Optimising Perioperative Care in Elective Hip and Knee Arthroplasty

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Abstract

Aim

To improve perioperative care in total hip and knee arthroplasty (THA and TKA).

Methods

This thesis is divided into two distinct parts. In the first part an orthopaedic-specific standardised, Enhanced Recovery After Surgery (ERAS) programme was designed, implemented and evaluated. As part of a review of the literature tranexamic acid (TXA) was identified as an important component of an orthopaedic-specific ERAS programme by reducing blood loss and mitigating the need for allogenic blood transfusion perioperatively. A national survey of arthroplasty surgeons was performed to illustrate current perioperative care practices with a special interest in the use of TXA.

Part 2 of the thesis investigated TXA in the setting of an orthopaedic-specific ERAS programme as a means to further hasten recovery and reduce perioperative morbidity. A review of the literature on TXA comparing the efficacy of systemic and topical routes was performed. In a multi-centred, randomised controlled trial (RCT) topical and systemic TXA was compared against a placebo group to determine if the route of administration influenced efficacy.

Results

An orthopaedic-specific ERAS programme was safely implemented into clinical practice at a single, public hospital in NZ and demonstrated a significant reduction in hospital length of stay (5 days v. 4 days; $p < 0.001$), less readmissions and less in-hospital costs. The survey of NZ arthroplasty surgeons revealed that the use of TXA in TKA and THA remained low perhaps due to concern regarding potential thromboembolic risks of systemic TXA. In the

RCT, systemic and topical TXA, given as a single 1.5 g intraoperative dose, were found to be equally efficacious in reducing perioperative blood loss among TKA patients when compared with placebo (topical: 723 ml v. systemic: 749 ml v. placebo: 1090 ml; $p < 0.0003$ and $p < 0.001$).

Conclusion

An orthopaedic-specific ERAS programme in THA and TKA can successfully be implemented resulting in quicker, early recovery without compromising patient safety. Within the setting of an established ERAS programme, a single intraoperative dose of TXA given during TKA significantly reduces perioperative blood loss. While not powered for thromboembolism risk the efficacy of locally administered TXA may encourage arthroplasty surgeons to use TXA more in the future.

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List of Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
ACCP	American College Chest of Physicians
AF	Atrial fibrillation
ANOVA	Analysis of variance
ASA	American Society of Anaesthesiologists
BMI	Body mass index
BV	Blood volume
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DVT	Deep vein thrombosis
EBL	Estimated blood loss
ERAS	Enhanced Recovery After Surgery
ESR	Erythrocyte sedimentation rate
GA	General anaesthesia
Hb	Haemoglobin
IDC	Indwelling catheter
IHD	Ischaemic heart disease
IL-6	Interleukin-6
INR	International normalised ratio
IO	Intraosseous
IPCD	Intermittent pneumatic compression devices
IV	Intravenous
IVF	Intravenous fluid
LA	Local anaesthetic
LMWH	Low molecular weight heparin
LOS	Length of stay
MEDD	Morphine equivalent daily dose
MIS	Minimally invasive surgery
MSC	Manukau Surgery Centre
MUST	Malnutrition Universal Screening Tool

NSAID	Non-steroidal anti-inflammatory
NZ	New Zealand
NZOA	New Zealand Orthopaedic Association
OA	Osteoarthritis
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
PE	Pulmonary embolus
PEP	Pulmonary Embolism Prevention
PONV	Postoperative nausea and vomiting
PRBC	Packed red blood cell
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPECT	Procedure Specific Postoperative Pain Management
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
REASON	Research into Elderly Patient Anaesthesia and Surgery Outcome Numbers
ROM	Range of movement
SA	Spinal anaesthesia
SLR	Straight leg raise
SRS	Surgical Recovery Scale
sTXA	Systemic tranexamic acid
TED	Thromboembolic deterrent
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
tTXA	Topical tranexamic acid
TXA	Tranexamic acid
TXA2	Thromboxane-2
UK	United Kingdom
USA	United States of America
VTE	Venous thromboembolism

Chapter 1: Introduction

The burden of hip and knee osteoarthritis

Osteoarthritis (OA) is a major cause of disability among the elderly, affecting upwards of one in eight adults.(1) It has a positive correlation with increasing age and it is therefore commonplace for older populations to be inflicted with this disease.(2) For many of these individuals, knee or hip pain and stiffness imparts marked functional limitations and contributes significantly to poorer quality of life (QoL) and takes a large toll on independence.(3)

Long-term sufferers find it difficult to perform simple, everyday activities; moreover, OA impacts negatively on QoL, mood and sleep.(4) QoL best captures the individual burden of OA.(1) In the United States of America (USA), OA is responsible for 15 million quality-adjusted life years (QALYs) lost annually. One study reported that knee OA sufferers aged 50–84 years experienced losses in QALYs over the remainder of their lives, ranging from 1.9 to 3.5 for non-obese and obese individuals, respectively.(3)

