112: 290-7

4 Ramsay N, Walker J, Tang R, Vaghadia H, Sawka A. Flexion-rotation manoeuvre increases dimension of the acoustic target window for paramedian thoracic epidural access. *British Journal of Anaesthesia* 2014; 112: 556-62

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Reference: 1. Mather LE, Chang DHT. Cardiotoxicity with modern local anaesthetics. Is there a safer choice? *Drugs* 2001;61(3):333-342.

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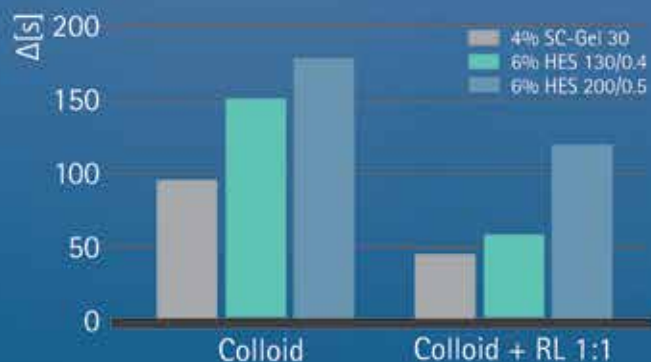
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EDITORIAL I

β-Blockers and cardiac protection: 5 yr on from POISE

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For many years, β-blockers have been regarded as the best drugs to protect patients with, or at risk for, coronary heart disease, from perioperative major adverse cardiac events (MACE). This was based on observational studies, randomized controlled trials (RCTs), experts' opinions, and guidelines. The strongest support was expressed in the 1997 guidelines of the American College of Physicians,¹ after very encouraging

results after administration of atenolol before non-cardiac surgery by Mangano and colleagues.² The guideline advocated the administration of atenolol to all patients with, or at risk for, coronary disease undergoing surgery. In the USA, initiation of perioperative β-blockade was regarded as having the greatest strength of evidence in its favour.³ However, a less supportive view was expressed in the American College of

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Cardiology/American Heart Association (ACC/AHA) guideline 2007.⁴ β -Blockers were considered to protect against myocardial ischaemia (as we had found in an RCT 20 yr earlier),⁵ they may reduce the risk of myocardial infarction and cardiac death in patients with known coronary artery disease. This followed the realization that some RCTs did not show statistically significant cardiac protection. Indeed, several studies did not show a statistically significant reduction in cardiac mortality,^{6–10} or non-fatal myocardial infarction.^{11–15}

A meta-analysis by Devereaux and colleagues¹⁶ of all RCTs of perioperative β -blockade failed to show statistically significant protection. These data were the justification for the POISE trial.

In 2008, the POISE study,¹⁷ the largest RCT in perioperative medicine ever undertaken, showed statistically and clinically significant cardiac protection but revealed an increase in all-cause mortality, disabling strokes, and hypotension. Because of the much smaller size of all previous RCTs, these risks may have been present but had never reached statistical significance. Subsequent meta-analysis confirmed both cardiac protection and significant risks associated with the initiation of β -blockade shortly before surgery.¹⁸ The result of POISE was criticized, especially the potential for high doses of metoprolol to be administered, and the choice of slow-release metoprolol.¹⁹

In 2009, new guidelines on the management of patients with heart disease undergoing non-cardiac surgery were published on both sides of the Atlantic by the ACCF/AHA²⁰ and the European Society of Cardiology (ESC) endorsed by the European Society of Anaesthesiology (ESA),²¹ respectively. Both sets of guidelines recommended to continue long-term treatment with β -blockers, to avoid high-dose β -blockade, and to consider the introduction of β -blockers in patients with known coronary artery disease, patients with reversible ischaemia on stress test, and in those at risk for coronary artery disease undergoing high-risk surgery, especially vascular surgery.²⁰ The European guideline regarded the above recommendations as Class I (as opposed to Class IIa for the American guidelines) and was more liberal suggesting that β -blockade could be initiated in patients undergoing intermediate-risk surgery (Class IIa).²¹ Both groups of experts advocated titration of β -blockade to slow heart rates (ESC 60–70 beats min^{-1} ; ACCF/AHA 60–80 beats min^{-1}) with the limit of at least 100 mm Hg systolic arterial pressure before administration of the next dose of β -blocker (ESC), or no hypotension (ACCF/AHA). Both advocated starting β -blockade at least 7 days, preferably 30 days before surgery. However, there is only limited supporting evidence for this approach.

In respect of the recommendation to continue chronic β -blockade perioperatively, there is good evidence from observational studies^{22–24} and one RCT²⁵ to support the continuing of chronic β -blockade during anaesthesia and surgery. The case for discontinuing therapy was first put forward by Crandell²⁶ who stated that 'antihypertensive drugs interfered with haemodynamic adjustments and could cause profound cardiovascular collapse in patients subjected to the stress of anaesthesia and surgery'. This approach was extended to β -blockers.²⁷ However, more recent studies have shown that

discontinuing therapy is associated with significant increases in perioperative morbidity and mortality.^{22–24} Indeed, maintaining chronic therapy has been shown by Wallace and colleagues²⁴ to be associated with a similarly improved outcome when compared with patients receiving acute perioperative β -blockade. In contrast, Ellenberger and colleagues²⁸ found that chronic therapy was superior to the introduction of β -blockers within the first 2 days of surgery.

We are now in 2013. The interpretation of existing data, coupled with new research, needs to be reconsidered. First, there is the problem of the alleged intellectual misconduct relating to the studies from Poldermans and colleagues at the Erasmus Medical Center. However, the correspondence between Poldermans and the Editor of the *American Journal of Medicine*²⁹ in response to the commentary by Chopra and Eagle³⁰ does nothing to throw a clearer light on the overall picture.

New meta-analysis

The second new development is the publication of a new meta-analysis by Bouri and colleagues³¹ which excludes what they regard as 'insecure' studies—namely, DECREASE³² and DECREASE IV³³ trials from the Erasmus Medical Center. Based on data from nine other clinical trials (10 529 patients), the investigators report that the treatment of patients undergoing non-cardiac surgery and receiving β -blockers according to the existing recommendations of the ACCF/AHA or ESC guidelines was subject to a significant 27% increase in the all-cause mortality risk. Translated into figures relevant to the UK, this would imply that the drugs could have resulted in >10 000 surgical deaths per year had guidelines been strictly followed! In addition, their use may be associated with a 73% increase in the incidence of non-fatal stroke, and 51% increased incidence of hypotension. On the benefit side, there was a 27% reduction in non-fatal myocardial infarction. If we return to the analysis of Bangalore and colleagues,¹⁸ they show similar outcomes, where any benefit of β -blockade is driven by trials with a high intrinsic risk for bias—namely, DECREASE and DECREASE IV.

When should we start β -blockers

In respect of the early start of β -blockade advocated by the current guidelines,^{20 21} only four studies have used this approach,^{8 13 32 33} and in two of them, β -blockade was not shown to be beneficial. In contrast, in two studies from Poldermans' group, early administration (at least 7 days before surgery) was beneficial. All the other RCTs started β -blockade the day of surgery. While an early start is logical, new data do not support this. Wallace and colleagues²⁴ collated observation in more than 37 000 non-cardiac operations. A protocol for perioperative β -blockade was available in their institution but was not mandatory. Patients were followed for 1 yr. Survival was best for those who had been given a β -blocker at the time of surgery, followed by those who had been maintained on β -blockade. Poorer survival was noted for those not on a β -blocker; worst outcome (unsurprisingly) was in those in

whom β -blockade had been withdrawn. Thus, in the groups of patients in whom β -blockade is supported by the current guidelines, late start, if early start was not possible should not preclude the introduction of β -blockade.

Another indication for perioperative β -blockade may be to obtund the adrenergic responses to noxious stimuli or to reduce myocardial ischaemia. Our analysis of 14 studies ($n=1298$ patients) shows this single-dose treatment to be effective in reducing perioperative myocardial infarction [odds ratio (OR) 0.17 (0.044–0.203), seven studies] and myocardial ischaemia [0.22 (0.135–0.353), eight studies]. These treatments were not associated with significant hypotension or bradycardia.

β -Blocker formulation

There has been controversy in respect of the choice of slow-release metoprolol in POISE. A large observational study by Wallace and colleagues³⁴ has shown in 3789 patients on continuing β -blockade that atenolol was associated with better protection in terms of 30 day and 1 yr mortality than metoprolol. Today, bisoprolol is used increasingly frequently and may also prove to be more protective than metoprolol.

Existing guidelines

Guidelines^{20, 21} underline that initiating β -blockade perioperatively should be limited to high-risk patients. This was largely based on the data from a very large cohort study by Lindenauer and colleagues.³⁵ The revised cardiac risk index (RCRI) was used to categorize cardiac risk. As the data concerned the years 2000 and 2001 and the management of patients with coronary artery disease have changed with the introduction of coronary stenting, especially in patients with acute coronary syndromes, it is interesting to see that observational data collected between 2005 and 2010 by London and colleagues³⁶ confirm that the benefits of β -blockade are only significant in patients with an RCRI of more than 1. The ACCF/AHA guideline²⁰ recommended perioperative β -blockade in patients undergoing high-risk surgery, especially vascular surgery. However, the observational study of London and colleagues³⁶ did not confirm benefits of exposure to β -blockade in vascular surgical patients irrespective of the RCRI. This is surprising and more research is needed in this group of patients.

β -Blocker titration

The recommendation of close titration of β -blockade with the goal of a heart rate of 60–70 beats min^{-1} is in principle desirable because of the need to maintain a long diastolic period to maximize flow in narrowed coronary arteries. However, there is the risk of severe bradycardia and cardiac failure as observed in a meta-analysis by Beattie and colleagues.³⁷ As hypotension was found in POISE to be an important contributor to perioperative strokes, the suggestion that 100 mm Hg systolic arterial pressure is sufficient before giving the next dose of the β -blocker is at least questionable. The current recommendation of the ACCF/AHA to withhold the β -blocker if there is hypotension (undefined) seems more logical as even moderately

hypertensive patients presenting for surgery may suffer complications if their arterial pressure decreases to and remains at 100 mm Hg for a prolonged period.

Anaemia and β -blockade

An observational study by Beattie and colleagues³⁸ has shown that as the nadir of haemoglobin decreases, the risk of MACE increases as the reduction reaches 60% of control and is much higher in β -blocked than in non- β -blocked patients. Similarly, Le Manach and colleagues³⁹ found that perioperative β -blockade was associated with an overall reduction in post-operative cardiac events. Hence, while cardiac protection was observed in those patients with low perioperative bleeding, patients receiving β -blockers who experienced severe bleeding had higher mortality and an increased frequency of multiorgan dysfunction syndrome. These important observations require confirmation in future studies because they may indicate a need to revise the threshold for blood transfusion in patients on β -blockers.

What for the future?

On August 5, 2013, a joint statement by the ACCF/AHA and ESC⁴⁰ stated: 'Our respective committees are undertaking a careful analysis of all relevant *validated* studies and always incorporate new trials and meta-analyses into our evidence review. In the interim, our current joint position is that the initiation of beta-blockers in patients who will undergo non-cardiac surgery should not be considered routine, but should be considered carefully by each patient's treating physician on a case-by-case basis'.

Before new guidelines are published, what may be a reasonable approach to perioperative β -blockade?

- Current β -blockade should be maintained, with the previously mentioned caveat of a potential risk in patients developing severe perioperative anaemia.
- Initiating β -blockade should be limited to high-risk patients undergoing high-risk surgery, especially in those who would be given β -blockade for co-existing medical reasons, that is, known coronary artery disease, reversible ischaemia on stress test.
- High-dose β -blockade should be avoided.
- Titration is recommended, but the ACCF/AHA guideline for heart rate (60–80 beats min^{-1}) is probably more appropriate owing to the risk of bradycardia with higher doses of β -blockade that can occur with the lower limit (60–70 beats min^{-1}) advocated by the ESC guideline.
- Titration should include clear instruction for each patient as to the level of arterial pressure required before the next dose of the β -blocker is given, as a function of pre-operative arterial pressure, as avoidance of hypotension is important.
- Starting β -blockade and titrating its effects over at least 7 days is logical. However, starting β -blockade on the day of surgery may still be legitimate where there is a clear

indication, such as the administration of a single premedicant dose to prevent exaggerated haemodynamic responses to laryngoscopy and intubation; or provide anxiolysis by reducing adrenergic responses; or prevent perioperative myocardial ischaemia.

- Metoprolol appears to be inferior to atenolol and in the future, bisoprolol is likely to become the drug of choice once more research has been carried out.
- As anaemia has been shown to markedly increase the risk of adverse cardiac events and mortality in the face of β -blockade, consideration should be given to increase the threshold for blood transfusion in these patients.

Declaration of interest

None declared.

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EDITORIAL II

Fluid management in association with neonatal surgery: even tiny guys need their salt

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The practice of giving i.v. fluids as part of routine paediatric care was established during the 1950s, and important initial questions to answer were what type of solution to give and at what infusion rates. In 1957, Holliday and Seger¹ published a seminal manuscript, recommending the well-known '4-2-1 rule', which almost immediately was adopted as a worldwide standard. The composition of a normal i.v. maintenance fluid was however somewhat more difficult to determine but was heavily influenced by the composition of normal breast milk, which has a sodium content in the range of 10–40 mmol litre⁻¹.² Thus, effectively hypotonic glucose solutions with a low sodium content came into wide-spread use maybe best exemplified by the British 4% glucose 0.18% sodium ('four and a fifth').³ The history since the 1950s has shown that the approach described above works sufficiently well in the vast number of routine paediatric cases.

However, using the standard Holliday and Segar volume recommendations paired together with the use of an i.v. solution with a sodium concentration that diverges substantially from that of the extracellular fluid does become a problem in a situation of a neuroendocrine stress response, either provoked by surgery or significant medical illness. The reason for

this is that the stress response includes a substantially increased secretion of anti-diuretic hormone (ADH) that will result in retention of free water. A physiologically more appropriate approach during these circumstances is to use a solution with a close to physiological concentration of sodium (120–140 mmol litre⁻¹) combined with the administration of a reduced infusion volume compared with the normal situation (50–70% of normal infusion rate).^{4–5} If not adhering to a more physiological approach, the stage is set for dilutional hyponatraemia that can be life-threatening or even fatal.^{6–11}

The insight that the paediatric use of i.v. low sodium solutions was unsuitable in the context of a stress response and that a sodium content closer to that of extracellular fluid is more appropriate was published as early as 1964.¹² However, since no appropriate i.v. solutions were commercially made readily available by the manufacturers, the regimen of using effectively hypotonic solutions in association with paediatric anaesthesia and surgery has continued in many centres even to this day. A questionnaire-based study from 2001 reported that 97% of UK-based anaesthetists routinely used effectively hypotonic i.v. solution intraoperatively in children.¹³ A similar study published in 2006, also surveying the UK practice,

reported no major change of practice with a majority of anaesthetists still using hypotonic solutions both intraoperatively and after operation (66% and 87%, respectively) and as many as 11% admitted that they even used the same hypotonic solutions for volume replacement.¹⁴

A paramount initiative to set things straight was taken by the French paediatric anaesthesia community in the early 1990s, spearheaded by Murat and colleagues. In a number of clinical studies, they could show that the perioperative use of an i.v. solution made available by the Paris pharmacy (Polyionique B66, 0.9% glucose with sodium 120 mmol litre⁻¹) did keep plasma sodium within the normal range during the postoperative period and did also avoid clinically relevant hypo- or hyperglycaemia.¹⁵⁻¹⁷ Furthermore, the use of this type of i.v. solution has also been found considerably safer should there occur unintentional over-infusion or if it would be used for volume replacement.¹⁸ This taken together with a still ongoing UK National Inquiry into the tragic outcomes of the use of hypotonic i.v. solutions in ill children¹⁹ and expert opinion^{3 20-23} has led to new and more appropriate recommendations.²⁴⁻²⁶ Currently, proper i.v. solutions are commercially available in a number of individual European countries and hopefully soon the main manufacturers of i.v. solutions will provide such solutions readily available to clinicians in all European countries.²⁶

Thus, currently the use of an intra- and postoperative i.v. solution containing close to physiological concentrations of sodium is recommended in children >6 months of age.¹⁷ However, until now, data for children 0-6 months of age have been scarce²⁷ and recommendations have mainly been based on extrapolations based on normal physiology combined with the insight that even our smallest children can and will respond with a relevant neuroendocrine stress response when subjected to surgical procedures.^{28 29} Studies focused on neonates and small infants in this context have been largely lacking.

It is therefore with great pleasure and satisfaction that we now can enjoy the results of yet another French initiative, which provide us with much sought after information in this regard. In this issue of the *BJA*, Edjo-Nkilly and colleagues³⁰ report data generated from 34 neonates (0-7 days old) undergoing a variety of neonatal surgical procedures. The main focus of their study was to investigate the effect on plasma sodium in relation to the amount of free water that was administered i.v. during the perioperative period. Despite the inherent problems with standardization associated with this type of study, the authors have been able to provide us with two new and very important pieces of insight in the neonatal context, apart from identifying a 12% overall incidence of postoperative hyponatraemia in this group of neonates.

First, the reduction in plasma sodium correlated only to the amount of free water that is administered intraoperatively and not to the amount of free water administered before operation. This makes sense for two reasons. Based on decades of clinical experience using regular i.v. maintenance solutions containing a low content of sodium, we know that normal children without any major ongoing stress response (as is the case before surgery) will be able to handle such

infusions without any risk of hyponatraemia. Thus, the lack of correlation to preoperative free water administration appears intuitively correct. However, as surgery commences, the neuroendocrine stress response will be initiated, including a rapid increase in ADH, which in turn will render the child unable to handle the challenge represented by continued administration of effectively hypotonic solutions. Secondly, intraoperative free water administration in excess of 6.5 ml kg⁻¹ h⁻¹ was found to be associated with a postoperative reduction in plasma sodium (≥ 4 mmol litre⁻¹) with a sensitivity and specificity of 0.7 and 0.5, respectively. This provides us with a very useful guideline to how much free water can be allowed during neonatal surgery with regard to the risk of producing clinically relevant postoperative hyponatraemia.

The data now published by Edjo-Nkilly and colleagues lend support for extending the current paediatric consensus regarding intra- and immediately postoperative use of i.v. solutions containing ~1% glucose with a near to normal content of sodium (120-140 mmol litre⁻¹)²⁶ to also include infants <6 months of age. Thus, give our little guys their salt during anaesthesia and surgery!

Declaration of interest

P.-A.L. is a member of the *BJA* Editorial Board and is also Section editor/Editorial Board member of *Paediatric Anaesthesia*.

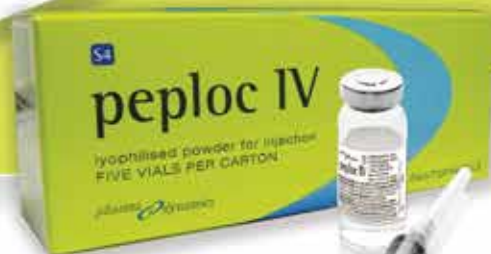
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* USPDI, Volume 1 2007, 27th Edition, pg 2267.

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REGIONAL ANAESTHESIA

Flexion-rotation manoeuvre increases dimension of the acoustic target window for paramedian thoracic epidural access

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Editor's key points

- The best patient position for identifying the thoracic epidural space is debated.
- This volunteer study used ultrasound to visualize the posterior longitudinal ligament and hence identify the thoracic epidural space.
- Using 10° dorsal table tilt and flexion with right rotation via a paramedian approach improved the acoustic target area.
- This position may facilitate epidural catheter placement but further studies are needed.

Background. The posterior longitudinal ligament (PLL) has been found to be a reliable measure of the acoustic target window for lumbar spinal anaesthesia and a predictive tool for difficult spinals. Currently, there is limited information on the PLL in the thoracic spine and its potential use for optimizing the acoustic target window during thoracic epidural placement. This study examined the effects of changes in body position on the length of the PLL as a measure of the acoustic target window for paramedian thoracic epidural access.

Methods. We performed thoracic ultrasonography on 30 adult volunteers to measure the length of the PLL at the T9/10 interspace, in five different positions: P1, neutral; P2, thoracic and lumbar flexion; P3, as in position 2 with dorsal table tilt to 10°; P4, as in position 2 with 45° rightward shoulder rotation; and P5, as in position 2 with 45° leftward shoulder rotation.

Results. The mean (sd) PLL length increased significantly from 9.9 (3.9) mm in P1 to 11.7 (3.4) mm in P2, 12.9 (3.1) mm in P3, and 13.8 (4.0) mm in P4 ($P < 0.01$, < 0.01 , and < 0.01 , respectively). The mean PLL length in P3 and P4 was also significantly longer compared with P2 ($P < 0.01$ and 0.01 , respectively).

Conclusions. In volunteers, flexion with 10° dorsal table tilt and flexion with right rotation significantly increased the length of the ipsilateral PLL, compared with the standard flexed sitting position, as visualized by paramedian ultrasonography at the level of T9/10.

Keywords: anaesthetic techniques, epidural; monitoring, ultrasound

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Thoracic epidural anaesthesia is a commonly used technique to provide postoperative analgesia. Although Pages¹ first described lumbar epidural anaesthesia, it was Dogliotti,² who described the upright sitting position with lumbar flexion for thoracic epidural anaesthesia. This position continues to be described essentially unchanged in modern textbooks of anaesthesia.³ However, there is limited research on optimizing patient position to facilitate thoracic epidural placement and no objective evidence to support one position over another. Another challenge in determining the effect of patient position on neuraxial access is the lack of suitable technology. Plain X-rays lack sufficient resolution and most commercially available CT and MRI scanners will not accommodate subjects in a sitting position; fluoroscopy and CT scans also subject

individuals to radiation exposure. Neuraxial ultrasonography is harmless in this regard and provides a dynamic real-time assessment of the relevant anatomy, the effect of position changes on the size of the acoustic window for epidural and spinal insertion.^{4 5}

The paramedian approach for thoracic epidural anaesthesia has the advantage of decreased incidence of dural puncture, vascular puncture, and paraesthesias.⁶ Grau and colleagues⁷ demonstrated that the paramedian approach also provides an optimal ultrasound 'acoustic' window between the thoracic vertebrae for visualizing pertinent structures in the epidural space. Furthermore, comparison of ultrasonography of the thoracic epidural space with magnetic resonance imaging has shown satisfactory correlation between the two with an

acceptable degree of precision in the depiction of structures.⁷ This approach overcomes the steep angulation of overlapping spinous processes and narrow intervertebral spaces, compared with a midline approach.^{7, 8} Although changes in the dimensions of the interspinous space and ligamentum flavum, as measured by ultrasonography, are proposed to be important factors in determining successful midline neuraxial needle insertion in the lumbar region, they have limited utility in the thoracic region because the ligamentum flavum is thin in the thoracic region and there is acoustic interference from the steeply angled spinous processes.^{5, 9–13} In addition, the posterior complex (ligamentum flavum, epidural space, and posterior dura) is not consistently visible so that its dimensions cannot be utilized as a guide to the width of the interlaminar window.¹³ In previous descriptions of ultrasound-guided neuraxial techniques, the importance of sonographic visualization of the PLL as a guidance structure for neuraxial puncture has been emphasized, because even though the PLL is part of the anterior aspect of the epidural space, clear visualization of the PLL is indicative of an 'open acoustic window', with an unobstructed path to the dura between the laminae, and may provide indication of the technical difficulty associated with neuraxial access.^{13–15} The posterior longitudinal ligament (PLL) can be easily visualized in the thoracic region via a paramedian view and it has been validated as a reliable screening tool for difficult spinal anaesthesia.^{4, 13, 15} The purpose of this study was to measure the 'acoustic target area' (defined as the visualized length of the PLL), at the T9–10 interspace, by paramedian ultrasonography in five seated positions (neutral, traditional flexed, flexed with 10° of dorsal table tilt, flexed with rotation to the right side, and flexed with rotation to the left side). We hypothesized that flexion and rotation may increase the dimension of this acoustic target area, and theoretically facilitate thoracic epidural needle insertion.

Methods

This study was approved by the Clinical Research Ethics Board of the University of British Columbia on September 14, 2012, and registered with the Office of Research Services of the University of British Columbia (H12-02141). Informed written consent was obtained from 30 healthy volunteer subjects recruited at Vancouver General Hospital. Inclusion criteria were the ability to achieve the five positions expected in the study and to provide written informed consent. We excluded volunteers with a history of spinal trauma, spinal surgery, or congenital spinal abnormality and allergy to ultrasound gel. Age, weight, height, and BMI were recorded for each participant.

All volunteers were sitting on a height-adjustable operating theatre table with feet fully supported, to bend the hips and knees to 90°. Spinal ultrasonography was performed in five study positions (Figs 1 and 2):

- P1. Neutral: no back flexion/extension.
- P2. Flexion: slouching of the shoulders with lumbar flexion and exaggeration of the thoracic kyphosis with arms around a pillow at chest level.

- P3. Table tilt: as in position 2 and dorsal table tilt to 10°.
- P4. Right rotation: as in position 2 and 45° rightward shoulder rotation.
- P5. Left rotation: as in position 2 and 45° leftward shoulder rotation.

Table tilt angle was limited to 10° because 15° was not tolerated by patients in a previous study;⁹ table tilt was measured using the Tiltmeter application (Integrasoft, Bridgewater, NJ, USA) on an iPhone 3G (Apple, Cupertino, CA, USA) and confirmed using a protractor with a hanging weight.⁹

Using a 2–5 MHz curvilinear transducer (Ultrasonix, Richmond, BC, Canada), the T9/10 intervertebral level was identified, by scanning in a longitudinal paramedian plane from the sacral plateau and moving cranially counting each laminae.¹⁶ Secondary confirmation of the level was performed by manual palpation of the spinous processes from the level of the sacral plateau. We chose to study the T9/10 level because an epidural catheter at this level has the potential of providing dermatomal analgesia for most thoracic and abdominal procedures and is the level most often used in our centre. A right longitudinal paramedian plane was used to achieve optimal images.^{17, 16} The laminae were identified by the 'sawtooth' ultrasound pattern and the ligamentum flavum/posterior dura visualized as a bright hyperechoic line. The PLL and posterior vertebral body were visualized as a deeper hyperechoic structure and identified in all images.

Two experienced fellows (N.R., J.W.) in anaesthesiology (>50 neuraxial ultrasound scans) performed the scans and measurements but could not be blinded to patient position. The first anaesthesiologist (N.R.) performed all the ultrasound scans and the second anaesthesiologist (J.W.) measured and recorded the length of the most superficial and inferior aspects of the PLL using the onscreen caliper tool. The first anaesthesiologist was blinded to the actual distances measured. The process of scanning and measurement was repeated in the same sequence for each of the five study positions in all subjects. The entire scans were recorded as a video file and re-measured by a third anaesthesiologist (R.T.), blinded to the patient positions and blinded to PLL measurements made by the second anaesthesiologist (J.W.). This second data set of PLL measurements was used to quantify inter-observer agreement.

Sample size was estimated based on data from a comparable study using a 1 mm change in target area dimensions, a 1 mm SD, an α of 0.05, and a power of 90% to yield a sample size of 16 subjects.⁹ Since an epidural needle is ~1 mm in diameter, any increase in target area dimensions of 1 mm can be theoretically important in determining successful access to the epidural space. After statistical consultation, we estimated a sample size of 30 volunteers would be adequate to show significant change in the mean length of the PLL (acoustic target area) in any of the five positions. The data were analysed using repeated-measures analysis of variance, in pairwise comparisons for measurements of the mean PLL length in each of the positions (with the Bonferroni adjustment to maintain $P < 0.05$). Tests of normality were performed

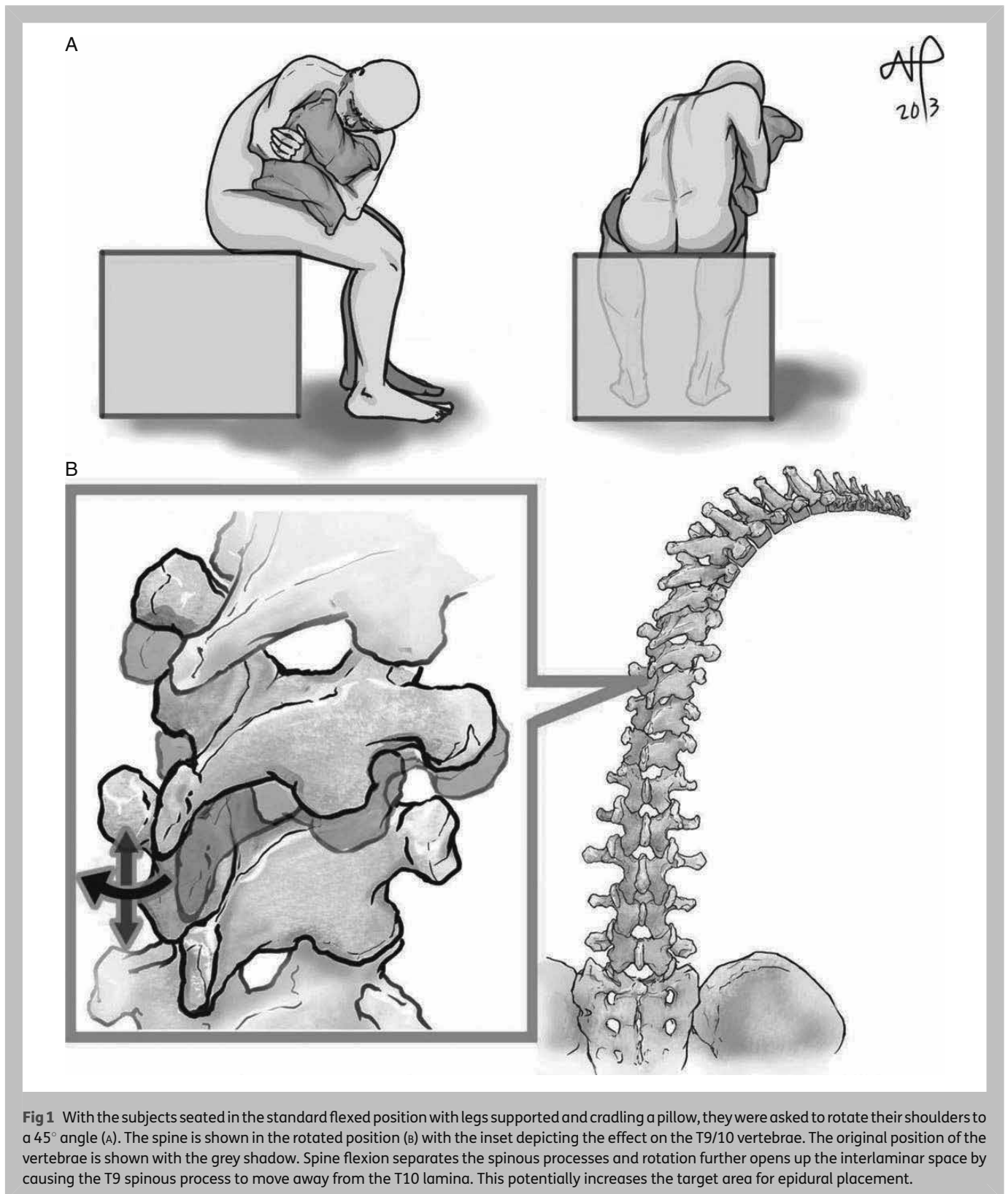


Fig 1 With the subjects seated in the standard flexed position with legs supported and cradling a pillow, they were asked to rotate their shoulders to a 45° angle (A). The spine is shown in the rotated position (B) with the inset depicting the effect on the T9/10 vertebrae. The original position of the vertebrae is shown with the grey shadow. Spine flexion separates the spinous processes and rotation further opens up the interlaminar space by causing the T9 spinous process to move away from the T10 lamina. This potentially increases the target area for epidural placement.

with the Kolmogorov–Smirnov (Lilliefors’ significance correction) and the Shapiro–Wilk checks. Intraclass coefficients (one-way random effects model) were used to evaluate the reliability and repeatability of the PLL measurements

performed by the two different anaesthesiologists. All data analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (Version 20.0), IBM Corporation, Armonk, NY, USA.



Fig 2 Illustration of 10° dorsal table tilt position. The subject in the image is demonstrating the P3 position (slouching of the shoulders with lumbar flexion and exaggeration of the thoracic kyphosis with arms around a pillow at chest level accompanied by 10° dorsal table tilt).

Results

Thirty volunteers participated; of which, 20 were males and 10 females. The mean (SD) age was 39.4 (10.1) yr; BMI was 24 (3.8) kg m⁻², with the mean height and weight being 174 (9.8) cm and 72.9 (3.8) kg, respectively.

In all eligible cases, the epidural space at T9–10 was easily identified on ultrasonography and the quality of ultrasound images was comparable with previous studies.^{4, 7–9} The characteristic acoustic shadow was seen anterior to the laminae corresponding to that of T9 and T10. The ligamentum flavum was seen as a hyperechoic structure and deeper to it was the hyperechoic PLL. The quality of the PLL images (Fig. 3) was good (Weed score >9).⁴ The superior and inferior limits of the PLL were sufficiently and clearly demarcated on the images to enable precise measurement of length with the onscreen caliper tool.

In all subjects, all images were successfully saved and archived, and there was no loss of data during screen capture mode, measurement mode, and archive retrieval mode. There was a progressive and significant increase in the length of the PLL in positions 2, 3, and 4 when compared with the neutral position 1, as shown in Table 1. In comparison with the standard flexed position for epidural insertion (P2), a 10° table tilt in addition to flexion (P3) and rotation (ipsilateral to the transducer) with flexion (P4) significantly increased the length of the visualized PLL (Table 1). Rotation (contralateral to the transducer) with flexion (P5) did significantly change the PLL length compared with position 1 but not compared with position 2. The correlation coefficient for measurement

of the PLL length by the two independent anaesthesiologists was 0.612 ($P < 0.05$).

Discussion

In this study, we measured the length of the PLL with ultrasonography to estimate the size of the interlaminar 'acoustic target window' for thoracic (T9–10) paramedian epidural access. We demonstrated that compared with the traditional flexed position for epidural placement, flexion with 10° dorsal table tilt and flexion with right rotation significantly increased the visualized length of the PLL as a measure of the acoustic target window.

The PLL as measured in our study and in previous studies is a composite echo of the anterior dura, PLL, and posterior vertebral body as it is not possible to delineate these structures as separate entities using currently available ultrasound technology.^{4, 7, 8} Distinguishing between the PLL, anterior dura, and vertebral body is difficult and not relevant for the objective of our study. The rationale for using the PLL is based on the premise that an 'open acoustic window' is suggestive of an unobstructed path of the ultrasound energy to pass between the laminae through the dura, to the PLL. The PLL has previously been validated as a useful tool for assessment of the acoustic target window for neuraxial needle placement in the lumbar spine. In 60 adults undergoing lower extremity joint surgery under spinal anaesthesia, Weed and colleagues⁴ demonstrated that the positive predictive value of a low PLL score (0–8, indicative of poor visibility) was 82%, which was associated with a greater number of needle passes and increased technical difficulty with lumbar spinal anaesthesia. The positive likelihood ratio of a low PLL score was 12.8 and the negative likelihood ratio was 0.55, indicating that poor PLL visualization is associated with a high diagnostic yield for identification of technical problems with neuraxial access. The rationale for using the paramedian view is based on the study by Grau and colleagues¹⁶ who imaged the spine in 60 individuals and found that the paramedian approach provided superior images of the neuraxial structures and a larger paramedian window compared with transverse and midline longitudinal approaches.

Visualization of the PLL and the clinical relevance of the observed changes in PLL length with position in our study also merit further discussion. Like Chin and colleagues,^{13, 14, 18} we found that the PLL was easily identifiable in all subjects in the thoracic region and was a reliable landmark for measurement. Interestingly, Jones and colleagues⁹ demonstrated an increase in the size of the acoustic target area by application of dorsal table tilt in the lumbar region but could not demonstrate any effect on interlaminar distances. However, we did not measure ligamentum flavum length as it is thin in the thoracic region and could not be reliably seen by ultrasound.^{13, 15, 17} In addition, the interlaminar distances were not measured because the corresponding measurement points on the laminae could not reliably be identified when subjects changed positions. The PLL, however, was the one structure that could be reliably visualized in the thoracic region in our

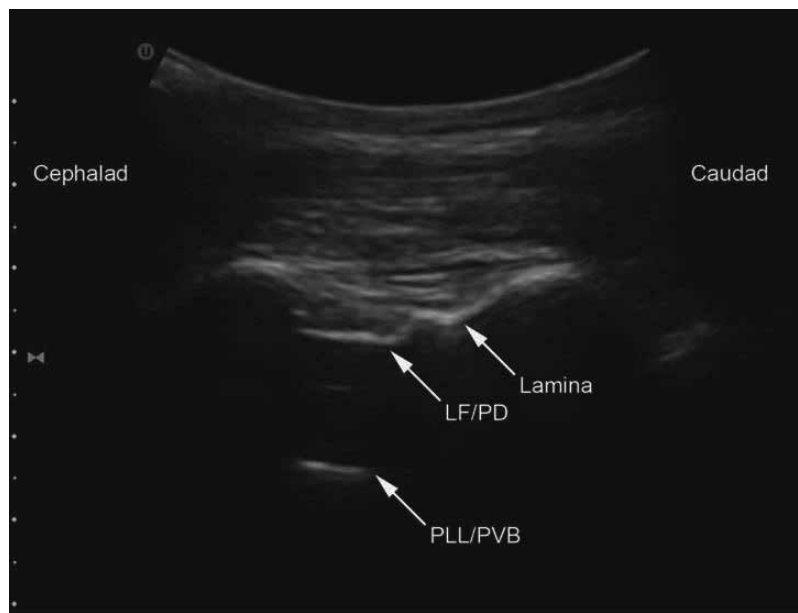


Fig 3 Paramedian longitudinal ultrasound image showing the lamina, ligamentum flavum (LF)/posterior dura (PD), and the PLL/posterior vertebral body (PVB) between the lamina of T9 and T10.

Table 1 Lengths of the PLL (in mm) visualized by right-sided paramedian ultrasonography, at T9/10 intervertebral level, in five differing positions mean (sd), and summary of statistical differences between the neutral position (P1) and posterior–anterior flexion (P2) compared with each of the other study positions

Volunteer position	P1 (Neutral)	P2 (PA flexion)	P3 (PA flexion and dorsal table tilt to 10°)	P4 (PA flexion and right ipsilateral rotation)	P5 (PA flexion and left contralateral rotation)
Posterior longitudinal ligament length	9.9 (3.958)	11.79 (3.427)	12.9 (3.144)	13.83 (4.027)	11.14 (3.159)
<i>P</i> -value compared with position P1		<0.01	<0.01	<0.01	<0.05
<i>P</i> -value compared with position P2	<0.01		<0.01	<0.01	0.1

study and in part this could be due to the significantly larger acoustic window to shadow ratio in the paramedian view¹⁶ and the image quality of the PLL (Fig. 3) was good (Weed score >9).⁴

Our principal finding was that dorsal table tilt and rotational movements of the spine increased the acoustic target area in the thoracic spine as indicated by the length of the PLL. Theoretically, a larger ‘target window’ should translate into a decreased incidence of bony contact and improve the success rate for correct placement of a needle for thoracic epidural anaesthesia. The magnitude of changes in the mean PLL length (from 9.9 to 13.8 mm) found in our study is comparable with changes in the mean ligamentum flavum length (from 10.7 to 11.2 mm) reported by Jones and colleagues.⁹ Since an epidural needle is ~1 mm in diameter, changes of such magnitude could theoretically make a difference in successful

access to the epidural space and is therefore clinically relevant. Our findings could also provide a scientific basis to a management algorithm whereby difficult epidural access in the standard position could be followed by an attempt in one of the other positions presented in this study.

Explanation of our findings is based on the functional anatomy and biomechanics of the spine.¹⁹ In the lumbar spine, flexion is the principal mechanism for widening the interspinous and interlaminar spaces to facilitate neuraxial access. In the thoracic region, the thoracic vertebrae permit flexion and rotation of the spine to open the interlaminar space.¹⁹ Based on published literature on kinematics and biomechanics of the spine, flexion of the spine at each interspace increases moving caudally down the thoracic spine; with 3–5° of movement at T1–2 and increasing to 6–20° at T11–12.¹⁹ Maximal flexion at the T9–10 interspace studied here has

been reported to be 8°. The application of dorsal table tilt most likely augments the degree of comfortable flexion achieved by a patient in the standard flexed position. Rotation of the spine in either direction at each interspace decreases moving caudally down the spine; at T1–2, there is between 4° and 14° of movement, at T9–10, there is 3–5° and decreases to 2–3° at T11–12.^{19 20} With rotation, there is separation of the adjacent laminae and the spinous process sweeps away from the midline to open up the interlaminar space. This has not been previously studied as a potential manoeuvre to aid in epidural placement.