Employment opportunities may be limited or even relinquished as a result of pain and immobility secondary to OA.(1) In Australia, half of individuals aged 45–64 years identified as having OA as their main condition were out of employment.(5) Furthermore, OA sufferers have a threefold risk of not participating in the workforce when compared with their healthy counterparts. In 2009, it was estimated that 80,000 individuals were absent from the Australian workforce secondary to OA.(5)

Despite only a small proportion of patients being hospitalised for symptoms of OA, most of the direct costs are attributed to hospital stays and orthopaedic procedures, the majority of these being for total joint replacements.(1) This was exemplified by a French cohort in which

50% of the direct costs of OA were incurred by hospitalised OA individuals – only 3% of the study group.(6) In the USA over a million joint replacements are performed per year at an estimated total cost of USD15 billion (1), though some estimates have been reported to be as high as USD42.3 billion.(7) These costs are projected to rise quickly owing to a growing population and also younger cohorts being offered joint replacement surgery. Earlier joint surgery equates to a higher chance of revision surgery, which can be double the cost of the index surgery, thus escalating costs further.

Thus, not only does OA have a huge impact on individuals, but from a societal perspective, the burden of OA has huge implications for productivity and healthcare resource consumption.

Despite New Zealand's (NZ) geographical isolation, it shares the increasingly universal problem of all developed countries around the world: a population that is both increasing and ageing. By the year 2051, it is expected that NZ's population over the age of 60 years will almost double, from 16% to 31%.(8) It is estimated that one in six adults in NZ currently suffer from arthritis.(9) NZ's ageing population, compounded by the baby boomers reaching their seventh decade of life, highlight the increasing demand for healthcare services, including hip and knee joint replacement surgery for OA. A steady rise in these surgeries across Organisation for Economic Co-operation and Development (OECD) countries since 2000 is reflective of the increasing, ageing population.(10) In NZ, the total annual cost of joint replacements, of which the majority were hips and knees, was estimated at NZD191 million in 2007.(8) As elsewhere, the demand for this procedure is contributed to by a rise in the number of younger adults requiring arthroplasty: 20% of hip replacements are performed in those aged less than 60 years.(11)

At the same time, societal attitudes are changing and pose a unique challenge to health systems across the globe. Expectations to live active lifestyles in later years are prevalent among the very populations that are burdened by the disease.(12) This has been brought to the attention of government policy makers, and maintaining independence into these twilight years has been identified by the Ministry of Health as a key goal for the older population in NZ.(13) Chronic disease, including hip and knee joint arthritis, can impact negatively on one's independence through severe pain and disability (14, 15), thus contributing to the huge burden of OA that has overwhelming implications that go beyond the individual.

Treatment of end-stage hip or knee osteoarthritis

The pathogenesis of OA is irreversible with no known cure. Preventative measures, including regenerative medicine, to slow progression of OA are currently being investigated, though the effects of these will not be realised for some time into the distant future.(16-18) Currently, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are the only proven treatments for end-stage OA that is unresponsive to medical treatments and when other non-pharmacological modalities have failed.

Efficacy of arthroplasty

Since the advent of the modern era of arthroplasty, sufferers of end-stage large joint disease have had a reliable and effective option for resolving their pain and immobility. The extent to which each patient responds is varied and depends on preoperative function, patient comorbidities and postoperative complications. However, for the overwhelming majority of patients who overcome the morbidity associated with THA and TKA, their outcomes are generally positive. Patients can expect significant reduction in pain, and improved mobility, QoL and function.(19-22) In general, both THA and TKA have been shown to demonstrate marked improvements in QoL for these patients in the short to medium term compared with preoperative levels.(11, 23)

The surgical stress of hip and knee arthroplasty

Hall and Salmon (2002) attempted to correlate physiological stress with postoperative fatigue following THA. Interestingly, they found that the severity of postoperative fatigue was not associated with rises in various cytokines and other inflammatory and stress markers (norepinephrine, epinephrine, cortisol, interleukin-6 [IL-6], and C-reactive protein [CRP]) during the 7 days after surgery.(24) This is in contrast to the situation seen in major abdominal surgery.(25) However, the authors found that preoperative level of fatigue was a positive predictor for postoperative fatigue. Higher levels of preoperative fatigue in this cohort undergoing this specific procedure may be a reflection of delays in timely access to this operation or a more comorbid population.