In this study, the ultrasound operator and the anaesthesiologist making the initial measurements could not be blinded to the patient position. To minimize reactive bias, the scanning anaesthesiologist was not allowed to see the PLL measurements and all PLL measurements were made by the second anaesthesiologist after all five scans had been saved in each patient. To further address observer and measurement bias, an independent consultant, blinded to the volunteer positions and previous PLL measurements, re-measured the PLL length on the archived images as suggested by Jones and colleagues.⁹ These data were utilized to obtain an intraclass correlation coefficient showing good agreement between the two measurements of PLL length. The order in which volunteers were positioned for scanning was not randomized because it was not practical or conducive to a systematic scanning technique. All our volunteers were young and healthy and had no difficulty assuming the required positions. Elderly, obese, and pregnant patients may not be able to tolerate these positions, so our study results may not be applicable to all populations. Two operators identified the start and endpoints of the visualized PLL to minimize structural identification error. The intrinsic software calculated the numerical value to minimize measurement inaccuracies. An important limitation of our study is that although the visualized portion of the PLL is increased in flexion-dorsal table tilt and flexion-right rotation, it can only be postulated that this increase in the 'acoustic target window' will translate into easier epidural insertion. Even though the study by Weed and colleagues⁴ is highly supportive of PLL as a predictor of difficult neuraxial insertion, the same cannot be said for our study until further validation in the form of clinical studies, which correlate PLL length in the thoracic region with the level of difficulty for epidural needle insertion.

We conclude that positioning the patient with either 10° of dorsal table tilt in flexion or right rotation in flexion increases interlaminar space as measured by an increased PLL length. Further clinical studies are required to determine if these positions improve the success rate of thoracic epidurals and allow for an easier and more efficient insertion.

Authors' contributions

N.R.: design, conduct of study, data analysis, and manuscript preparation; J.W.: design, conduct of study, data analysis, and manuscript preparation; R.T.: study design, conduct of

study, and manuscript preparation; H.V.: study design and manuscript preparation; A.S.: conduct of study and manuscript preparation.

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Declaration of interest

R.T. and A.S. both received equipment and travel support from Ultrasonix and acted as consultants for Ultrasonix in 2012.

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CARDIOVASCULAR

Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery

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Editor's key points

- The perioperative use of colloid solutions has potential benefits in cardiac surgical patients, but may affect coagulation.
- In this randomized study of 240 patients, the use of high volumes of colloid (50 ml kg⁻¹ day⁻¹) had no effect on the primary outcome measure, blood loss from chest drains.
- However, blood transfusion requirements were lower when a crystalloids-only fluids regimen was used.
- The infusion of high volumes of colloids caused more haemodilution and had greater adverse effects on coagulation.

Background. Infusion of 5% human albumin (HA) and 6% hydroxyethyl starch 130/0.4 (HES) during cardiac surgery expand circulating volume to a greater extent than crystalloids and would be suitable for a restrictive fluid therapy regimen. However, HA and HES may affect blood coagulation and could contribute to increased transfusion requirements.

Methods. We randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml kg⁻¹ day⁻¹ of either HA, HES, or Ringer's lactate (RL) as the main infusion fluid perioperatively. Study solutions were supplied in identical bottles dressed in opaque covers. The primary outcome was chest tube drainage over 24 h. Blood transfusions, thromboelastometry variables, perioperative fluid balance, renal function, mortality, intensive care unit, and hospital stay were also assessed.

Results. The median cumulative blood loss was not different between the groups (HA: 835, HES: 700, and RL: 670 ml). However, 35% of RL patients required blood products, compared with 62% (HA) and 64% (HES group; $P=0.0003$). Significantly, more study solution had to be administered in the RL group compared with the colloid groups. Total perioperative fluid balance was least positive in the HA group [6.2 (2.5) litre] compared with the HES [7.4 (3.0) litre] and RL [8.3 (2.8) litre] groups ($P<0.0001$). Both colloids affected clot formation and clot strength and caused slight increases in serum creatinine.

Conclusions. Despite equal blood loss from chest drains, both colloids interfered with blood coagulation and produced greater haemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.

Keywords: blood loss; coagulation; colloids; fluid regime; Ringer's lactate; rotation thromboelastometry; transfusion

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Controversy exists about the optimal perioperative fluid management in patients undergoing major surgery. Prevention of fluid overload intraoperatively has been associated with less postoperative complications.¹ In addition, the transfusion of packed red blood cells (PRBCs) is associated with increased morbidity and mortality after cardiac surgery.² Thus, avoiding transfusion might also be important to improve outcome of patients undergoing cardiac procedures.

Crystalloids, in the form of Ringer's lactate (RL), and colloids such as hydroxyethyl starches and 5% human serum albumin (HA) are commonly used for intraoperative fluid management during heart surgery. The latter two have a more profound volume expansion effect than crystalloids and would therefore

be more suitable for a restrictive fluid therapy.³ However, hydroxyethyl starch solutions have been shown to impair coagulation^{4,5} and renal function.^{6–11} Six per cent hydroxyethyl starch 130/0.4 [Voluven®] (HES) is a newer generation tetra-starch formulation with a lower molecular weight, which might affect coagulation to a lesser degree than hydroxyethyl starch solutions with higher molecular weight.^{12–15} However, a recent meta-analysis stated that insufficient data are available for the effect of HES on the bleeding tendency in cardiac patients.¹⁶ In comparison with HES, HA has been used since the 1970s during cardiac surgery mainly for two reasons: first, HA is able to coat the fluid pathway surface and thereby reduces platelet activation and consumption

with concomitant release of inflammatory mediators.^{3 17–19} Secondly, HA prevents a substantial decrease in colloid oncotic pressure.²⁰ Likewise, RL has also been used for many years during heart surgery, either as the sole replacement fluid or in combination with HA or HES.²¹ Since large volumes are generally administered throughout the procedure, even RL might influence coagulation via dilution of coagulation factors.

We hypothesized that 6% HES 130/0.4 would increase blood loss from the chest drains. Thus, the main objective of our study was to compare external blood loss from chest drains between groups receiving HA 5%, 6% HES 130/0.4, or RL as the main infusion during cardiac surgery. Blood transfusions, total perioperative fluid balance, thromboelastometry variables, course of serum creatinine and platelet count, intubation time, intensive care unit (ICU), and hospital stay were also assessed.

Methods

Participants

This randomized, double-blind, single-centre trial, which was conducted over the course of four consecutive years at our department was approved by the institutional review board and reported to the national regulatory authority (Gov Identifier: NCT 01174719). All 240 patients provided written informed consent before inclusion. Inclusion criteria were: patients undergoing elective cardiovascular surgery [i.e. coronary artery bypass grafting (CABG), valve repair or replacement, and surgery of the ascending aorta] on cardiopulmonary bypass (CPB). Exclusion criteria were known allergy to hydroxyethyl starch or albumin, preoperative anaemia, emergencies, treatment with acetylsalicylic acid <3 days before surgery, GPIIb/IIIa antagonists use <7 days before surgery, coagulation disorders [i.e. INR >1.2, activated partial thromboplastin time (aPTT) >40 s, platelet count <100 g litre⁻¹], BMI >40 kg m⁻², left ventricular ejection fraction <20%, renal dysfunction defined as serum creatinine >1.5 mg dl⁻¹, proven heparin-induced thrombocytopenia, and danaparoid or lepirudin treatment during the month before the operation.

Randomization, fluid regimen, and blinding

Eligible patients were randomized into three groups comprising 80 patients each with the following fluid regimens:

HA group: 5% albumin up to 50 ml kg⁻¹ day⁻¹, additional RL as required;

HES group: 6% HES 130/0.4 up to 50 ml kg⁻¹ day⁻¹, additional RL as required;

RL group: RL up to 50 ml kg⁻¹ day⁻¹, additional RL as required.

An independent IT specialist was in charge of randomization, which was performed using a random number generator. The local pharmacy prepared the study solutions that were supplied in identical 250 ml bottles. Blinding was performed with the help of opaque covers that were placed around the bottles and the infusion sets.

Procedures

Anaesthesia was induced with midazolam (0.1 mg kg⁻¹), propofol (1.0–1.5 mg kg⁻¹), fentanyl (3–10 µg kg⁻¹), and cisatracurium (0.2 mg kg⁻¹) and maintained with sevoflurane (target BIS value 40–50), and fentanyl (0.05–0.1 µg kg⁻¹ min⁻¹). Fluid administration was started with 250–500 ml of the study solution during induction of anaesthesia. The CPB circuit was primed with 1500 ml study solution together with 5000 IE heparin, and 100 ml mannitol 20%. Patients received either aprotinin (10⁶ IU after anaesthesia induction plus 10⁶ IU added to the CPB prime) or tranexamic acid (either 1.0 or 1.5 g after anaesthesia induction plus the same dosage in the CPB prime according to the patient's body weight and renal function). Tranexamic acid was used as antifibrinolytic after November 2007 when sale of aprotinin was suspended by Bayer. After anticoagulation with heparin (300 IE kg⁻¹) and achieving an activated clotting time (ACT) >400 s, CPB was performed using non-pulsatile flow at 2.5 litre min⁻¹ m⁻², a non-heparin-coated circuit, and a membrane oxygenator (Quadrox™, Maquet, Hirrlingen, Germany, or Dideco Compactflow™, Mirandola, Italy). Mild-to-moderate hypothermia was induced (30–34°C) and norepinephrine was given if necessary to maintain a mean arterial pressure > 60 mm Hg. Buckberg cardioplegic solution was used for myocardial preservation. Additional RL was added to the extracorporeal circuit when filling of the CPB reservoir was insufficient. During and after weaning from CPB, transoesophageal echocardiography was used to monitor myocardial performance and the impact of fluid loading and inotropic support on ventricular function. Further fluid management and also vasopressors and/or inotropic use was at the discretion of the attending consultant and not controlled by protocol. All study cases were performed by experienced cardiac anaesthesia fellows supervised by senior cardiac anaesthesiologists. Intraoperative fluid therapy with study solution was restricted to two-thirds of the maximally allowed daily dose (i.e. 33.3 ml kg⁻¹). It was assumed that anaesthesia and surgery would require a greater fluid load than the immediate postoperative period. Additional fluid requirements were met with RL in order to avoid accidental overdosage of either of the two colloids. The last third of the study solution (i.e. 16.7 ml kg⁻¹) was kept for the initial volume replacement in the ICU that also guaranteed that the total permitted dose would not be administered within a short period of time.

Rotation thromboelastometry (ROTEM® Pentapharm CO, Munich, Germany) *ex vivo* coagulation variables were examined using predefined tests: INTEM (ellagic acid activated intrinsic pathway) and FIBTEM (with platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation).²² The samples were analysed within 120 s after blood was drawn from the central venous catheter and coagulation was initiated with activators using a semi-automated electronic pipette system according to the manufacturer's instructions. Coagulation was allowed to proceed for 50 min. Automatic ROTEM variables were: clotting time (CT), clot formation time (CFT), α -angle, maximum clot firmness (MCF), and clot lysis.

These variables have been validated using standard coagulation tests.^{22 23} ROTEM quality control measures were undertaken weekly by our laboratory staff. Reference ranges for ROTEM thromboelastometry variables were taken from a multi-centre investigation.²⁴

Blood transfusion was performed according to STS-SCA transfusion guidelines.^{25 26} Transfusion triggers for the transfusion of PRBCs were: haemoglobin (Hb) concentrations of ≤ 7.0 g dl⁻¹ during and ≤ 8.0 – 9.0 g dl⁻¹ after CPB.

Administration of fresh-frozen plasma, platelets, and coagulation factors was based predominantly on ROTEM variables and the pre- and postoperative coagulation profile of each patient. After appropriate reversal of residual heparin, fresh-frozen plasma and factor concentrates were given in the presence of prolonged CT and CFT_{INT} and normal ACT. Fibrinogen was given when MCF_{FIB} was < 8 mm, and platelets were transfused when MCF_{FIB} was > 8 mm. In the ICU, Normotest[®] > 1.5 , aPTT > 60 s, fibrinogen concentration < 1 g litre⁻¹, and platelet count $< 50 \times 10^9$ litre⁻¹ prompted transfusion of fresh-frozen plasma, platelets, or both.

Outcome variables

The primary outcome variables were clinical bleeding based on chest tube drainage over the first 24 h after CPB. Secondary outcomes were transfusion of PRBCs, fresh-frozen plasma, platelets, fibrinogen, factor concentrate, changes in Hb, thromboelastometry variables, and the total amount of study solution, total amount of administered fluid, fluid balance, intubation time, and length of hospital stay. Furthermore, the units of PRBC transfused within the second and the sixth postoperative day (POD), and also the course of Hb, platelets, and creatinine until POD 6 were compared between the groups. Δ creatinine was calculated as maximal creatinine value within 48 h minus baseline creatinine.²⁷ Since aprotinine was replaced by tranexamic acid during the investigation period, we also compared utilization of these agents between the groups. Hb levels were compared at the start of anaesthesia (baseline), after release of the aortic cross-clamp (surgery), upon arrival in the ICU, 24 h after surgery, and on the morning of the sixth POD. The length of stay in the ICU and mortality within 90 days were recorded as safety variables.

Statistical analysis

The sample size calculation was based on data from our institutional data bank, where the actual blood loss from 99 CABG patients was found to be 714 ml with a standard deviation (SD) of 370 ml. The study was powered to detect a difference in blood loss of 185 ml (i.e. half SD) between the active control (RL) and HA or HES with a type I error rate of 0.05 and a power of 0.08 for a two-sided *t*-test with correction for multiple comparisons. Consequently, a sample size of 80 patients per group was required.

Data are given as mean (SD). Non-normally distributed variables are expressed as median (25% and 75% percentiles). Non-parametric statistical tests were used for analysis if no normal distribution could be achieved by log transformation.

Analyses of variance models were used for comparison of the log-transformed cumulative blood loss over 24 h after surgery, the infused study medication, and the cumulative postoperative fluid balance over 24 h between the three groups. Repeated-measures analyses of covariance (ANCOVA) models were used to test for differences in the log-transformed MCF_{FIB} and CFT_{INT} values between study groups, considering baseline values as covariates and time (arrival at the ICU vs 24 h after surgery) as repeated factor. Repeated-measure ANCOVA was also used for comparison of Hb, platelets, and creatinine levels between the groups, additionally considering values during surgery in the model. For all pair-wise comparisons between the study groups, the Tukey *post hoc* test was used to adjust for multiple comparisons. The non-parametric Kruskal–Wallis test was used to test for differences in non-study fluids, cumulative dose of study fluid expressed as ml kg⁻¹ day⁻¹, crystalloid to colloid ratio, intubation time, urine output, and Δ creatinine values between the groups. The χ^2 test was used to compare frequencies of patients receiving PRBC, FFP, platelets, fibrinogen, and factor concentrates between study groups. All *P*-values are reported as results of two-sided tests and values of < 0.05 were considered statistically significant.

Results

A total of 240 patients randomized into three groups were included in the study. Patients' characteristics and intra- and postoperative data are shown in Table 1. Four patients were excluded for the following reasons: one patient from the HA group developed urticaria after induction of anaesthesia and the study was terminated as a possible allergic reaction to the study solution could not be ruled out. Another three patients, two from the HA group and one from the RL group, were either haemodynamically unstable or became hypoxaemic after CPB and required either support with an intraaortic balloon pump or ECMO. Minor violations of the study protocol occurred in two patients. One patient mistakenly received 1000 ml Voluven[®] and another patient 600 ml of HA during the ICU stay within the study period, without being excluded from the study. Unblinding revealed that both patients were in the HES group. However, in the first patient, the cumulative amount of colloids (HES as study solution and additional Voluven[®]) did not exceed 50 ml kg⁻¹ day⁻¹. In the second patient, the sum of the administered study solution and the given HA was also within the tolerable range of 50 ml kg⁻¹ day⁻¹. Owing to inappropriate filling of an HA bottle with HES by our pharmacy, the HES group comprised 81 patients and the HA group only 79; of whom, three patients had to be excluded as mentioned above. The recruitment profile is depicted as a CONSORT flow diagram in Figure 1.

Although there was a trend towards lower blood loss over chest tubes in the RL group, the primary study endpoint, namely chest tube drainage over 24 h after surgery, was not significantly different between the groups ($P=0.085$; Table 2). There was, however, a significant group difference in the quantity of blood transfusion ($P=0.0004$). Patients in the RL group

Table 1 Patients' characteristics and perioperative data. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; ESL, logistic EuroSCORE; BMI, body mass index; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; VR, valve replacement or reconstruction; Combined procedure: valve and CABG surgery, or double valve replacement or valve replacement with composite graft; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; ICU, intensive care unit; vasopressors use is defined according to SOFA score; RRT, renal replacement therapy. Values are either: numbers (n), percentages (%), means (sd), medians (25/75% percentile), or medians (lowest–highest value). * $P < 0.05$ compared with colloid groups

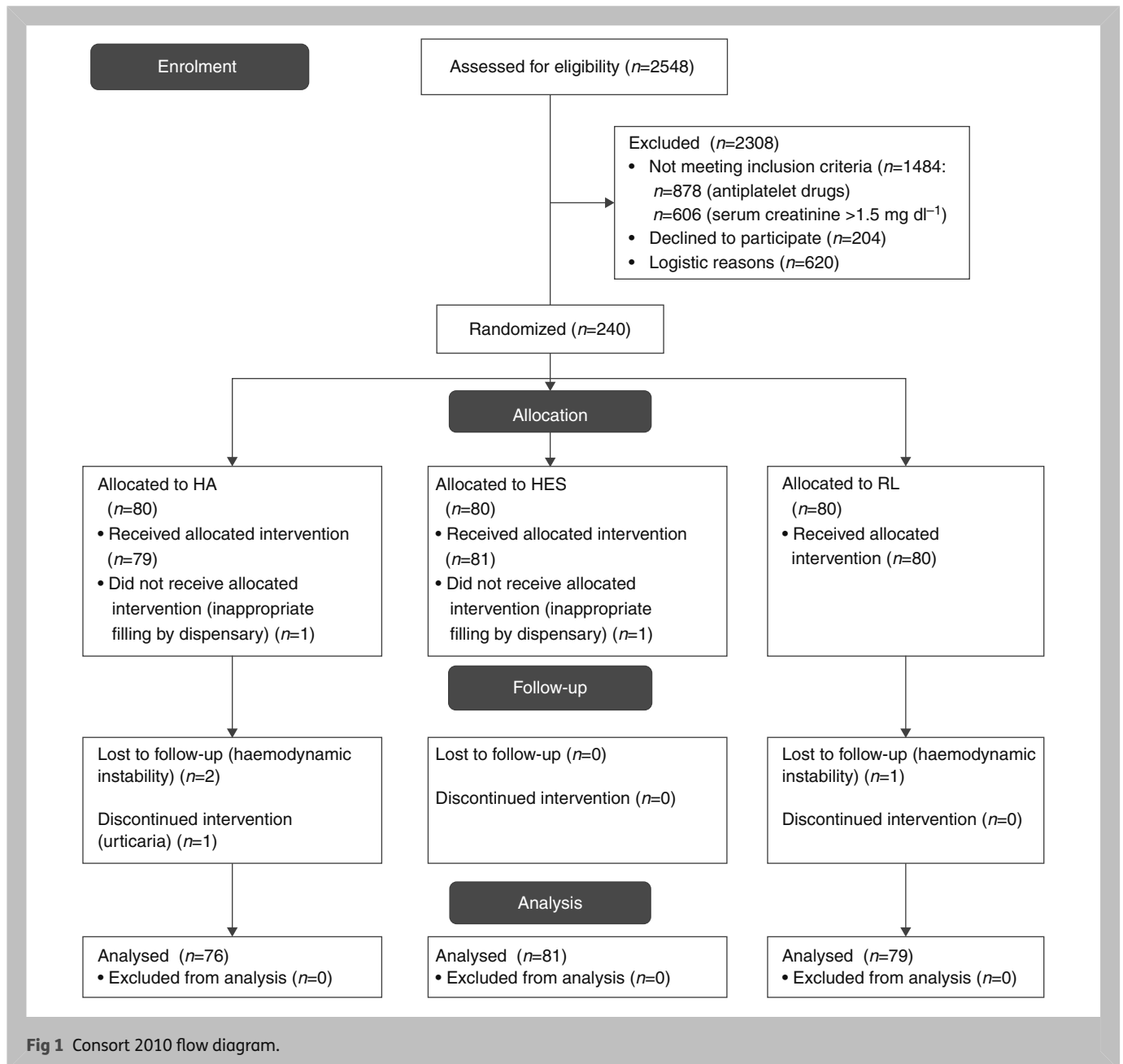
	HA (n=76)	HES (n=81)	RL (n=79)
Patient characteristics			
Male/female (n)	53/23	52/29	61/18
Age (yr)	66 (23–85)	67 (28–87)	67 (24–87)
BMI (kg m^{-2})	27 (4)	27 (4)	27 (4)
ESL	5 (6)	6 (6)	5 (5)
LVEF (%)			
>50	33	34	33
30–50	29	36	35
<30	34	33	33
Type of surgery (%)			
CABG	37	33	30
VR	29	37	34
Combined procedure	32	32	36
Duration (min)			
Anaesthesia	333 (74)	328 (76)	314 (55)
CPB	107 (32)	99 (42)	105 (40)
ACC	70 (23)	64 (29)	71 (28)
Use of antifibrinolytics (n)			
Aprotinin	24	24	25
Tranexamic acid	52	55	54
Use of vasopressors (%)			
Low	70	75	72
High	59	54	56
Postoperative data			
Time to extubation (min)	580 (455/735)	562 (485/824)	530 (450/725)
ICU stay (day)	1 (1/16)	1 (1/48)	1 (1/16)
Hospital stay (day)	14 (7/66)	14 (8/55)	13 (6/164)
Δ Creatinine _{0–48 h} (mg dl^{-1})	0.06 (–0.02/0.15)	0.02 (–0.05/0.11)	–0.02* (–0.13/0.07)
RRT (n)	2	1	0
Mortality 90 day (n)	2	1	0

received fewer PRBCs compared with HA ($P=0.0015$) and HES patients ($P=0.0002$). In addition, the percentage of patients receiving either PRBCs or any blood product was significantly lower in the RL group. In contrast, there was no difference for both variables when HA and HES patients were compared (Table 2). Most units of PRBC were given perioperatively during the first 24 h. There were no significant group differences in the number of PRBC units transfused within PODs 2–6 [HA: 2.04 (0.45); HES: 2.14 (0.79); RL: 2.15 (0.91) $P=0.544$]. Most PRBC units transfused during this period were ordered between POD 3 and 5. No significant inter-group differences were noted for transfused FFP and platelets. A greater percentage of patients in both colloid groups received fibrinogen. Regarding the amount of coagulation factor concentrates, no significant differences were found between the three groups.