One other study by Hall et al. endeavoured to define the pattern of changes in circulating hormones and cytokines up to a week after surgery in 158 uncomplicated THA and TKA patients.(26) All parameters measured in the postoperative period were significantly increased compared with preoperative levels. The authors noted an unexpected sustained elevation of cortisol levels in both procedures and suggest that this elevation was due to elevated IL-6 levels as this has been observed *in vitro* to stimulate the hypothalamic-pituitary-adrenal axis.(27) Evidence refuting this association is the early rise in cortisol levels (2 hours) not being mirrored by a rise in IL-6 levels. A steep rise in CRP levels between 24 and 48 hours was also observed, followed by a gradual decline for the remainder of the study period. Similar patterns in CRP levels have been observed in other series of arthroplasty cohorts.(28, 29) The predominating source of the observed rise in CRP in this setting has been hypothesised to be due to bone or marrow trauma.(30, 31) Macrophages are an important source of acute phase proteins, including CRP, and are more common in bone and marrow than in muscle.(30) Despite many authors demonstrating appropriate rises in

inflammatory cytokines in response to orthopaedic surgery, none have found an association with the severity of postoperative fatigue or delays in recovery.

Ng et al. demonstrated that after local administration of corticosteroid (triamcinolone 40 mcg) in patients undergoing unilateral knee arthroplasty, patients had significantly lower CRP and erythrocyte sedimentation rate (ESR) levels (days 1, 2 and 3; $p < 0.001$), had greater range of flexion (days 1 and 2; $p < 0.04$) and were able to achieve a straight leg raise earlier than the control (day 2 v. day 6; $p < 0.01$).(32) Thus, reduction in CRP and ESR (inflammatory cytokines) through corticosteroid (anti-inflammatory) administration coincides with achieving early functional milestones suggesting quicker recovery. However, a causal relationship remains to be seen. It is tempting to attribute a hastened recovery and possibly reductions in postoperative fatigue to decreases in the inflammatory response, as has been shown in colorectal surgery.(33)

Special considerations for the hip or knee arthroplasty candidate

It is well accepted that older patients presenting for all types of surgery harbour higher rates of chronic diseases, including cardiovascular disease, respiratory disease, osteoporosis, anaemia of chronic disease, renal disease and cognitive impairment.(34) Moreover, with increasing age there is a noticeable reduction in functional capacity of organs, resulting in less reserve to endure the stress of surgery and anaesthesia.(34) Both increasing age and comorbid disease have been shown to contribute to the risk of postoperative mortality.(35, 36) In order for patients to reap the benefits of THA or TKA, they must first overcome the short-term morbidity of surgery itself. Major surgery, including THA and TKA, leads to significant postoperative morbidity, including cardiovascular and respiratory complications, pulmonary embolus (PE), deep vein thrombosis (DVT), postoperative nausea and vomiting (PONV), postural hypotension, postoperative anaemia, pain and rarely, death.(1, 34, 37) The

reasons for this are multiple and are largely dependent on patient factors, hospital resources and perioperative care knowledge. This has implications for rehabilitation and a safe and timely discharge.

In THA, postoperative complications have been associated with poorer functional outcomes out to one year. However, this is largely a reflection of the severity of preoperative comorbidities.(38) More concerning is the positive correlation that postoperative adverse events have with rates of mortality, including THA.(37) The REASON study (Research into Elderly Patient Anaesthesia and Surgery Outcome Numbers) was a multicentre observational trial of over 4000 elderly surgical patients across 23 hospitals in Australia and NZ. The authors of this study found four preoperative and three postoperative factors to be important predictors of 30-day mortality in this population. The postoperative factors included systemic inflammation (odds ratio [OR] 2.5), acute renal impairment (OR 3.3) and an unplanned intensive care unit admission (OR 3.1).(39) Reducing the incidence of these factors requires preoperative planning and early detection and intervention.

In this older surgical population, it is not uncommon for patients to present with multiple age-related, pre-existing diseases that leave them prone to adverse perioperative events. And so it is no surprise that this older cohort has the highest mortality rates among surgical patients.(36)

Venous thromboembolism

Venous thromboembolic risk is significantly increased with THA and TKA: incidences of postoperative venous thromboembolism (VTE) have been reported as high as 60% prior to routine VTE prophylaxis.(40) Despite attempts to reduce this risk, including appropriate mechanical and chemical prophylaxis, modern anaesthesia and early mobilisation, the incidence of symptomatic VTE continues to range from 1% to 2%.(41)

Additional concerns surround the treatment of symptomatic events, especially if DVT or PE occurs soon after the operation. For the majority of units, anticoagulants at therapeutic doses (low molecular weight heparin [LMWH]: 1 mg/kg/day; warfarin international normalised ratio [INR]: 2–3) are used to treat clots. This has implications for wound healing and haematoma formation, which in themselves create ongoing morbidity and places these patients at additional risk for infection – an equally catastrophic complication.

Postoperative anaemia

Postoperative anaemia following elective arthroplasty can lead to prolonged hospital stay and delays in rehabilitation, and is often poorly tolerated in patients with cardiovascular disease.(42, 43) Hip and knee joint surgery is associated with significant blood loss.(44) In 2000, a survey performed of blood use in England reported that 41% of all units of blood were received by surgical patients. Eight per cent of the total numbers of units were administered to patients undergoing THA, TKA and hip fracture surgery and these surgeries together were the leading indications for blood transfusion among surgical patients.(45) Myers et al. reported significant differences in mean length of stay (LOS) in their cohort of 225 THA patients. Anaemic patients on average spent 7 days longer in hospital than non-anaemic patients (18 days versus 11 days; $p < 0.001$).(46)

In surgical patients with concomitant chronic disease, including cardiovascular disease, the risk of death and severe morbidity is significantly higher than for those individuals without cardiovascular disease.(47) As alluded to, large blood losses can be expected in arthroplasty surgery owing to exposed intramedullary ends, vascular subcutaneous tissues and concomitant anticoagulation. Perioperative surgical bleeding can be significant enough that it lowers thresholds for clot formation, cardiovascular events (acute myocardial infarction) and renal dysfunction. Postoperative anaemia can also induce postural changes in blood

pressure, nausea and vomiting, and dizziness, which all impair surgical recovery. Hence, a population laden with one or more chronic diseases in this setting marks the importance of blood conservation as they are less resilient to haemodynamic changes.

Clinical question

This group of patients therefore poses a challenging dilemma, not only for the surgical and medical teams, but also for those responsible for allocating scarce health resources. How do surgical/medical teams get adult patients who are (1) older and (2) likely to have chronic disease and therefore are at risk for postoperative complications through their operations so that they may benefit from joint surgery, and ultimately regain function and independence?

Perioperative care

Enhanced Recovery After Surgery

Enhanced Recovery After Surgery (ERAS) protocols have been hypothesised to address these issues. Pioneered by Prof Henrik Kehlet in colorectal surgery, ERAS protocols have been used extensively around the world and in many places are considered standard practice in gastrointestinal surgery.(48) The aim of ERAS is to attenuate the stress response induced by surgery. Attempts to address this issue through searching for the best available evidence in the current literature and putting it into clinical practice has led ERAS to what it is today. Traditional care has the surgeon and anaesthetist as the two key stakeholders in a patient's care. In contrast, ERAS takes a much broader approach, in which all staff have important parts to play in healthcare delivery. This collaborative approach is the cornerstone for ERAS implementation, sustainability and future directions allowing focussed engagement in all aspects of the patient's perioperative journey; from their first specialist appointment before surgery to the day of discharge and follow up.

Larger series in the United Kingdom (UK) and Denmark have reported reductions in LOS, morbidity and mortality with ERAS in elective orthopaedics.(49, 50) In the largest series of ERAS in arthroplasty (n = 6000), Khan et al. showed a significant reduction in 30-day mortality (0.1% v. 0.5%, p = 0.03) as compared with traditional care. Similarly, the incidence of myocardial infarction dropped significantly (0.4% v. 0.9%, p = 0.03) in the

ERAS group. Consistent reductions in LOS have largely been attributed to patient education or expectations and buy-in from multidisciplinary staff enthusiastic about the benefits of ERAS. Reductions in LOS in some places must be interpreted with caution. In the USA, reductions in LOS in this setting have also been reported; however, discharge dispositions do differ and an increasing number of patients are transferred to rehabilitation facilities to see out their remaining convalescence, thus giving a different interpretation of hastened recovery.(51)

Important key stakeholders and those responsible for policy making have observed these benefits from a societal and economic perspective. Some advocates of enhanced recovery protocols have proposed cost savings through reducing LOS.(52) Larsen et al. performed a cost-utility study that was linked to a previous randomised control trial investigating the effect of accelerated perioperative care in THA and TKA.(53) They captured indirect costs, including QoL data, via the EQ-5D questionnaire at multiple time points postoperatively. The EQ-5D measures five domains of QoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The accelerated intervention was less costly (ERAS: [Danish Krone] DKK 87,657 ± 39,915; Control: DKK 71,768 ± 41,544) and more effective for THA (QALY ERAS: 0.83 ± 0.10; 0.78 ± 0.15). In TKA and unicompartmental knees, the accelerated intervention was less costly (ERAS: DKK 70,644 ± 38,437; Control: DKK 95,367 ± 61,293) and equally effective. Similarly, Khan et al. reported a cost savings of roughly EUR3.5 million based on their reduction in LOS observed in their ERAS cohort.(49) If the reported costs savings are real, then this has important implications for ameliorating the rising economic affliction facing healthcare systems both here and globally.