Changes in Hb levels over time and between the groups were significantly different (Fig. 2). During surgery, Hb significantly

declined from baseline in all groups. However, patients in the RL group showed the least decline during surgery ($P < 0.0001$) and at arrival in the ICU ($P < 0.0001$). Twenty-four hours after surgery, patients in the HA group presented with the lowest Hb values compared with the HES ($P < 0.0001$) and the RL group ($P < 0.0001$). No difference was observed between HES and RL patients at this time point. Likewise, no difference was noted in Hb values among the three groups on POD 6 [HA: 10.1 (1.3), HES: 10.3 (1.1) RL: 10.2 (1.1)]. Similar changes were found for platelet count until POD 6 (Fig. 3B).

ROTEM thromboelastometry variables are depicted in Table 3. MCF_{FIB} values decreased in all groups during surgery but remained within the reference range in the HA and the RL groups. The lowest value was observed in the HES group at arrival in the ICU ($P < 0.0001$). An increase in MCF_{FIB} values was found in all groups between arrival in the ICU and 24 h after surgery ($P < 0.0001$). Values in the HA group were



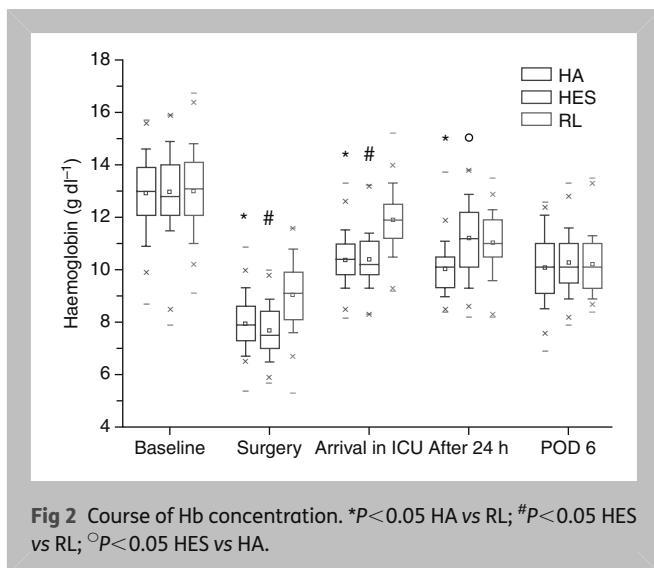
significantly lower at this time point when compared with the HES ($P=0.027$) and the RL group ($P<0.001$). No statistically significant difference was found between the RL and the HES groups ($P=0.083$). CFT_{Int} values increased intraoperatively. They were significantly different ($P<0.0001$) between the groups on ICU arrival with the highest values being detected in the HES group and the lowest in the RL group. Twenty-four hours after surgery, the HA group showed significantly prolonged CFT_{Int} than patients of the RL ($P<0.0001$) and the HES groups ($P=0.004$). No significant difference was found between the HES and the RL groups at this time ($P=0.193$).

We recorded statistically significant group differences regarding the total amount of infused study solution

($P=0.0024$). We observed no difference between the colloid groups but significant differences between HA and RL ($P=0.0051$), and also HES and RL, respectively ($P=0.0016$; Table 4). Similarly, the fluid balance was significantly different between the groups ($P<0.0001$). The HES group had a more positive total fluid balance than the HA group ($P=0.0116$), and the RL group an increased fluid balance compared with both HES ($P=0.0262$) and HA ($P<0.0001$). The crystalloid to colloid ratio was lower in the HA relative to the HES group ($P=0.028$). There were no group differences regarding urine output ($P=0.952$, Table 4). Serum creatinine levels were significantly higher in the HA group immediately after surgery when compared with the HES and RL groups and remained elevated

Table 2 Chest tube drainage and transfusions until the first 24 h after surgery. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; PRBCs, packed red blood cells; FFP, fresh frozen plasma. Chest tube drainage and PRBCs are expressed as median (25/75% percentiles). All other variables are depicted as percentages. *P*-value as determined by univariate analysis

	HA (n=76)	HES (n=81)	RL (n=79)	<i>P</i> -value
Chest tube drainage (ml)	835 (545/1253)	700 (540/1090)	670 (455/1015)	0.0850
PRBCs (ml)	300 (0/600)	300 (0/600)	0 (0/300)	0.0004
PRBCs (units)	1 (0/2)	1 (0/2)	0 (0/1)	0.0004
PRBCs intraoperative (ml)	0 (0/600)	0 (0/600)	0 (0/300)	0.0119
PRBCs postoperative (ml)	0 (0/275)	0 (0/250)	0 (0/0)	0.0333
FFP (%)	8	10	5	0.5152
Platelets (%)	7	14	5	0.1186
Fibrinogen (%)	12	16	4	0.0383
Factor concentrate (%)	3	6	3	0.3921
Percentage of patients receiving				
PRBCs (%)	58	61	34	0.0013
Any blood product (%)	62	64	35	0.0003



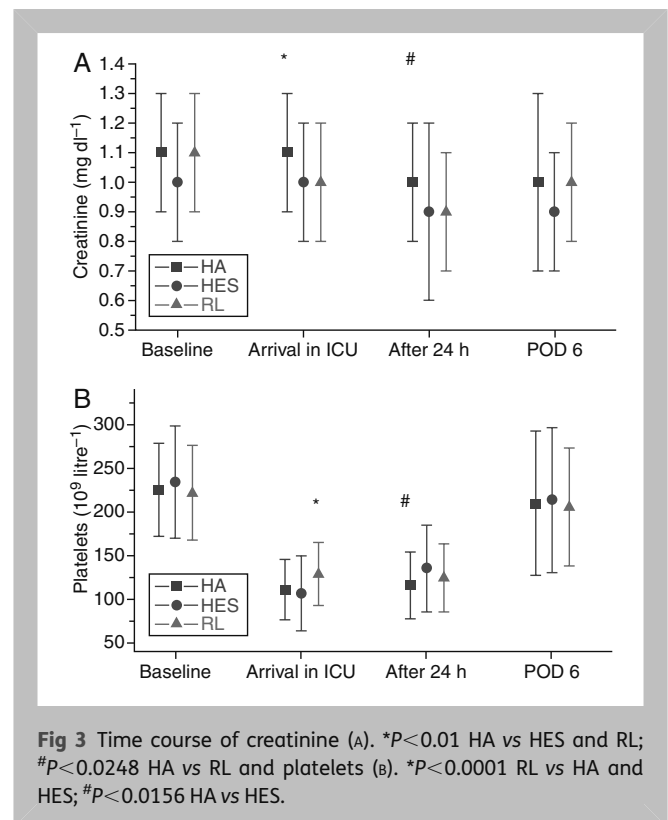
in relation to the RL group 24 h after surgery (Fig. 3A). Δ Creatinine only increased in the colloid groups (Table 1).

Ten patients, seven in the HES and three in the HA group, required reexploration for bleeding, either on the day of surgery or on POD 1. One patient in the HES and one in the HA group, and also two patients of the RL group had reoperations after POD 5. Three patients died within 90 days, one in the HES group (1.2%) and two in the HA group (2.5%) (Table 1).

Usage of the two different antifibrinolytic agents was not significantly different between the groups (*P*=0.982; Table 1).

Discussion

This is the first randomized controlled trial that directly compares the new-generation 6% hydroxyethyl starch 130/0.4 [Volumen®] (HES) and HA against RL for fluid management during cardiac surgery. Two hundred and forty patients were included and randomized in three groups with 80 patients



per group. We used large volumes of fluid, as $50 \text{ ml kg}^{-1} \text{ day}^{-1}$ is the upper recommended daily limit for HES. We deliberately chose this dosage to maximize the chance of demonstrating a significant effect. We found that fluid therapy with neither study solution caused increased external blood loss via chest tubes after operation. However, transfusion of PRBC and transfusion of any blood product during the first 24 h of the study were increased in both colloid groups, both intraoperatively and after operation.

Table 3 Thromboelastometry analysis. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; CFT, clot formation time; MCF, maximal clot firmness. *P*-values are given as determined by univariate analysis. **P*<0.05 RL vs HES; #*P*<0.05 HA vs RL; †*P*<0.05 HES vs HA; NS, not significant (according to *post hoc* analysis). Values are expressed as medians (25/75% percentile)

	HA (n=76)	HES (n=81)	RL (n=79)	<i>P</i> -value
CFT _{INT} (reference range: 40–100 s)				
Baseline	69 (57/82)	69 (57/81)	74 (64/83)	NS
Arrival in ICU	137 (111/175) [#]	185 (137/253) [†]	107 (85/138)*	<0.0001
After 24 h	100 (85/125) [#]	89 (75/112) [†]	84 (71/109)	0.0042
MCF _{FIB} (reference range: 9–25 mm)				
Baseline	19 (15/22)	19 (15/22)	18 (15/21)	NS
Arrival in ICU	10 (9/13) [#]	7 (6/10) [†]	13 (11/17)*	<0.0001
After 24 h	15 (13/19) [#]	18 (14/21) [†]	18 (16/20)	0.0266

Table 4 Perioperative fluids, fluid balance, and urine output. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate. Values for fluid balance are expressed as means (SD). Study solution, non-study fluids, cumulative doses of study solution as ml kg⁻¹ day⁻¹, crystalloid to colloid ratio, and urine output as non-normally distributed values are expressed as medians (25/75% percentile). *P*-value is given for the univariate analysis. Non-study fluids are including crystalloid solutions, analgesics, antibiotics, and glucose–electrolytes. Fluid balance was calculated from infused study solution, non-study fluids, transfusions, fibrinogen, factor concentrate, and urine output and also blood loss from drainage

	HA (n=76)	HES (n=81)	RL (n=79)	<i>P</i> -value
Study solution (ml)				
Intraoperative	2500 (2250/3000)	2500 (2250/2750)	3000 (2500/3500)	<0.0001
Postoperative	750 (500/1000)	625 (500/1000)	750 (500/1000)	0.7717
Total	3250 (2750/3750)	3000 (2750/3500)	3500 (3000/4000)	0.0027
Non-study fluids				
Intraoperative	2800 (2250/3557)	2350 (1900/2900)	3450 (2474/4350)	<0.0001
Postoperative	4757 (3102/5407)	5450 (4380/7090)	5570 (4350/6800)	0.0003
Total	7504 (5378/9147)	7870 (6902/10 220)	8700 (7419/11 143)	0.0006
Fluid balance (ml)				
Intraoperative	3969 (1173)	3573 (1125)	4836 (1298)	<0.001
Postoperative	2272 (1874)	3755 (2454)	3565 (2190)	0.0114
Total	6228 (2456)	7365 (2980)	8336 (2810)	<0.0001
Study solution (ml kg ⁻¹ day ⁻¹)	44 (34/49)	42 (35/48)	47 (41/49)	0.0084
Crystalloid to colloid ratio	1.4 (0.9/2)	1.7 (1.2/2.5)	NA	0.0281
Urine output _{0–24 h} (ml)	2705 (2010/3455)	2734 (1980/3400)	2930 (2070/3540)	0.9518

Our results are in line with published studies and meta-analyses comparing crystalloids and colloids for cardiac surgery. Colloids at all times produced a less positive fluid balance yet postoperative bleeding often did not differ between crystalloids and colloids.^{3 28} Studies comparing albumin with non-protein colloids during cardiac surgery were in the majority in favour of albumin regarding transfusion requirements and mortality.^{29–31} However, in those studies, older generation starches were used which consisted of high molecular weight molecules with high molar substitution and the new-generation HES 130/0.4 6% was not included. In contrast, perioperative volume replacement with up to 50 ml kg⁻¹ HES or 50 ml kg⁻¹ 4% human serum albumin in children undergoing congenital heart surgery resulted in fewer allogenic blood transfusions in the HES group compared with the albumin group (median: 18 vs 29 ml kg⁻¹).³² This was explained by a more

profound haemodilution induced by 4% albumin. Both colloids were, however, not compared against a crystalloid solution.

In a recent meta-analysis by Navickis and colleagues, it was concluded that hydroxyethyl starches were associated with increased blood loss, reoperation for bleeding, and blood product transfusion in relation to albumin after adult cardiac surgery. However, insufficient data still are available for HES.¹⁶ Previous trials investigating blood loss and transfusion requirements in adult cardiac surgery patients to date either compared HES with hydroxyethyl starch 200/0.5^{33 34} or HES with crystalloids.^{35 36} In two smaller studies (*n*=15 per group), Schramko and colleagues compared HES with Ringer's acetate and 4% gelatine³⁷ and with hydroxyethyl starch 200/0.5 and 4% albumin, respectively.³⁴ The latter, however, had no study arm with a crystalloid solution as an active control. No difference in blood loss and transfusion

requirement was found between HES and hydroxyethyl starch 200/0.5 given at a median dose of 33 ml kg^{-1} . After dual antiplatelet therapy, Lee and colleagues also could not find a difference in perioperative blood loss between crystalloids and HES when administered up to 30 ml kg^{-1} . Furthermore, Tiryakioglu and colleagues did not observe a negative effect on chest tube drainage and need for transfusion when 1500 ml HES was used for CPB prime instead of Ringer. Although the novel HES preparation was reported to have only a minimal effect on haemostasis,¹⁵ HES impaired fibrin formation and clot strength after cardiac surgery following a total dose of 15 and 28 ml kg^{-1} but did not negatively affect blood loss.^{34, 37} Similarly, in the study by Choi and colleagues,³⁸ both 500 ml HES and 500 ml HA in the pump prime negatively affected blood coagulation in patients undergoing mitral valve surgery. In contrast to data published by Schramko and colleagues,³⁴ both colloids (i.e. HA as well) equally prolonged fibrin formation and fibrin build-up, depressed the α -angle, depressed the maximal amplitude, and shear elastic modulus. Presumably, the HES and HA groups therefore also showed no difference in intra- and post-operative blood loss, in the amount of co-administered colloids and crystalloids, in urine output, and in the amount of transfused units of PRBC, FFP, and platelets. Again, both colloids were not compared against a crystalloid solution.

In contrast, patients in this trial received up to 50 ml kg^{-1} study solution. Therefore, dilution of coagulation factors and also platelets and platelet dysfunction should even be more pronounced. This could account for the increased CFT_{INT} in both colloid groups and the decreased MCF_{FIB} in the HES group on arrival in the ICU. A slight increase in CFT_{INT} was also noticed in the RL group. The median CFT_{INT} values returned to normal in all groups after 24 h. Changes of CFT_{INT} and MCF_{FIB} were most distinct in the HES group, whereas in the RL group, changes were least. We chose these two ROTEM variables as they were most affected after infusion of HES—even at smaller doses.³⁷ All patients in our study routinely received antifibrinolytic drugs and hyperfibrinolysis was not observed in any patient. Whereas enhancement of fibrinolysis,³⁹ depletion of circulating coagulation factors⁴⁰ and reduced platelet count can be detected by ROTEM, impairment of platelet function due to CPB,⁴¹ and the administration of HES^{14, 42} and HA¹⁸ might be better tracked by specific platelet function tests.⁴¹ As we did not perform such tests, we cannot comment on the impact of both colloids on platelet function in the present trial.

Nevertheless, the difference in transfusion requirements in our study can be explained either by the negative impact of the two colloids on blood coagulation but also by the more profound haemodiluting effect, which decreased Hb levels earlier below 7.0 and below $8-9 \text{ g dl}^{-1}$, which were our triggers to give PRBC during and after CPB, respectively. This would explain the fact that more units of PRBC were transfused in the HES and HA groups, both intraoperatively and immediately after operation. In contrast, fluid management with RL in this study was associated with the lowest rate for transfusion of blood products, but also with a more positive fluid balance. Albumin, HES, and RL are not considered equipotent intravascular volume expanders, but their relative potencies are variable.

Crystalloids are generally considered to be less potent volume expanders than colloids, which initially increase plasma oncotic pressure, preload, and cardiac output. Albumin had a plasma volume expanding potency that is 40% higher than that of saline.⁴³ In relation to HA, the volume expansion effect of HES seems to be rather small.^{10, 11} Accordingly, fluid balance in this study was highest in the RL group and lowest in the HA group, whereas fluid balance in the HES group was intermediate. This is also reflected by the crystalloid to colloid ratio that was lower in the HA group in relation to HES. The volume expansion effect was mainly pronounced intraoperatively, where more non-study fluids had to be given in the RL group, particularly to maintain adequate filling of the CPB reservoir. Vasopressor use was not different between our groups, which is in line with previous studies that compared HES with control fluids.^{11, 44, 45}

As has been shown previously, perioperative transfusion of PRBCs and the necessity for reexplorations are strongly associated with increased mortality, and also pulmonary and infectious complications.² Although mortality was low in our trial, which was not powered to detect group differences in mortality, the three patients who died within 90 days had been allocated to the HES and the HA groups, respectively. Similarly, reoperations due to bleeding complications were numerically higher in the two colloid groups.

This study has several limitations. It was conducted as a double-blind, randomized, controlled trial to detect significant group differences in external blood loss via the inserted chest tubes. It was not powered to detect differences in major complications (e.g. re-exploration, renal replacement therapy), and mortality. Much larger trials would have been needed to answer those questions. However, the observed positive Δ creatinine values in both colloid groups indicate that these patients were at increased risk for renal replacement therapy and greater mortality.²⁷ Furthermore, group differences in transfusion of any blood product and PRBC were highly significant, which signifies that the trial was sufficiently powered to detect such differences. Although there was no strict protocol for volume substitution when compared with vasopressor use, fluid administration in all groups was guided by the results from the transoesophageal echo exam and by clinical experience of a senior staff anaesthesiologist who had profound knowledge in transoesophageal echocardiography. The incidence of pruritus, a patient-relevant safety outcome variable, whose pathogenetic mechanism is tissue storage of starch molecules,⁴⁶ was not recorded. In a previous study that specifically addressed this issue, we found that 4.6% of patients treated with HES were affected.⁴⁷ However, several weeks may elapse after exposure to hydroxyethyl starches until onset of pruritus, which complicates proper assessment of groups at risk.