In a NZ context this has significant implications for addressing the Ministry of Health's priorities for the four year period Health budget (2012-16).(54) This document highlights

the need for increasing number of elective surgeries (4000 per year), reducing waiting times for patients to see a specialist and for their operation, all within a reduced budget. These priorities were made in anticipation of the increasing, ageing population and attenuating the costs associated with this group of patients. By hastening recovery safely in THA and TKA patients, it is anticipated that greater elective throughput can be achieved; thus, by optimising and standardising perioperative care, an orthopaedic-specific ERAS pathway is an appropriate strategy to address these priorities.

Local experience

In 2005, Professor Andrew Hill, a ward charge nurse and a colorectal nurse specialist, visited Denmark to observe and take notes on how ERAS was delivered in their colorectal unit. Inspired by what he had seen, Prof Hill returned with fresh vigour to implement ERAS for their colorectal patients, knowing there was huge scope for improvement. December 2005 marked ERAS implementation for colorectal patients at the Manukau Surgery Centre, Auckland. Patients managed according to the new pathway demonstrated significantly fewer complications, less perioperative fluid requirement and reduced hospital stay.(55) Subsequent analysis on the same cohort of patients identified direct cost savings of up to NZD7000 per ERAS patient when taking into account the set-up costs (i.e., flights to Denmark, salary of research fellow).(56)

Similarly, in obesity-related surgery in the same institution, using the colorectal-specific ERAS programme as a template, Lemanu et al. designed and evaluated ERAS in patients undergoing laparoscopic sleeve gastrectomy.(57) The randomised controlled trial (RCT) of 116 patients showed that patients managed according to ERAS had less hospital stay, reduced associated in-hospital costs and similar morbidity compared with their control and historical groups.

Enhanced Recovery After Surgery function

ERAS' strengths lie in its standardisation of evidence-based perioperative care interventions that are delivered by the whole multidisciplinary staff, from the preoperative nursing staff through to the ward staff. Unlike colorectal and other general surgical procedures, it is yet to be established exactly what an ERAS perioperative care protocol in an elective arthroplasty setting entails, especially in an NZ setting. Experience of ERAS in bowel surgery at the Manukau Surgery Centre will undoubtedly facilitate easier implementation of an orthopaedic-specific ERAS programme at the same institute, which has been highlighted by others as a key factor of its success.(55, 58) Although the principles remain the same, there is no gold standard for an orthopaedic-specific ERAS programme, and hence Chapter 2 suggests key perioperative care interventions used in the setting of elective THA and TKA. In association with local resources, this would be used as a template for establishing an ERAS protocol at Middlemore Hospital and, secondly, hospitals across the country as part of the ERAS National Collaborative. Chapter 4 evaluates an orthopaedic-specific ERAS programme and compares outcomes with an historical cohort of patients. Prior to ERAS implementation, it was important to determine the *status quo* and ask arthroplasty surgeons across the country via an online survey about what specific perioperative care interventions they employed for patients undergoing these surgeries. This survey is described in Chapter 3.

Blood conservation

Tranexamic acid

Central to an ERAS protocol in orthopaedic surgery is prevention of significant blood loss and perioperative anaemia with the use of tranexamic acid (TXA). TXA is a synthetic derivative of lysine that is responsible for binding reversibly to plasminogen, effectively inhibiting clot degradation.(59) TXA is used by many orthopaedic surgeons to reduce perioperative blood loss and subsequent transfusion of blood products in elective THA and TKA. In several reviews, systemic TXA significantly reduced blood loss and transfusion rates when compared with placebo, without an increased risk of VTE.(60-62)

The evidence for its use to date is overwhelming, and when not contraindicated, it should be employed by all arthroplasty units as part of their standard practice. However, despite the vast evidence for its use in arthroplasty, some surgeons remain cautious over its safety profile when given systemically. Even though TXA is not clot promoting, inhibiting clot breakdown theoretically may increase the likelihood of clot formation. This is of real concern for surgeons in patients who have had previous VTE. For this reason, some surgeons have utilised TXA as a topical application directly into the surgical field to reduce systemic absorption and avoid VTE.(63-65)

Intraarticular administration has been touted as having less systemic absorption and higher local concentrations to further enhance its blood-conserving properties. TXA, administered topically in TKA, has also been reported to reduce swelling, which may have the additional advantage of earlier mobility and less pain.(66) With these additional benefits in mind, this may be perceived as a superior route. However, it needs to be shown that it provides efficacy equivalent to the more widely accepted systemic route. Chapters 5 and 6 investigate TXA and its systemic and local uses in TKA.