We conclude that all three fluid therapies did not affect our main outcome variable, namely chest tube drainage over 24 h after cardiac surgery with CPB. However, the transfusion rate of PRBCs or of any blood product was higher in both colloid groups, since the transfusion trigger was reached earlier due to more profound haemodilution in conjunction with a negative impact of HES and HA on blood coagulation. In addition, as Δ

creatinine increase solely occurred in these two groups, patients treated with these agents may also face an increased likelihood for kidney injury. Consequently, the use of large amounts of HES and HA in elective cardiovascular surgery, as it was the case in this trial, might be harmful, since it appears to be associated with an increased risk for blood transfusion and the need for renal replacement therapy.

Authors' contributions

K.S.: patient recruitment, data collection, and writing manuscript. E.M.B.: generation of study protocol, administration of study for Ethics committee and local authority, patient recruitment, writing and editing manuscript, and corresponding author. A.L.: generation of study protocol and editing manuscript. A.K.: statistical analysis. S.L.: data collection and preparation of tables and figures. M.D.: patient recruitment and manuscript editing. M.J.H.: generation of study protocol and fund raising.

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Declaration of interest

None declared.

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Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block

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Editor's key points

- Surgical conditions may be affected by the depth of neuromuscular block.
- This small study assessed conditions rated on a five-point scale by a single surgeon during retroperitoneal laparoscopic procedures.
- Surgical conditions were rated significantly better under deep neuromuscular block.
- The rating of surgical conditions on video analysis differed markedly between anaesthetists and the surgeon.

Background. The routine use of neuromuscular blocking agents reduces the occurrence of unacceptable surgical conditions. In some surgeries, such as retroperitoneal laparoscopies, deep neuromuscular block (NMB) may further improve surgical conditions compared with moderate NMB. In this study, the effect of deep NMB on surgical conditions was assessed.

Methods. Twenty-four patients undergoing elective laparoscopic surgery for prostatectomy or nephrectomy were randomized to receive moderate NMB (train-of-four 1–2) using the combination of atracurium/mivacurium, or deep NMB (post-tetanic count 1–2) using high-dose rocuronium. After surgery, NMB was antagonized with neostigmine (moderate NMB), or sugammadex (deep NMB). During all surgeries, one surgeon scored the quality of surgical conditions using a five-point surgical rating scale (SRS) ranging from 1 (extremely poor conditions) to 5 (optimal conditions). Video images were obtained and 12 anaesthetists rated a random selection of images.

Results. Mean (standard deviation) SRS was 4.0 (0.4) during moderate and 4.7 (0.4) during deep NMB ($P < 0.001$). Moderate block resulted in 18% of scores at the low end of the scale (Scores 1–3); deep block resulted in 99% of scores at the high end of the scale (Scores 4 and 5). Cardiorespiratory conditions were similar during and after surgery in both groups. Between anaesthetists and surgeon, there was poor agreement between scores of individual images (average κ statistic 0.05).

Conclusions. Application of the five-point SRS showed that deep NMB results in an improved quality of surgical conditions compared with moderate block in retroperitoneal laparoscopies, without compromise to the patients' peri- and postoperative cardiorespiratory conditions.

Trial registration. The study was registered at clinicaltrials.gov under number NCT01361149.

Keywords: laparoscopy; nephrectomy; neuromuscular block; prostatectomy; rocuronium; sugammadex; urological surgical procedures

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Administration of muscle relaxation is essential in a variety of procedures as it causes an improvement of surgical conditions. For example, King and colleagues¹ demonstrated that the routine use of neuromuscular blocking agents reduced the frequency of unacceptable surgical conditions in radical prostatectomies. Improvement of surgical conditions may be even more important when the surgeon has to work in a narrow space surrounded by muscles such as in the case of retroperitoneal laparoscopic surgery. It may be argued that in retroperitoneal laparoscopic surgery, a deep neuromuscular block (NMB), with train-of-four (TOF) values of 0 and a post-tetanic count (PTC) of 1–2, would further improve working conditions. However, the use of deep NMB may come with complications including long-reversal times, incomplete recovery of

neuromuscular function compromising respiratory, and upper airway function, or the return of NMB after a period of seemingly normal neuromuscular function (recurarization).^{1–3}

The development of sugammadex enables rapid reversal of deep NMB. Sugammadex is a modified γ -cyclodextrin, especially created to bind the free plasma molecules of the neuromuscular blocking agent rocuronium to which it has high affinity.⁴ Recent studies demonstrate that sugammadex produces rapid reversal of deep NMB after administration of high-dose rocuronium.⁵ Theoretically, the combination of rocuronium and sugammadex makes it possible to achieve deep NMB and consequently further improve surgical conditions in retroperitoneal laparoscopic surgery without the fear for prolonged reversal times or incomplete recovery of

† C.H.M. and M.B. contributed equally to this paper.

neuromuscular function. However, the association between the depth of NMB and surgical conditions has not been evaluated as yet.

In the current study, we investigated the effect of a deep NMB (TOF 0, PTC 1–2) against a moderate block (TOF 1–2) on surgical conditions in patients undergoing retroperitoneal laparoscopic surgery for a prostatectomy or (partial) resection of a kidney. Surgical conditions were rated using a five-point surgical rating scale (SRS) by one dedicated surgeon with ample experience in these surgeries (R.F.B.). We hypothesize that deep NMB is associated with improved ratings by the surgeon. Secondary end points of our study included the assessment of the level of agreement between anaesthetists (the providers of the NMB agents and consequently responsible for a large part of the surgical conditions) and surgeon in terms of their rating of the surgical conditions. To that end, 30 s video images of the surgical field, obtained at the time of scoring by the surgeon, were rated by the anaesthetists.

Methods

The study (acronym BLISS trial) was carried out between November 2012 and February 2013 at the Leiden University Medical Centre (Leiden, The Netherlands) and was performed according to guidelines of Good Clinical Practice and Good Research Practice. Approval of the protocol was obtained from the institutional review board (Commissie Medische Ethiek, Leiden, The Netherlands). Patients scheduled to undergo an elective laparoscopic prostatectomy or nephrectomy (partial or total) were approached 2 weeks before surgery and received oral and written information about the study. All patients who were willing to participate gave written informed consent before enrolment. The study was registered at clinicaltrials.gov (NCT01361149); the protocol was published earlier online.⁶ The design of the study was randomized (deep NMB against standard or moderate block) and blinded (the surgical team, the research team and the anaesthetists who scored the video were all blinded to the treatment); the attending anaesthetist was not blinded. Randomization was performed using a computer-generated randomization code. The code was presented to the attending anaesthetist who prepared the medication and took care of patient dosing during anaesthesia.

Patients enrolled in the study had prostate or renal disease and were all eligible for surgical resection by laparoscopic approach. All procedures were performed by one surgeon (R.F.B.). Excluded from participation were patients with ASA class >III, age <18 yr, inability to give informed consent, known or suspected neuromuscular disease, allergy to medication to be used during anaesthesia, a (family) history of malignant hyperthermia, renal insufficiency (serum creatinine >2 times normal, urine output <0.5 ml kg⁻¹ h⁻¹, glomerular filtration rate <60 ml h⁻¹, or proteinuria), previous retroperitoneal surgery, and a body mass index of ≥ 35 kg m⁻².

Perioperative protocol

All patients received total i.v. anaesthesia with propofol and sufentanil. During the procedure, routine monitoring was

applied [electrocardiography, arterial blood pressure, heart rate, electroencephalographic monitoring using the Philips bispectral index (BIS) module system (Philips, Eindhoven, The Netherlands)]. Propofol dosing was such that BIS values remained within the range of 40–50. Additionally, the cardiac output was measured non-invasively using an inflatable finger cuff attached to the Nexfin haemodynamic monitor (*bmeye*, Amsterdam, The Netherlands).

With respect to NMB the patients were randomly assigned to one of the two treatment groups:

Group 1: moderate NMB, in which the goal was to realize a moderate NMB (TOF 1–2 twitches). NMB was induced with a bolus dose of atracurium of 0.5 mg kg⁻¹, followed by a continuous infusion of mivacurium of 0.5 mg kg⁻¹ h⁻¹. In the case of deviations from the target TOF values, the pump speed could be increased or decreased or a bolus dose could be given. This was left to the discretion of the attending anaesthetist. We used atracurium/mivacurium in Group 1 rather than low-dose rocuronium, as this combination is the current standard of care in our hospital. This approach enables us to qualify our current local practice against a new paradigm, which is deep NMB for the chosen surgical procedures.

Group 2: deep NMB, in which the goal was to realize a block of zero twitches in the TOF, but 1–2 twitches in the PTC. To that end, patients received a loading dose of rocuronium of 1.0 mg kg⁻¹ followed by a continuous infusion of 0.6 mg kg⁻¹ h⁻¹. In the case of deviations from the target TOF and PTC, the pump speed could be increased or decreased or a bolus dose could be given. This was left to the discretion of the attending anaesthetist.

In the case of poor or extremely poor surgical conditions (as scored by the surgeon, see below), mivacurium or rocuronium infusion rates were increased by 20% after the administration of a bolus dose of 15 mg.

At the end of surgery, all patients received a reversal agent: neostigmine after a moderate NMB (1–2 mg combined with 0.5–1 mg atropine) and sugammadex (4 mg kg⁻¹) after a deep NMB. Extubation occurred when the TOF ratio was >0.9.

Administration of all drugs was performed by the attending anaesthetists and not corresponded to the surgical team or the anaesthesia research team.

Monitoring

Neuromuscular function using an acceleromyograph was measured at the wrist (TOF-watch-SX, MSD BV, Oss, The Netherlands). The TOF-watch generates an electrical stimulus to the ulnar nerve and measures contractions of the adductor pollicis muscle (causing adduction of the thumb) through a sensor attached to the tip of the thumb. The thumb was placed in a flexible adaptor that applied a constant preload to the thumb. Before administration of any NMB agent, the device was calibrated according the specifications of the manufacturer. To that end, before administration of any neuromuscular blocking agent, but after induction of general anaesthesia, the following procedures were conducted to

standardize the neuromuscular monitoring: (i) application of a tetanic ulnar nerve stimulation (50 Hz for 5 s); (ii) calibration of the TOF watch; and (iii) performing a series of TOF measurements ensuring that the TOF ratio differs by <5% between measurements. If the TOF ratio differed by >5% the TOF watch was recalibrated. The TOF ratio was normalized to the values obtained during the calibration procedure. After these steps, the neuromuscular blocking agent was administered according to protocol.

The number of thumb twitches upon electrical stimulation of the ulnar nerve was measured and recorded. At 15 min intervals, the TOF was measured and in the case of TOF=0, this was followed by the PTC. In our study, a TOF of 1–2 reflects a standard block and a PTC of 1–2 reflects a deep NMB. Finally, when four twitches were present in the TOF, the ratio of the fourth to the first twitch was determined (the TOF ratio).

Surgical rating scale

During the laparoscopic procedure, the surgeon scored the surgical working conditions at 15 min intervals according to a five-point ordinal scale ranging from 1 (extremely poor conditions) to 5 (optimal conditions) (Table 1). Extremely poor (Score 1) indicates that the surgeon is unable to work because of coughing or of the inability to obtain a visible field because of inadequate muscle relaxation; poor (Score 2) indicates that there is a visible field, but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements, or both; acceptable (Score 3) indicates that there is a wide visible field but muscle contractions, movements, or both occur regularly; good (Score 4) indicates a wide working field with sporadic muscle contractions, movements, or both; excellent (Score 5) indicates a wide visible working field without any movement or contractions. In the

case of a sudden deterioration of conditions additional measurements could be added. The feasibility of this method of scoring was investigated during five surgical procedures not included in the study.

Video images

Each time the surgeon rated the surgical conditions a 30 s video image was captured using a camera connected to the endoscopic probe placed in the retroperitoneal surgical space. The procedure was such that the images collected give a visual indication of the surgical condition at the time of scoring. A randomized subset of these images ($n=10$) was presented to 12 anaesthetists with ample experience in giving anaesthesia for urological laparoscopic procedures. They were asked to give a rating to the surgical condition using the same five-point scale as used by the surgeon. These anaesthesia experts were blinded to the level of NMB and goals of the study.

Data acquisition

The following clinical variables were collected on the case record form for further analysis: anaesthesia-related variables [drug dosages, BIS, time from reversal to optimal extubation conditions (TOF ratio >0.9)], haemodynamic variables (arterial blood pressure, heart rate, cardiac output, and cardiac index), ventilatory variables (tidal volume, breathing rate, and breathing pressure), surgical variables (SRS, intra-abdominal pressure, and duration of surgery), and post-anaesthesia care-related variables [time spent in the post-anaesthesia care unit (PACU), respiratory rate, oxygen saturation, pain score (on an 11-point numerical rating scale from 0, no pain, to 10, most severe pain imaginable), occurrence of nausea/vomiting and sedation (on a five-point scale ranging from 0, normal alertness to 5, not aroused by a painful stimulus)]. Recurrent observations were made at 15 min intervals both during anaesthesia and in the PACU.

Sample size and statistical analysis

The sample size was based on the expectation of the surgeon for the distribution of the surgical ratings between the two treatment conditions: rating during the moderate block=5 occurs in 10% of cases, 4 in 20%, 3 in 55% 2 in 10%, and 1 in 5%; rating during the deep block=5 in 70% of cases, 4 in 20%, 3 in 10%, 2 in 0%, and 1 in 0%. These anticipated frequencies result in an odds ratio of 21 for optimal conditions (SRS=5) vs non-optimal conditions (SRS<5). Ten thousand simulations were performed to obtain the power for a given sample size with moderate block as a fixed distribution and a simulated distribution of the deep block condition assuming proportionality of the odds ratio with an odds ratio of 21 and analysing the results with a proportional odds model using the score test. The power ranged from 82% at a sample size of 14 (7 in each group) to 97% ($n=12$ per group). A sample size of 24 was chosen to take into account any margin of uncertainty around the effect size.

The data analysis was based on the intent-to-treat approach. The primary end point of the study was the influence of the depth of the NMB on the SRS. For each patient, the

Table 1 The surgical rating score

- | | |
|---|--|
| 1 | <i>Extremely poor conditions:</i> the surgeon is unable to work because of coughing or because of the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional neuromuscular blocking agents must be given |
| 2 | <i>Poor conditions:</i> there is a visible laparoscopic field, but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements, or both with the hazard of tissue damage. Additional neuromuscular blocking agents must be given |
| 3 | <i>Acceptable conditions:</i> there is a wide visible laparoscopic field but muscle contractions, movements, or both occur regularly causing some interference with the surgeon's work. There is the need for additional neuromuscular blocking agents to prevent deterioration |
| 4 | <i>Good conditions:</i> there is a wide laparoscopic working field with sporadic muscle contractions, movements, or both. There is no immediate need for additional neuromuscular blocking agents unless there is the fear of deterioration |
| 5 | <i>Optimal conditions:</i> there is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional neuromuscular blocking agents |

final score was the average of all 15 min SRS values. The treatment effect on the final score was tested using a *t*-test (SigmaPlot version 12.5, Systat Software, Inc., San Jose, CA, USA). Secondary end points were (i) the assessment of the level of agreement between anaesthetists and surgeon in terms of their rating of the surgical conditions and (ii) the effects of level of NMB on haemodynamic variables during surgery, time to TOF > 0.9, and relevant variables in the PACU (pain rating, sedation levels, and cardiorespiratory variables). All variables were averaged over time to get an indication of their mean value. Treatment effects were evaluated on the average data by *t*-test.

The scores of each of the 12 anaesthetists were compared with that of the surgeon's score using the κ statistic (also known as Cohen's κ) and population Bland-Altman analysis.⁷⁻⁹ The κ statistic calculates the agreement between a pair of scores over and above what is expected from chance, where $\kappa = [P(A) - P(E)] / [1 - P(E)]$, $P(A)$ is the proportion of scores that agree and $P(E)$ is the proportion of scores that would agree by chance.⁷⁻⁸ Kappa values between 0 and 0.2 are indicative of poor to slight agreement, values between 0.2 and 0.4 indicate fair agreement, 0.4 and 0.6 moderate agreement, 0.6 and 0.8 substantial agreement, and 0.8 and 1 near complete to complete agreement.¹⁰ Bland-Altman plots give the difference between paired measurements (scores) against the mean of the values, which results in values for bias and limits of agreement to describe how closely measurements from two sources are related.⁹

All values presented are mean (SD) unless otherwise stated. *P*-values < 0.05 were considered significant.

Results

A total of 30 patients were screened. In four patients, one or more exclusion criteria were met. The others were randomized.

Two patients withdrew consent before treatment; two others replaced them. See Figure 1 for the flow chart of the study. Patient characteristics are given in Table 2 showing that the two treatment groups were similar in physical characteristics, gender, types of surgery, and haemodynamic variables. Duration of surgery was similar between treatment groups and ranged from 80 to 240 min with average surgical times of 141 and 144 min for standard care and deep NMB, respectively (Table 3).

Anaesthesia

Depth of anaesthesia, as measured by the BIS of the electroencephalogram, was similar between treatment groups [moderate block 42 (5) vs deep block 44 (6)]. NMB in patients receiving a standard treatment was moderate with an average TOF of 2.2 (0.9) during surgery. Patients receiving a deep NMB had zero twitches in the TOF and 1.6 (1.5) twitches in the post-tetanic count. During surgery, the dosages of the anaesthetic (propofol) or analgesic (sufentanil), the intra-abdominal pressure and haemodynamic variables were similar between treatments (Table 3).

Rating of surgical conditions during laparoscopic surgery

The rating of the surgical field was significantly different between treatments with a mean rating of 4.0 (0.4) (range 3.5-4.5, median 3.9) during a moderate NMB with TOF 1-2 and 4.7 (0.4) (range 4.0-5.0, median 4.9) during a deep block with PTC 1-2 ($P < 0.001$, Fig. 2). The distribution of all ratings taken during surgery is shown in Figure 3. From these data, the significant difference between the moderate (TOF 1-2) and deep (PTC 1-2) blocks is apparent from the fact that 18% of scorings during moderate block was in the SRS range of 1-3 (scores rated as less than good), while 99% of scoring

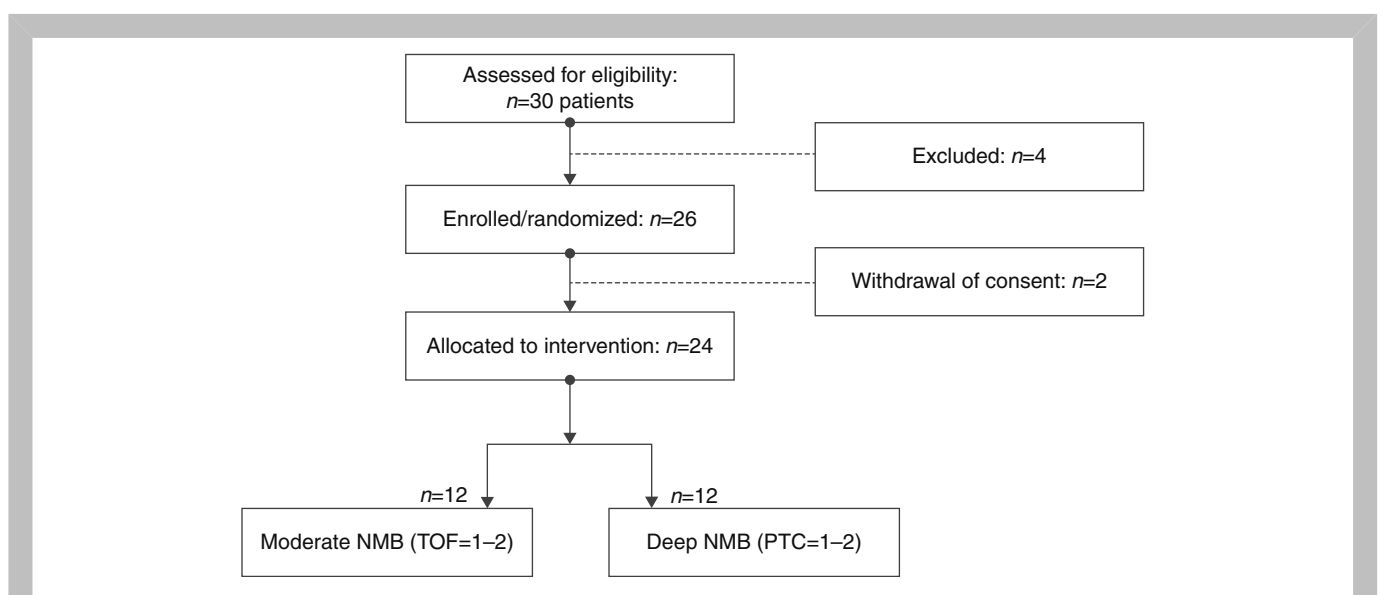


Fig 1 Study flow chart.