Aim of thesis

Hip and knee OA is a leading cause of disability in all parts of the world. Its prevalence, an ageing population and the rising obesity epidemic underline its significance to healthcare providers in NZ. For end-stage disease, THA and TKA are common interventions to relieve the individual burden of OA and are well-established surgical management options. However, considerable costs are associated with this procedure and it is important for health providers to ensure all patients have successful outcomes with minimal harm. This thesis, therefore, endeavours to improve resource utilisation in THA and TKA surgeries and ensure patients reap the intended benefits of their surgery by attenuating the surgical insult. The thesis is separated into two major areas of focus:

1. Optimising perioperative care in order to reduce variation, improve clinical outcomes and reduce associated costs with THA and TKA.
2. Reducing significant blood loss in the postoperative period as a means of further enhancing recovery after total knee arthroplasty in both the short and medium terms.

Chapter 2: Optimising arthroplasty perioperative care – a review

Introduction

THA and TKA provoke a physiological stress response.(67) This stress induces a pro-inflammatory cascade of events that contributes to postoperative complications, and prolonged convalescence, rehabilitation and recovery. This extended healing process has a multifactorial aetiology with biological, psychological and social factors implicated.(68)

Understanding and appreciation of the surgical stress response and immediate postoperative recovery period has allowed targeting of key aspects of a patient's preoperative, intraoperative and postoperative experience, aiming to minimise physiological and psychological insults. Evidence-based interventions at each of the corresponding stages of the pathway, when combined, are intended to have greater impact than the sum of the individual components. The structured organisation of a standardised perioperative care pathway such as ERAS in elective THA and TKA is based on these principles.

Across the globe, interest in standardising perioperative surgical care has gained momentum. Over the past two decades, fast-track, accelerated rehabilitation, ERAS or clinical pathway programs have successfully been implemented in a range of elective surgeries.(69, 70) Elective THA and TKA are no different. A large retrospective study of total joint replacement surgery found that adherence to standardised perioperative care interventions correlated positively with reduced rates of complications and a shorter hospital stay independent of hospital volume.(71) Multiple centres have demonstrated benefits of standardising perioperative care pathways in elective THA and TKA surgeries; however, there is considerable variation in the interventions included in the pathways.(72-92) The aim of this review chapter was to assess the evidence for defined components within an ERAS

pathway for patients undergoing THA and TKA, in order to develop an evidence-based platform for the clinical evaluation of other perioperative care interventions.

Search strategy and criteria

This study consists of a systematic review, used to identify perioperative care interventions to be considered when formulating an ERAS pathway, and a narrative review, used to report on the existing literature assessing the efficacy of the perioperative care interventions identified.

Systematic review

Search strategy: A comprehensive review of the literature was performed in accordance with methods outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(93) Medline, PubMed, PsycINFO and the Cochrane Central Register of Controlled Trials were searched from inception to January 2013 using search terms shown in Table 1. References from recovered studies were also manually scrutinised.

Table 1. Database search terms

Search terms
exp Arthroplasty, Replacement, Knee/ OR exp Arthroplasty, Replacement, Hip/
AND
Fast Track.mp. OR ERAS.mp. OR enhanced recovery after surgery.mp. OR Accelerated Rehabilitation.mp.
AND
exp Postoperative Complications/ OR exp "Length of Stay"/ OR exp Patient Satisfaction/ OR exp Infection/ or exp Wound Infection/ OR exp Pulmonary Embolism/ or exp Venous Thrombosis/ or dvt.mp. OR exp Death/ OR exp Myocardial Infarction/ OR exp Stroke/ OR exp Dislocations/ OR exp Pain/

Study selection: Perioperative care interventions were identified from studies comparing ERAS to standard perioperative care in the setting of elective primary THA and TKA. Studies were excluded in which patients underwent unicompartmental procedures, bilateral

or simultaneous joint arthroplasty, revision surgery, acute arthroplasty or minimally invasive surgery (MIS).

Narrative review

The perioperative care interventions were used as individual search terms to perform a secondary narrative review of the literature utilising the aforementioned medical databases. Each term was used in conjunction with other search terms, such as "hip arthroplasty" and "knee arthroplasty". Additional perioperative interventions were retrieved from recommended guidelines and also from the researcher's own experience with ERAS protocols in bariatric and colonic surgery.(69, 70) This chapter is therefore presented as a narrative of the current literature describing evidence for interventions that should be considered when formulating an ERAS programme in THA and TKA.

Results

The systematic review recovered 22 articles from which key perioperative interventions were established. Four preoperative, eight intraoperative and four postoperative interventions were identified from these articles (Table 2).

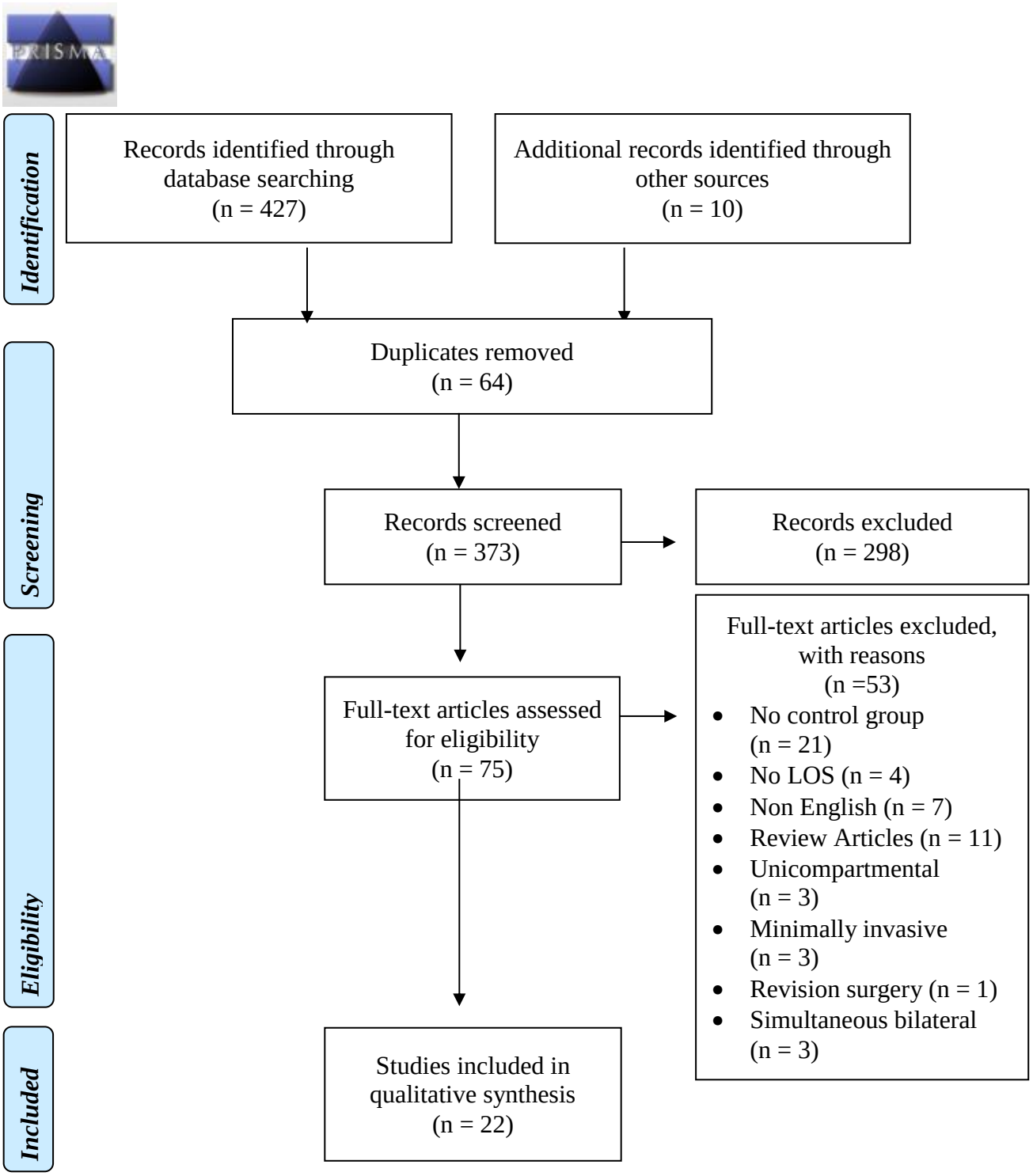


Figure 1. PRISMA flow diagram

Table 2. Studies evaluating ERAS principles and strength of evidence for interventions as reported by authors

Study (year)	Preoperative interventions	Strength	Intraoperative interventions	Strength	Postoperative interventions	Strength	LOS and conclusions
Isaac et al. (2005) *TKA*	Patient education Discharge planning	Good Good	Spinal anaesthesia with IT diamorph + light sedation LIA (bupivacaine+ adrenaline) Avoidance of surgical drains	Unclear Good Good	Same day mobilisation Multimodal analgesic regime	Good Good	Mean LOS 3.6 (AR) v. 6.6 days (control). Authors report that an organised multidisciplinary approach combined with small modifications in the surgical and anaesthetic technique can safely reduce LOS in TKA.
Larsen et al. (2008a, 2008b) *THA, TKA*	Information day, 1 week prior to surgery date, accompanied by one relative Nutrition screening	Strong Unclear	No modifications made to surgical or anaesthetic technique		Mobilise day of surgery Intensive rehabilitation (> 8 hours of mobilisation/day)	Unclear Good	Mean LOS 4.4 (AR) v. 8.8 days (control). Authors attribute most of the LOS reduction to new nurse-led organisation, information day and early and more aggressive mobilisation.