Table 2 Patient characteristics and screening measurements. All values are mean (sd) unless otherwise stated. BMI, body mass index; ABP, arterial blood pressure; HR, heart rate; CO, cardiac output; CI, cardiac index. Haemodynamic measurements were obtained before induction of anaesthesia

	Moderate NMB (n=12)	Deep NMB (n=12)
Prostate surgery (n)	7	7
Renal surgery (n)	5	5
Gender (M/F)	10/2	10/2
Age (median, range)	59 (28–74)	60 (24–70)
Weight (kg)	83 (14)	83 (10)
Height (cm)	180 (10)	180 (9)
BMI (kg m ⁻²)	25.8 (3.2)	25.9 (3.9)
ABP systolic (kPa)	19.6 (2.1)	18.9 (1.5)
ABP systolic (mm Hg)	147 (16)	142 (11)
ABP diastolic (kPa)	11.2 (2.2)	11.5 (1.6)
ABP diastolic (mm Hg)	84 (15)	86 (12)
HR (min ⁻¹)	71 (12)	73 (15)
CO (litre min ⁻¹)	5.9 (1.6)	5.8 (2.4)
CI (litre min ⁻¹ m ⁻²)	3.0 (0.8)	3.1 (1.0)

Table 3 Measurements during surgery. NMB, neuromuscular block; BIS, bispectral index; TOF, train-of-four; PTC, post-tetanic count; SRS, five-point surgical rating scale; AP, arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index. Values are mean (sd). **P*<0.001 vs moderate NMB

	Moderate NMB (TOF 1–2)	Deep NMB (PTC 1–2)
Duration of surgery (min) (range)	141 (50) (80–240)	144 (35) (90–195)
BIS	42 (5)	44 (6)
Propofol (g)	1.6 (0.8)	1.6 (0.4)
Sufentanil (µg)	73 (30)	78 (22)
Rocuronium (mg)		223 (81)
Atracurium (mg)	37 (10)	–
Mivacurium (mg)	41 (24)	–
TOF	2.2 (0.9)	0
PTC	–	1.6 (1.5)
SRS	4.0 (0.4)	4.7 (0.4)*
Retroperitoneal pressure (kPa)	1.5 (0.05)	1.4 (0.2)
AP systolic (kPa)	15.3 (2.6)	15.4 (1.7)
AP systolic (mm Hg)	115 (20)	116 (13)
AP diastolic (kPa)	9.1 (0.9)	9.2 (1.2)
AP diastolic (mm Hg)	68 (7)	69 (9)
HR (min ⁻¹)	67 (10)	69 (13)
CO (litre min ⁻¹)	4.9 (1.4)	5.6 (2.0)
CI (litre min ⁻¹ m ⁻²)	2.5 (0.8)	2.8 (0.9)

in the deep block was in the SRS range 4–5 (good and excellent scores). Variability in the individual ratings was higher for a block with TOF=1–2 (mean coefficient of variation of ratings

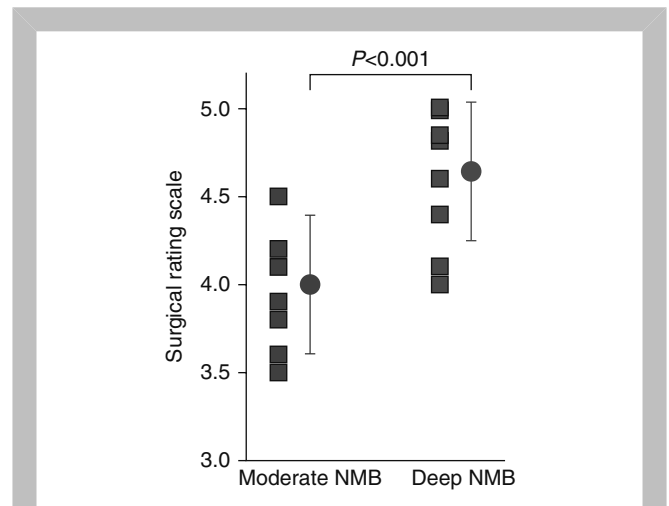


Fig 2 Surgical ratings by the surgeon during laparoscopic surgeries using the five-point SRS (see Table 1). Squares denote the individual mean ratings obtained during surgery. Circles are the mean of the means (sd). Standard indicates standard of care; deep NMB, deep neuromuscular block.

of surgical sessions 26%) compared with block with TOF=0 and PTC=1–2 (5%).

Measurements after surgery

Reversal of the NMB in patients with a deep block with sugammadex resulted in acceptable extubation conditions (TOF ratio >0.9) after 5.1 (2.4) min. In contrast, similar extubation conditions were obtained after 10.9 (4.9) min (*P*<0.01) in patients with TOF 1–2 and reversal with neostigmine. In the PACU, no differences were observed in respiration, pain, and sedation levels (Table 4).

Rating of surgical condition by anaesthetists

A random set of 10 video images was scored by 12 anaesthetists. The distribution of the surgeon's ratings of these 10 images is shown in Figure 4A; the corresponding distribution of ratings of the anaesthetists is shown in Figure 4B. Compared with the surgeon their ratings were skewed to the right and agreement with the surgeon's ratings was poor (agreement between scores ranged from 0 to 40%). The κ statistic was 0.05 (range –0.25 to 0.25). The Bland–Altman analysis resulted in a significant bias of –0.43 (0.21) (*P*=0.03) and large limits of agreement of 2.87 and –3.72, and a between-subject variance of 0.25 (Fig. 4c).

Discussion

This is the first study to assess the impact of a deep NMB (PTC 1–2) on surgical working conditions. The main results of our study are: (i) a deep NMB (TOF 0 and PTC 1–2) is associated with higher (i.e. improved) ratings from the surgeon compared with a moderate NMB (TOF 1–2) during laparoscopic prostatectomies and nephrectomies, indicating a significant improvement of surgical conditions; (ii) ratings from anaesthetists and surgeon of video images of the surgical field showed

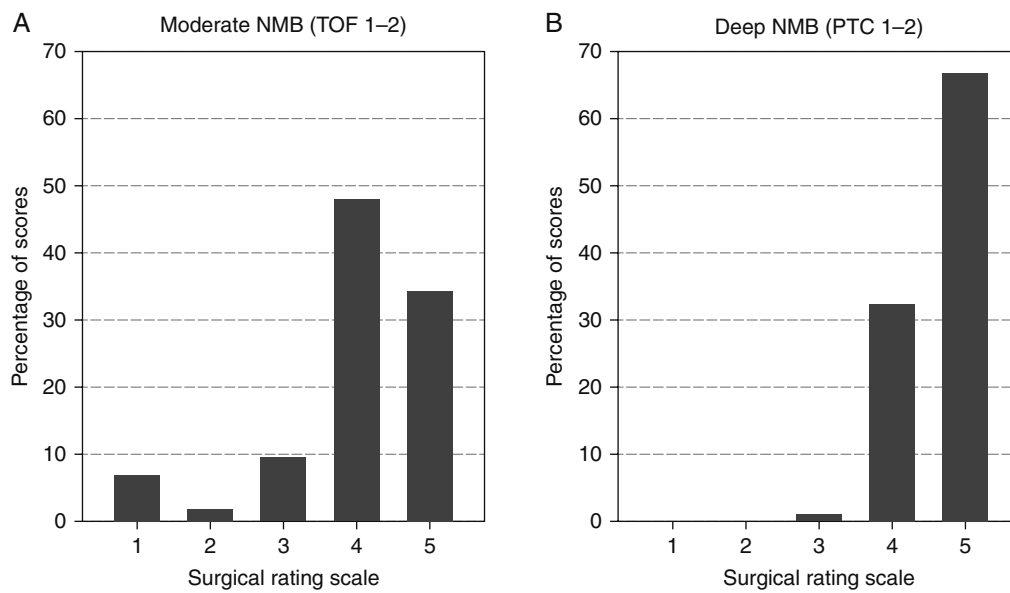


Fig 3 Distribution of the surgical ratings obtained during standard of care (A) and during deep NMB (B). NMB, neuromuscular block.

Table 4 Measurements after surgery. Values are mean (sd). TOF, train-of-four; PACU, post-anaesthesia care unit; Sp_{O₂}, arterial haemoglobin oxygen saturation

	Moderate NMB (TOF 1–2)	Deep NMB (PTC 1–2)
Sugammadex (mg)		380 (101)
Neostigmine (mg)	1 (0)	
Time to TOF ratio >0.9 (min)	10.9 (4.9)	5.1 (2.4)
Time in PACU (min)	86 (19)	86 (25)
Sp _{O₂} (%)	98.6 (1.8)	98.2 (1.4)
Breathing rate (min ⁻¹)	14.5 (2.2)	14.5 (2.2)
Pain score (10-point scale)	2.6 (1.6)	2.1 (2.2)
Sedation score (five-point scale)	2.0 (0.6)	1.3 (1.0)

little agreement. In the current study, we chose to study retroperitoneal laparoscopic surgeries for two urological procedures [prostatectomy and (partial) nephrectomy] as these procedures are confined to a narrow working space where adequate (deep) muscle relaxation is of high importance and an effect of less optimal muscle relaxation on the quality of the surgical field is rapidly apparent.

Surgical rating scale

The five-point rating scale used in our study was developed in close cooperation with the surgeon involved in our project, who has ample experience in the performed procedures. It was decided that while the scoring system should integrate all qualitative aspects that are important to the surgeon when judging the surgical working field, it should remain as simple as possible. A scoring system with >5 points was

initially considered, such as an 11-point numerical quantitative scale (e.g. numerical rating or visual analogue scales from 0 to 10, cf. Ref. 8); however, it was decided to rank the surgical field qualitatively from extremely poor, via poor, acceptable, good to optimal conditions (see Table 1 for an explanation of the different ratings). Further, to reduce variability in scoring between assessors just one surgeon was requested to score the surgical field in our study. Our system is similar to other scoring systems. For example, the Clinical Global Impression (CGI) rating scale is a seven-point qualitative scale in which physicians rate the severity of a patient's mental illness relative to the physician's past experience.¹¹ The CGI and our scoring systems are subjective but in our case the ample experience of the surgeon gives credibility to the procedure. Indeed, the results of our study indicate that the surgeon was able to discriminate between a moderate and a deep NMB. The difference of 0.7 points (a difference of 18%) was regarded as important and clinically significant by the surgical team. We argue that the ability of our scoring system to discriminate between two distinct anaesthetic regimes indicates the validity of the five-point SRS we developed.

Still, our study should be considered a proof-of-concept trial and further validation of the SRS is mandatory. Therefore, one should be cautious in extrapolation of our results to other procedures and other surgeons. Other surgeons may rate the surgical condition differently and other procedures may require a different anaesthetic, surgical approach, or both. In an attempt to get an indication of the ability of other surgeons with ample experience in laparoscopic surgery to apply the scoring system, we invited eight surgeons, specialized in laparoscopic surgery for gastroenterological procedures, to score the 10 videos earlier presented to the anaesthetists. Their κ statistic was on average 0.50 indicative of moderate agreement. As

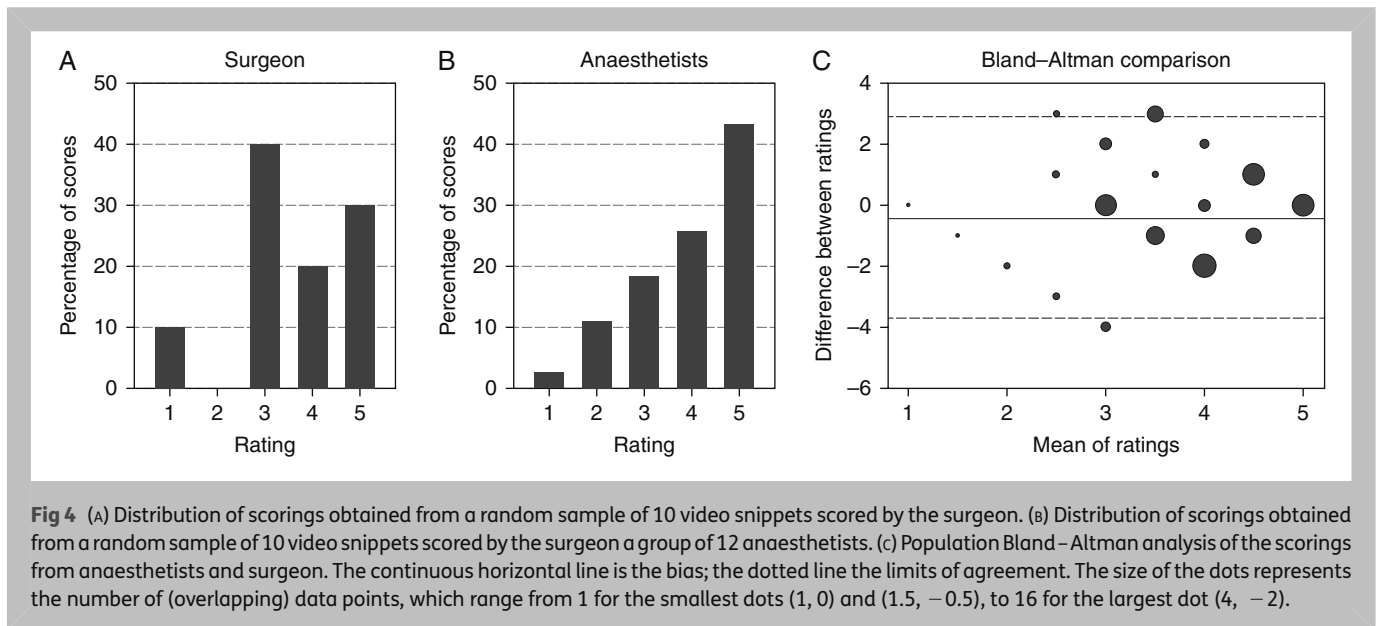


Fig 4 (A) Distribution of scorings obtained from a random sample of 10 video snippets scored by the surgeon. (B) Distribution of scorings obtained from a random sample of 10 video snippets scored by the surgeon a group of 12 anaesthetists. (C) Population Bland–Altman analysis of the scorings from anaesthetists and surgeon. The continuous horizontal line is the bias; the dotted line the limits of agreement. The size of the dots represents the number of (overlapping) data points, which range from 1 for the smallest dots (1, 0) and (1.5, -0.5), to 16 for the largest dot (4, -2).

expected, this agreement is substantially greater than that between surgeon and anaesthetists. It further shows that different surgeons (in this case with a different subspecialty) rate the surgical field differently. The current study was specifically aimed at scoring urological procedures performed in narrow retroperitoneal space. The results show a clinically relevant benefit of deep NMB for the surgeon involved in this study. Whether this benefit will also be relevant to other surgeons performing similar surgeries and possibly even for other laparoscopic procedures, such as for bariatric laparoscopic surgery is the topic of further research.

Deep neuromuscular block

Our *a priori* estimation of SRS distributions came close for the deep NMB but was underestimated for the moderate block. Good and optimal conditions were achieved during standard care (good 48% and optimal 34%) although at a lower frequency than during deep NMB (good 32% and optimal 67%). This indicates that in 82% of measurements during standard care and in 99% during deep NMB conditions were good to optimal. However, variability in ratings was high for moderate NMB compared with deep NMB: 26% vs 5%. Still, also in deep NMB, the range of scores (mean ranged from 4 to 5) was considered high and is still open for improvement. Possibly, further improvement may be obtained by (more) strictly controlling anaesthetic depth, analgesic state, and arterial carbon dioxide concentrations. In the current study, respirator settings were such that end-tidal carbon dioxide concentrations were between 4.4 and 6 kPa (33 and 56 mm Hg). High arterial carbon dioxide concentrations stimulate the respiratory neuronal pool in the brainstem, which activates the phrenic nerve.¹² As a consequence diaphragm contractions may persist despite a deep NMB. The NMB at the diaphragm is less intense than at the adductor pollicis muscle.^{13 14} Indeed,

some of the video images showed movement related to diaphragm contraction unrelated to the ventilator-induced inspiration–expiration sequence or cardiac contractions despite TOF values of zero. The surgeon scored such conditions at the low end of the SRS. In laparoscopic bariatric surgery, the working space volume and visibility increased in response to NMB.¹⁵ In the current study, the retroperitoneal pressure was kept constant to 1.3–1.5 kPa (9–11 mm Hg) in both groups and it may be assumed that the working space volume was greater in the deep NMB group. However, the scoring by the surgeon is only in part based on the perceived volume of the retroperitoneal space. Other factors similarly influence the surgeon's working conditions and consequently play an additional role in his scoring. For example, muscle contractions (including the diaphragm) and resultant movement of other structures are important as well. Further studies should address these issues.

We tested deep vs moderate block using two different drug regimens. The reason for this was that this approach enabled us to compare our current practice with atracurium and mivacurium with an approach that not only allows us to induce a deep NMB but also allows rapid reversal of that deep block. As our end point was to compare the depth of the NMB irrespective of the drugs used to induce that state, we do not believe that this influenced our outcome significantly. We observed that full reversal after deep NMB occurred after 5 min. It is important, however, to realize that measurements were made at 5 min intervals and full reversal with TOF ratios >0.9 may have occurred earlier (for sugammadex reversal to TOF ratio >0.9 is expected after 2–3 min).

Scoring by anaesthetists of the surgical field

An important finding in our study is that the agreement of scores between the anaesthetists and surgeon was poor. This indicates that the anaesthetists are less well able to measure

the quality of surgical conditions from the video images and hence derive insufficient information from these images regarding the working conditions of the surgeon. It may be argued that in our study observing a 30 s video image does not provide sufficient input to assess the quality of surgical condition in non-surgically skilled personnel. This certainly may be true, but in our study, and possibly also in clinical practice, the anaesthetists base their impression of the surgical field primarily on the volume of the working space and the visibility of retroperitoneal tissues (most importantly related to the absence or presence of blood in the image obscuring relevant structures) without addressing muscle contractions and other movements visible on the video image. In our hospital, live video images of the laparoscopic field are presented to the anaesthetists during each case and these, together with his/her clinical experience and interaction with the surgeon, form the basis of the anaesthetic regimen, including the additional use of neuromuscular blocking agents when surgical conditions are deemed poor. Some anaesthetists may not be willing to induce a deep NMB. This may be related to their inability to adequately judge the operating field from the video screen but additionally to their fear for suboptimal post-surgical conditions. Evidently, this may be the cause of some discussion in the operating theatre. To prevent such situations, we suggest that surgeons and anaesthetists communicate their wishes and intentions before the procedure (e.g. during preoperative *time-out*) and closely cooperate in obtaining optimal working conditions. Here, we show that providing a deep NMB improves surgical conditions.

Authors' contributions

C.M. was involved in the conception of the study idea and design of the study. He performed part of the experiments, participated in the data analysis, and writing of the paper. M.B. participated in the writing of the protocol, performed part of the experiments, and participated in the writing of the paper. R.F.B. was involved in the design of the study and participated in the development of the surgical rating scale, performed all surgeries, and scored the quality of the surgical field at 15 min intervals. L.P.A. was involved in the writing of the protocol and the interpretation of the results, and writing of the paper. A.D. was involved in the inception of the study idea, the design of the study, wrote the protocol, performed part of the experiments, analysed the data, interpreted the results, and wrote the paper.

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Declaration of interest

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Five-minute parameter of thromboelastometry is sufficient to detect thrombocytopenia and hypofibrinogenaemia in patients undergoing liver transplantation

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Editor's key points

- Rapid diagnosis of coagulopathy is critical to appropriate treatment of perioperative bleeding.
- Early parameters of clot formation measured by rotational thromboelastometry were studied in liver transplant patients.
- The clot amplitude at 5 min correlated with low platelet counts and low fibrinogen concentration, which might serve as a rapid guide to transfusion in these patients.

Background. Early detection of coagulopathy is important to prevent bleeding during liver transplantation (LT). Rotation thromboelastometry (ROTEM[®]) provides the earliest parameter of clot amplitudes at 5 min (A5). We evaluated whether A5 correlates with platelet count (PLT) and fibrinogen concentration (Fib) and can predict thrombocytopenia and hypofibrinogenaemia in hypocoagulable patients undergoing living-donor LT (LDLT).

Methods. A total of 3446 retrospective ROTEM[®] measurements, including 1139 EXTEM, 1182 INTEM, and 1125 FIBTEM, with simultaneously measured PLT and Fib, were analysed during LDLT in 239 patients. The correlations between A5 and maximum clot firmness (MCF) index, PLT, and Fib were calculated. Receiver operating characteristic analysis with area under the curve (AUC) was used to assess A5 thresholds predictive of PLT and Fib.

Results. The median PLT was 47 000 mm⁻³ and the median Fib was 100 mg dl⁻¹ during LDLT. The A5 parameters of EXTEM (A5_{EXTEM}) and INTEM (A5_{INTEM}) were highly correlated with MCF ($r=0.96$ and $r=0.95$, respectively), PLT ($r=0.76$ and $r=0.77$, respectively), and Fib ($r=0.63$ and $r=0.64$, respectively). A5 of FIBTEM (A5_{FIBTEM}) was also correlated with MCF ($r=0.91$) and Fib ($r=0.75$). A5_{EXTEM} thresholds of 15 and 19 mm predicted PLT < 30 000 mm⁻³ (AUC=0.90) and < 50 000 mm⁻³ (AUC=0.87), respectively, whereas A5_{FIBTEM} 4 mm predicted Fib < 100 mg dl⁻¹ (AUC=0.86). Biases from A5_{EXTEM} and A5_{FIBTEM} to their MCFs were 16.4 and 1.3 mm, respectively.

Conclusions. A5 as an early variable of clot firmness is effective in detecting critically low PLT and Fib. A5 can therefore be a reliable fast index guiding transfusion therapy in hypocoagulable patients undergoing LDLT.

Keywords: blood coagulation; liver transplantation; thromboelastometry

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Patients who undergo liver transplantation (LT) often experience massive bleeding requiring transfusion. The transfusion of many allogeneic blood products, however, without a fast and reliable monitoring system, can further aggravate the haemostatic disorders of these patients, resulting in poor overall outcomes.^{1–4} Early detection and timely correction of coagulopathy are crucial in preventing further exacerbation of bleeding diathesis and in breaking the vicious cycle of coagulopathy during LT, in addition to improving overall patient outcomes.

Rotation thromboelastometry (ROTEM[®] delta, TEM International GmbH, Munich, Germany) is a point-of-care coagulation monitoring system that evaluates the viscoelasticity of whole blood, allowing the entire clotting process, from clot initiation and formation to clot stability, to be assessed.^{5–6} In contrast to conventional laboratory tests [e.g. measurements of platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen concentration (Fib)], ROTEM[®] can measure early variables, such as clot

amplitude at 5 min (A5) and 10 min (A10) after clotting time (CT) in EXTEM, INTEM, and FIBTEM. Owing to its rapid assessment of PLT and Fib, ROTEM[®] is frequently used to guide transfusion therapy.^{7–10} Moreover, a recent study with a large database demonstrated that early measures of clot firmness, including A5, A10, and clot amplitude at 15 min (A15), are linearly correlated with ROTEM[®] determined maximum clot firmness (MCF), allowing the fast and reliable prediction of MCF in non-cardiac patients, including those with subnormal, normal, and supranormal MCF values.¹¹

The A10 of EXTEM (A10_{EXTEM}) was shown to be rapid and valuable in predicting coagulation status, and also being useful in assessing the need for perioperative transfusion of platelets and fibrinogen.⁸ The correlations of the more rapid A5 with PLT count and Fib concentration have not been determined, and it remains unclear whether A5 could determine quantitative PLT and Fib level in hypocoagulable patients undergoing living-donor LT (LDLT) surgery. We therefore assessed whether A5 on ROTEM[®]

analysis is an early and reliable index for the transfusion of PLT and Fib during LDLT. We also assessed A5 cut-off values predicting thrombocytopenia and hypofibrinogenaemia in patients undergoing LDLT.

Methods

Patients

A total of 401 patients who underwent LT at Asan Medical Center, Seoul, Republic of Korea, between June 2010 and May 2011 were enrolled. Of these, 162 patients were excluded from this analysis, including 73 who received orthotopic LT, 53 who had incomplete ROTEM[®] and laboratory test data, and 36 patients aged <18 yr. The remaining 239 LDLT recipients were included in this retrospective analysis. Records about anaesthesia, available on computerized databases, were analysed retrospectively. This study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Anaesthetic technique

General anaesthesia for LDLT surgery was performed according to our institutional standard protocol.¹² Briefly, anaesthesia was induced with i.v. thiopental, fentanyl, and vecuronium, and maintained with 1% sevoflurane, a 50% O₂/air mixture, and continuous infusion with fentanyl and vecuronium. Twenty-gauge femoral and radial arterial catheters were inserted to monitor arterial pressure and to sample blood. A 7.5 French pulmonary artery catheter (Swan-Ganz CCombo V CCO/SvO₂/CEDV, Edwards Lifesciences LLC, CA, USA) was inserted to monitor haemodynamic variables. Body temperature was measured using a thermistor in a pulmonary artery catheter. Transfusions of packed red blood cells, fresh-frozen plasma, and cryoprecipitate were based on clinical decisions or guided by standard laboratory tests or the transfusion algorithm based on ROTEM parameters. According to institutional standards, transfusions were administered to maintain PT < 2.0 INR, Fib > 100 mg dl⁻¹, and PLT > 30 000 mm⁻³. Synthetic colloidal solution was not used, but solutions of 5% albumin with balanced crystalloid were administered during LDLT.

Blood sampling and thromboelastometry

During LDLT, standard coagulation assays and ROTEM[®] tests were routinely performed, using blood samples at pre-established time points, including 1 h after induction of general anaesthesia, 1 h after surgical incision, 30 min after hepatectomy, and 30 min after graft reperfusion and after hepatic artery anastomosis. ROTEM[®] tests were performed according to the manufacturer's instructions, using equipment and test reagents provided by Tem International GmbH. The ROTEM[®] device was placed in the operating theatre and all tests were performed by transplantation anaesthesiologists or anaesthesia nurses trained to perform ROTEM[®] tests. Of the ROTEM[®] tests performed, inadequate runtime, patients who received thrombin inhibitor or signs of hyperfibrinolysis were excluded. Finally, 1139 EXTEM, 1182 INTEM, and 1125 FIBTEM tests were included in the study. ROTEM[®] variables recorded included: (i) clotting time (CT), defined as the time (s) from the start of

measurement to the initiation of clotting, defined as a clot firmness of 2 mm; (ii) clot formation time (CFT), defined as the time (s) from initiation of clotting until a clot firmness of 20 mm; (iii) MCF, defined as the maximal amplitude (mm) of the graphical trace of clot firmness; (iv) α -angle (α), defined as the tangent to the graphic trace at an amplitude of 2 mm; and A5 and A10 (mm), which reflect the amplitudes 5 and 10 min, respectively, after CT. At each time point, blood samples were withdrawn from the radial artery, and haemoglobin, PT, PLT, and Fib were measured.

Standard coagulation assays

PT was assessed using Thromborel S kits (Siemens Healthcare Diagnostics, GmbH, Marburg, Germany), and fibrinogen was assayed using the Dade Thrombin Reagent (Siemens Healthcare Diagnostics). All tests were performed using an automatic coagulation analyser (Sysmex CA-7000, Siemens Healthcare Diagnostics).

Statistical analyses

Continuous variables were expressed as median (inter-quartile range) or mean [standard deviation (sd)]. Between-group comparisons were evaluated using the χ^2 test, Fisher's exact tests, *t*-tests, and Mann-Whitney *U*-tests, as appropriate. Correlations between standard coagulation test results and those performed on ROTEM[®] were analysed using Spearman's rank correlation coefficient (*r*). The Bland-Altman analyses¹³ were performed to estimate the mean difference (bias) (sd) between early measures of clot firmness (A5 and A10) and MCF. Receiver operating characteristic (ROC) curves and the area under the

Table 1 Patient characteristics and laboratory data. Values are expressed as median (inter-quartile range) or percentage, as appropriate

Variable	
Preoperative patient characteristic data	
Age (yr)	53 (48–57)
Gender, male (%)	76.0
Body mass index (kg m ⁻²)	23.8 (21.7–25.9)
Model for end-stage liver disease score	14 (10–21)
Child-Pugh score	8 (6–10)
Liver disease (%)	
Hepatitis B virus-related cirrhosis	67.7
Hepatitis C virus-related cirrhosis	7.0
Alcoholic cirrhosis	12.7
Autoimmune	1.4
Others	11.2
Diabetes (%)	27.9
Hypertension (%)	2.2
Intraoperative laboratory data	
Haemoglobin (g dl ⁻¹)	9.5 (8.6–10.7)
Platelets ($\times 10^3$ mm ⁻³)	47 (32–64)
Prothrombin time (INR)	1.8 (1.6–2.2)
Fibrinogen (mg dl ⁻¹)	100 (77–137)

curve (AUC) was used to determine the optimal cut-off values of A5, A10, and MCF on EXTEM, INTEM, and FIBTEM predicting PLT counts $<30\,000$ and $<50\,000\text{ mm}^{-3}$ and Fib concentrations $<100\text{ mg dl}^{-1}$. Sensitivity and specificity were also calculated. All statistical analyses were performed using Medcalc® (Medcalc Software, Mariakerke, Belgium) statistical software. A two-tailed P -value of <0.05 was considered statistically significant.

Results

The patient characteristics, intraoperative laboratory data, and liver transplant results of the 239 included patients are shown in Table 1. During LDLT, the median (inter-quartile range) PLT was $47\,000$ ($32\,000$ – $64\,000$) mm^{-3} , the median Fib was 100 mg dl^{-1} (77 – 137 mg dl^{-1}), and the median PT was 1.8 (1.6 – 2.2) INR, demonstrating that these patients

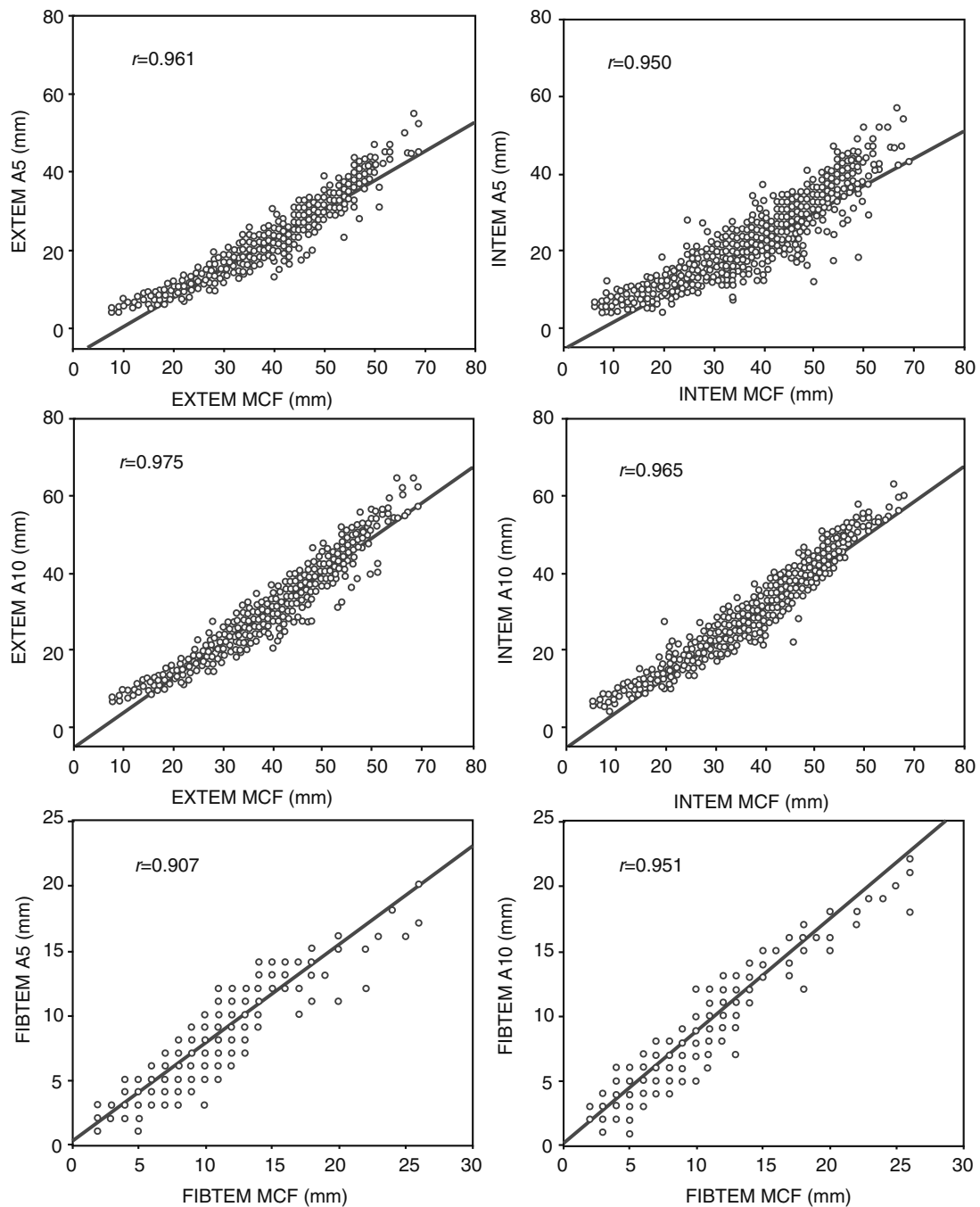


Fig 1 Correlations between early ROTEM parameters and MCF. Early ROTEM parameters (A5 and A10) on all ROTEM assays (EXTEM, INTEM, and FIBTEM) demonstrated excellent correlations with MCF.

were in a hypocoagulable state. We found that 1026 analyses (90.1%) of MCF_{EXTEM} and 1069 (90.4%) of MCF_{INTEM} presented values below the reference range (<50 mm each), whereas in FIBTEM analysis, 823 assays (73.2%) of MCF_{FIBTEM} were below the reference range (MCF_{FIBTEM}<9 mm). Correlation analyses between ROTEM[®] parameters (A5, A10, and MCF of EXTEM, INTEM, and FIBTEM) are shown in Figure 1. Among the ROTEM[®] parameters, both A5_{EXTEM} ($r=0.961$, $P<0.0001$) and A10_{EXTEM} ($r=0.975$, $P<0.0001$) were highly correlated with MCF_{EXTEM}, and also with MCF_{INTEM} ($r=0.950$ and $r=0.965$, respectively; $P<0.0001$ each). In addition, A5_{FIBTEM} ($r=0.907$, $P<0.0001$) and A10_{FIBTEM} ($r=0.951$, $P<0.0001$) showed high correlation with MCF_{FIBTEM}.

Intraoperative ROTEM[®] data and biases calculated from the Bland–Altman analyses of A5 and A10 for EXTEM, INTEM, and FIBTEM parameters are shown in Table 2. Intraoperative trends of ROTEM[®] data and laboratory parameters are shown in Figure 2. Because the scatterplot seemed to follow a curvilinear relationship between ROTEM[®] data and conventional coagulation parameters, we performed both linear and curvilinear fitting (Fig. 3). The curvilinear fits showed better correlations for all comparisons. A5_{EXTEM}, A10_{EXTEM}, and MCF_{EXTEM} showed better correlations with PLT ($r=0.76$, $r=0.76$, and $r=0.75$, respectively, $P<0.001$ each) than with Fib ($r=0.63$, $r=0.65$, and $r=0.63$, respectively, $P<0.0001$ each), indicating that MCF parameters are explained better by PLT than by Fib. In addition, A5_{INTEM}, A10_{INTEM}, and MCF_{INTEM} showed good correlations with PLT ($r=0.77$, $r=0.77$, and $r=0.75$, respectively, $P<0.001$ each) and Fib ($r=0.64$, $r=0.66$, and $r=0.62$, respectively, $P<0.0001$ each), and A5_{FIBTEM}, A10_{FIBTEM}, and MCF_{FIBTEM} were correlated with Fib ($r=0.75$, $r=0.76$, and $r=0.75$, respectively, $P<0.0001$ each) (Fig. 3).

ROC curve analysis showed that the cut-off values of A5_{EXTEM} and A10_{EXTEM} predicting PLT<30 000 mm⁻³ were 15 mm (sensitivity: 86%, specificity: 77%) and 22 mm (sensitivity: 85%, specificity: 78%), respectively, and that their cut-off values to predict PLT<50 000 mm⁻³ were 19 mm (sensitivity: 82%,

specificity: 78%) and 27 mm (sensitivity: 82%, specificity: 77%), respectively. AUCs of A5_{EXTEM} and A10_{EXTEM} were 0.90 and 0.898, respectively, for PLT<30 000 mm⁻³ and were 0.871 and 0.867, respectively, for PLT<50 000 mm⁻³ (all $P<0.0001$) (Fig. 4).

The cut-off values of A5_{INTEM} and A10_{INTEM} were 16 mm (sensitivity: 82%, specificity: 86%) and 22 mm (sensitivity: 85%, specificity: 83%), respectively, for predicting PLT<30 000 mm⁻³, and 19 mm (sensitivity: 82%, specificity: 77%) and 27 mm (sensitivity: 79%, specificity: 79%), respectively, for predicting PLT<50 000 mm⁻³. AUCs of A5_{INTEM} and A10_{INTEM} were 0.914 and 0.915, respectively, for PLT<30 000 mm⁻³ and were 0.873 and 0.869, respectively, for PLT<50 000 mm⁻³ (all $P<0.0001$) (Fig. 4).

ROC curve analysis showed that A5_{FIBTEM} and A10_{FIBTEM} predicting Fib<100 mg dl⁻¹ were 4 mm (sensitivity: 81%, specificity: 77%) and 5 mm (sensitivity: 76%, specificity: 82%), respectively. The AUCs of A5_{FIBTEM} and A10_{FIBTEM} for Fib<100 mg dl⁻¹ were 0.86 and 0.87, respectively (all $P<0.0001$) (Fig. 4).

Discussion

The first major finding of our study was that all correlations and ROC curve analyses, including AUCs, were very similar for A5_{EXTEM} and A10_{EXTEM} and for A5_{INTEM} and A10_{INTEM}, strongly suggesting that A5 is as precise as A10, but can more rapidly predict MCF, thrombocytopenia, and hypofibrinogenaemia in patients undergoing LDLT. Secondly, A5_{EXTEM} and A5_{INTEM} were similar in predicting MCF, with both showing good correlations with PLT and Fib, suggesting that they can be used interchangeably, despite INTEM and EXTEM reflecting different coagulation pathways. Thirdly, FIBTEM analysis showed that the difference (bias) between A5_{FIBTEM} and MCF_{FIBTEM} was small, only 1.3 mm in patients with hypofibrinogenaemia (median Fib=100 mg dl⁻¹). In addition, the ROC curves of A5_{FIBTEM} and A10_{FIBTEM} for Fib<100 mg dl⁻¹ yielded almost identical AUCs, indicating that A5_{FIBTEM} was as useful as A10_{FIBTEM} in consistently predicting hypofibrinogenaemia. Lastly, although replacement guidelines for thrombocytopenia and hypofibrinogenaemia during LT surgery vary widely among institutions, the critical PLT triggering transfusion is generally thought to range from 30 000 to 50 000 mm⁻³.^{14 15} We therefore analysed the correlations between A5 parameters on ROTEM[®] analysis and the commonly used quantitative cut-off values for PLT<30 000 mm⁻³ and <50 000 mm⁻³ and Fib<100 mg dl⁻¹ during LT.^{8 15}

Because conventional laboratory tests have long turn-around times in clinical settings, determining when to start a transfusion and the amounts of allogeneic blood products transfused into patients with massive bleeding is difficult. Therefore, early variables assessed by point-of-care ROTEM device, which are available within 10–20 min, have been increasingly used to trigger transfusion of platelets and fibrinogen-rich products. Trigger values were based on evidence that these variables could successfully determine thrombocytopenia and hypofibrinogenaemia in patients undergoing LT and cardiac surgery and those with severe

Table 2 Intraoperative ROTEM[®] data and bias for A5 and A10 on the Bland–Altman analyses. Data were expressed as median (inter-quartile range) or mean (SD). NA, not available. A5, clot amplitude at 5 min; A10, clot amplitude at 10 min; MCF, maximum clot firmness

Variables	EXTEM	INTEM	FIBTEM
Clot time (s)	71 (52–103)	229 (197–278)	59 (46–95)
Clot formation time (s)	235 (173–307)	231 (164–309)	NA
α-Angle (°)	49 (39–58)	52 (42–61)	NA
A5 (mm)	19 (15–25)	20 (15–25)	5 (3–7)
A10 (mm)	27 (22–34)	27 (22–33)	5 (4–8)
MCF (mm)	37 (31–43)	37 (31–43)	6 (4–9)
Bias for A5 (mm)	16.4 (3.7)	16.2 (3.6)	1.3 (1.4)
Bias for A10 (mm)	8.8 (2.7)	8.8 (2.8)	0.7 (1.0)

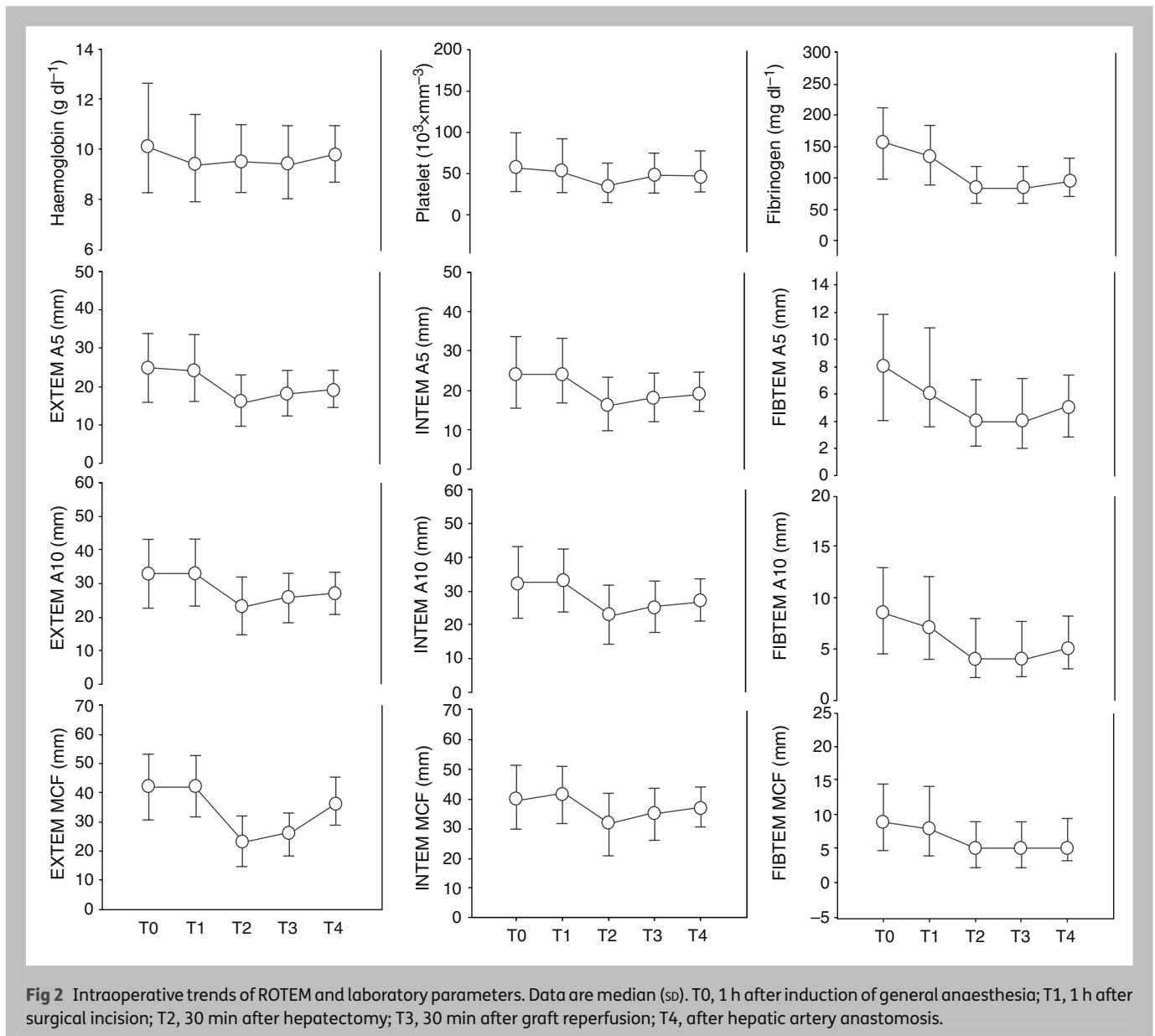


Fig 2 Intraoperative trends of ROTEM and laboratory parameters. Data are median (SD). T0, 1 h after induction of general anaesthesia; T1, 1 h after surgical incision; T2, 30 min after hepatectomy; T3, 30 min after graft reperfusion; T4, after hepatic artery anastomosis.

trauma.^{8 11 16–18} In trauma patients, an $A10_{\text{FIBTEM}}$ of 5 mm was the threshold that best predicted hypofibrinogenaemia ($<100 \text{ mg dl}^{-1}$), whereas an $A15_{\text{INTEM}}$ of 46 mm best predicted thrombocytopenia ($<50\,000 \text{ mm}^{-3}$).¹⁸ During LT surgery, our results demonstrated that both $A10_{\text{EXTEM}}$ and $A10_{\text{INTEM}}$ of 27 mm were the thresholds best predicting thrombocytopenia ($<50\,000 \text{ mm}^{-3}$), whereas an $A10_{\text{FIBTEM}}$ of 5 mm best predicted hypofibrinogenaemia ($<100 \text{ mg dl}^{-1}$). These findings are in agreement with previous studies showing that an $A10_{\text{FIBTEM}}$ of 5 mm was optimal in trauma patients¹⁸ and that an $A10_{\text{EXTEM}}$ of 29 mm was the optimal cut-off for thrombocytopenia ($<50\,000 \text{ mm}^{-3}$) during LT.⁸

Notably, this study was the first to show that A5 is a reliable early parameter that can substitute for both A10 and MCF in patients in a hypocoagulable state observed during LDLT (median $\text{MCF}_{\text{EXTEM}}=37 \text{ mm}$ and median $\text{MCF}_{\text{FIBTEM}}=6 \text{ mm}$). Among the ROTEM[®] parameters, the A5 and A10 indices of

both EXTEM and INTEM showed excellent correlations with their MCF values, and $A5_{\text{FIBTEM}}$ and $A10_{\text{FIBTEM}}$ were highly correlated with $\text{MCF}_{\text{FIBTEM}}$. These results are comparable with the excellent correlations observed for A5 and A10 with their MCFs in a heterogeneous study population that included individuals with subnormal, normal, and supranormal MCF values.¹¹ Our findings also demonstrated that the correlation coefficients of $A5_{\text{EXTEM}}$ and $A10_{\text{EXTEM}}$ with PLT, $A5_{\text{INTEM}}$ and $A10_{\text{INTEM}}$ with PLT, and $A5_{\text{FIBTEM}}$ and $A10_{\text{FIBTEM}}$ with Fib were almost identical. Therefore, these results strongly indicate that A5 is as accurate as A10, allowing earlier parameters to guide PLT transfusion during LT.⁸

We observed biases between early variables (A5 and A10) and MCF of ROTEM[®] analyses. Because the median values of $\text{MCF}_{\text{EXTEM}}$, $\text{MCF}_{\text{INTEM}}$, and $\text{MCF}_{\text{FIBTEM}}$ were 37, 37, and 6 mm, respectively, our data characterize patients with subnormal MCF. In EXTEM and INTEM assays, the biases between A5 and A10 and MCF were 16 and 9 mm, respectively. Therefore, to

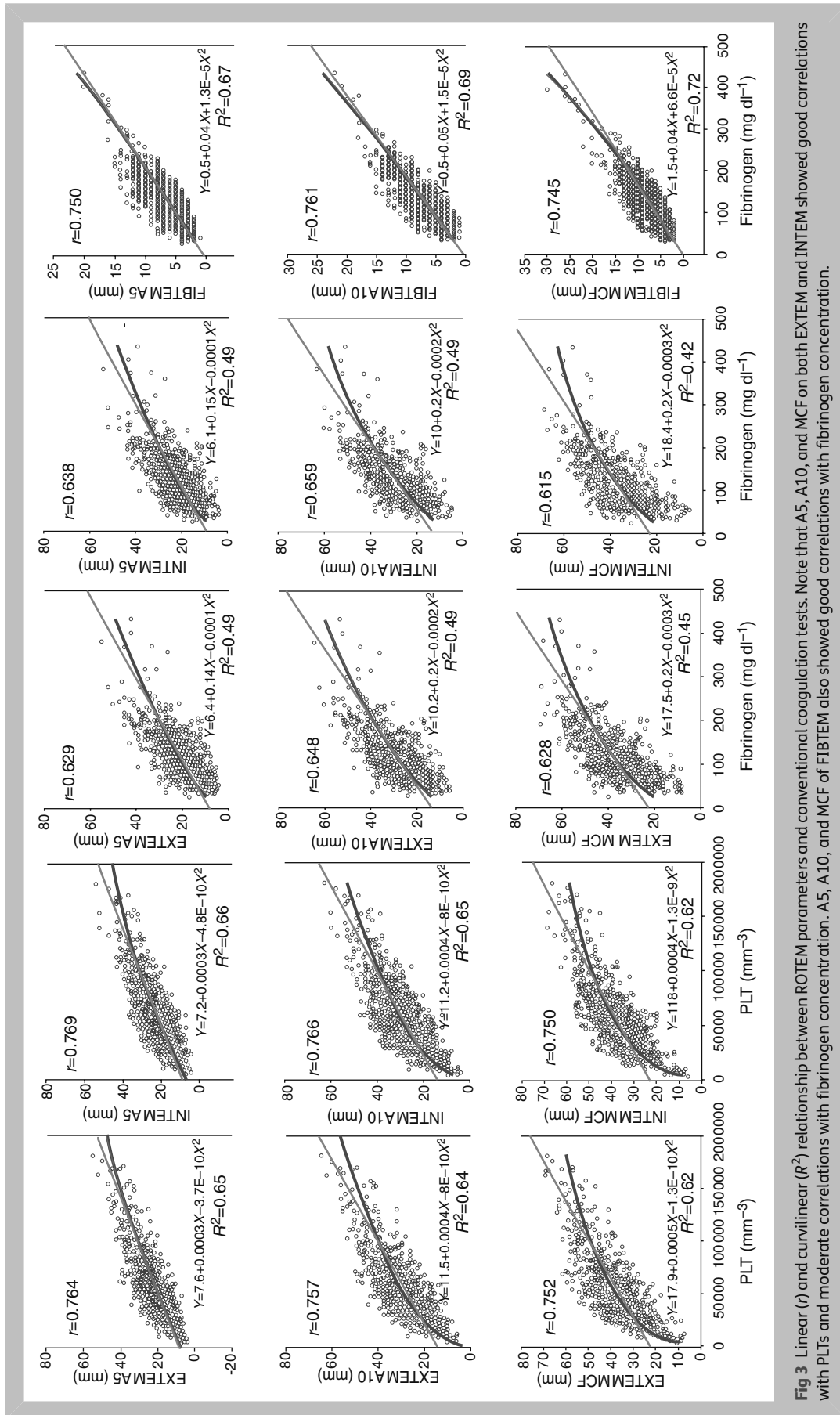


Fig 3 Linear (r) and curvilinear (R^2) relationships between ROTEM parameters and conventional coagulation tests. Note that A5, A10, and MCF on both EXTEM and INTEM showed good correlations with PLTs and moderate correlations with fibrinogen concentration. A5, A10, and MCF of FIBTEM also showed good correlations with fibrinogen concentration.

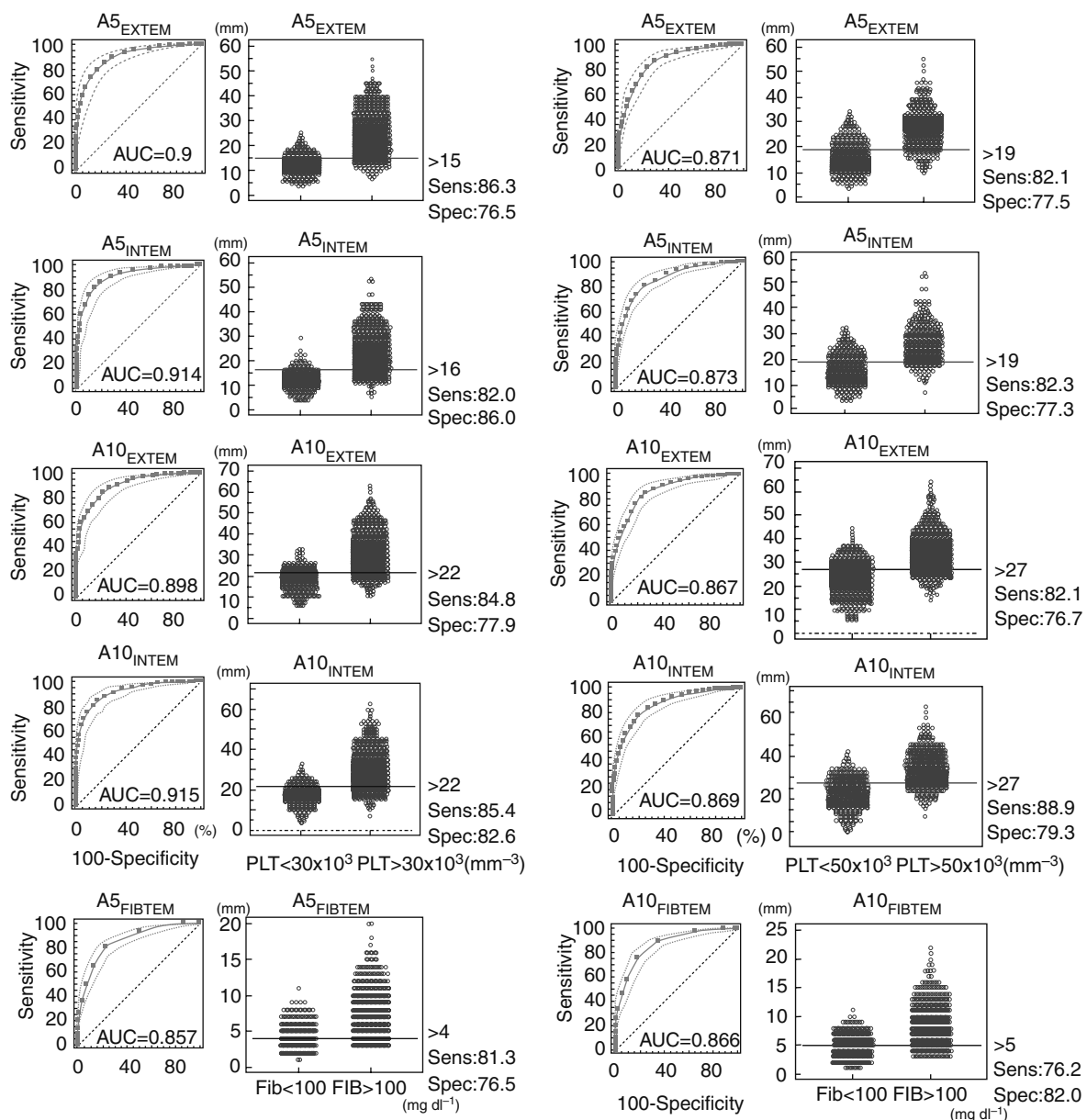


Fig 4 ROC curves of A5 and A10 on EXTEM, INTEM, and FIBTEM predicting thrombocytopenia and hypofibrinogenaemia. AUC values of A5 and A10 on both EXTEM and INTEM were good predictors of PLTs $<30 \times 10^3$ and $<50 \times 10^3$ mm⁻³. AUC values of A5, A10, and MCF on FIBTEM were good predictors of fibrinogen <100 mg dl⁻¹.

determine the approximate value of their MCFs, 16 mm should be added to the A5 value and 9 mm to the A10 value in patients undergoing LT. A previous study, however, reported that 19 mm should be added to A5 and 10 mm to A10 (11 mm for patients with $MCF_{EXTEM} < 50$ mm) to obtain rough estimates of their MCFs.¹¹ These discrepancies were more pronounced in FIBTEM assays, in that 4.5 mm was added to A5 and 3.4 mm to A10 mm (1.95 mm in patients with $MCF_{FIBTEM} < 9$ mm) to obtain rough estimates of MCF_{FIBTEM} .¹¹ In contrast, we found that only ~1 mm (1.3 and 0.7 mm, respectively) had to be added to the A5 and A10 values of MCF_{FIBTEM} in patients

undergoing LT. There are several possible reasons for the differences between our study and previous studies.¹¹⁻¹⁹ First, the characteristics of the patient populations in the previous study included all non-cardiac patients, regardless of MCF values. A comparison of study populations showed that 73% and 90% in our study were below the reference ranges on the FIBTEM ($MCF_{FIBTEM} < 9$ mm) and EXTEM ($MCF_{EXTEM} < 50$ mm) assays, compared with 14.3% and 49.1%, respectively, in the earlier study.¹¹ Secondly, preexisting differences in conventional laboratory parameters between studies might have an effect on ROTEM® analyses. Tripodi and colleagues¹⁹

demonstrated that PLT was the most important determinant in MCF in patients with stable cirrhosis, in which the study population showed low PLT with nearly normal Fib. In contrast, our study population showed both low PLT [47 000 (32 000–64 000) vs 65 000 (24 000–178 000) mm^{-3}] and Fib [100 (77–137) vs 199 (108–423) mg dl^{-1}], respectively, compared with that study.¹⁹ Thirdly, differences in the use of colloids might have an effect on the observed bias, particularly for FIBTEM. Synthetic colloids such as hydroxyethyl starch solutions are known to have an impact on fibrin polymerization, resulting in decreased MCF.^{20 21} However, as we used only albumin for colloid solution during LDLT, our data would not be affected by synthetic colloids in the bias between early variables of clot firmness (A5 and A10) and MCF. This difference might result in increased bias between A5 (A10) and MCF, in particular in FIBTEM, between our study and the earlier study.¹¹ Taken together, because of the potentials for selection and observation biases among different studies (e.g. differences in gender, ethnicity, clinical conditions, types of fluid replacement, etc.), care should be taken when interpreting the results of bias between early variables (A5 and A10) and MCF of ROTEM[®] analyses.

Our study had several limitations. First, it was a retrospective, single-centre study, suggesting caution in interpreting our results as there might have been observation bias and bias in patient selection. Secondly, we did not assess the predictability of transfusion requirements based on ROTEM[®] analysis or standard coagulation tests. Further studies are needed to evaluate whether threshold levels of ROTEM[®] parameters can estimate clinical bleeding and guide transfusion therapy to improve treatment of haemostatic derangements associated with LDLT.

In conclusion, our findings indicate that A5 as an early variable of clot firmness in thromboelastometry is effective to detect thrombocytopenia and hypofibrinogenaemia in hypo-coagulable patients undergoing LT. A5 on ROTEM[®] analysis might be the earliest, most reliable index in selecting transfusion guidelines based on PLT and Fib during LDLT.

Authors' contributions

J.-G.S.: study design, study data analysis, manuscript preparation, and revision; S.-M.J.: study design and data analysis; I.-G.J.: data collection and analysis; H.-M.L.: data analysis; G.-S.H.: study design, study conduct, data analysis, manuscript preparation, and revision.

Declaration of interest

None declared.

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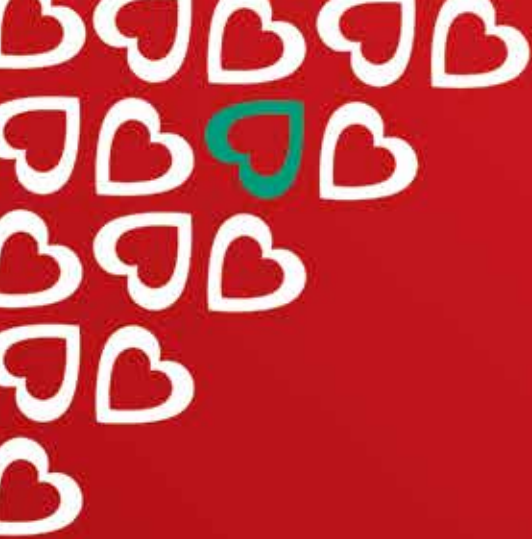
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