Study (year)	Preoperative interventions	Strength	Intraoperative interventions	Strength	Postoperative interventions	Strength	LOS and conclusions
Malviya et al. (2011) *THA, TKA*	Patient education Premedication: dexamethasone and gabapentin night before surgery	Strong Unclear	Tranexamic acid (15 mg/kg) at induction Spinal anaesthesia, no intrathecal opioids LIA (levobupivicaine) – continued postop	Strong Good Good	Same day mobilisation	Unclear	Mean LOS 4.8 (ER) v. 8.5 days (control). Significant cost savings through reduction in LOS. Tranexamic acid reduces need for allogenic blood transfusion.
Raphael et al. (2011) *THA, TKA*	Patient education class Discharge planning	Unclear Good	Spinal anaesthesia LIA (ropivacaine + epinephrine ± morphine ± ketorolac)	Good Good	Same day physiotherapy session once spinal worn off Multimodal, opioid-sparing analgesic regime Chemoprophylaxis: Clexane	None Good None	Mean LOS 47 hours (FT) v. 116 hours (control). The authors agree on research into the components of an ERAS pathway and identify which ones are necessary and will lead to improved patient outcomes.

Study (year)	Preoperative interventions	Strength	Intraoperative interventions	Strength	Postoperative interventions	Strength	LOS and conclusions
Wellman et al. (2011) *THA*	Patient education Prehabilitation Premedication: Celecoxib (not contraindicated), oxycodone SR and gabapentin	Good Unclear Good	General anaesthesia LIA (bupivacaine + epinephrine) Pre-emptive antiemetics – Ondansetron, metoclopramide, dexamethasone MIS: Superior capsulotomy technique	Unclear Unclear Strong Unclear	Same day mobilisation Aggressive rehabilitation Chemoprophylaxis: warfarin for 6 weeks Multimodal analgesic regime	Unclear Good None Good	Mean LOS 1.65 (AR) v. 3.54 days (control). Authors conclude that not one single intervention would result in the observed reduction in LOS, but the combination of all interventions yields consistent improvements in early recovery.
Den Hertog et al. (2012) *TKA*	Patient education on day of surgery	Good	Spinal anaesthesia without IT opioids PCEA for 24 hours	Good None	Day of surgery mobilisation Aggressive rehabilitation	Good Strong	Mean LOS 6.75 (FT) v. 13.20 days (control). Early achievement of functional milestones allowing safe discharge confers a sustainable effect on the mid-term outcome.

Study (year)	Preoperative interventions	Strength	Intraoperative interventions	Strength	Postoperative interventions	Strength	LOS and conclusions
McDonald et al. (2012) *TKA*	Educational group sessions and DVD Discharge planning	Strong Good	Spinal anaesthesia without IT opioids, propofol sedation LIA (ropivacaine) – continued postop Tranexamic acid (2.5 g)	Good Good Unclear	Day of surgery mobilisation Aggressive rehabilitation Multimodal analgesic regime	Good Good Strong	Median LOS 4 (ER) v. 6 days (control). Changes in clinical practice as a result of the ER program make it difficult to determine how each intervention change contributed to the observed study results.
Scott et al. (2012) *THA, TKA*	Preoperative preparation, patient education and counselling	Good	Spinal anaesthesia LIA Tranexamic acid Restrictive/Goal directed fluid therapy	Good Good Good Unclear	Early mobilisation Opioid-sparing analgesic regime	Strong Good	Median LOS 4 (ER) v. 5 days (control). Early mobilisation reduces thromboembolic events and LOS.

Notes. THA = total hip arthroplasty; TKA = total knee arthroplasty; LOS = length of stay; AR = accelerated rehabilitation; LIA = local infiltration analgesia; ER = enhanced recovery; FT = fast-track; IT = intrathecal; PCEA = patient controlled analgesia

Preoperative phase

Preoperative education

Information given in a timely, culturally sensitive manner with appropriate support is associated with a reduction in anxiety, hospital stay and pain in the immediate postoperative period.(50, 72, 84) Most centres with perioperative care pathways have preoperative education sessions and highlight their importance in managing patient expectations.(50, 72, 74-78, 82, 84, 85, 88, 89, 91) These detail the perioperative care plan, goal setting and expectation management, including an aim for discharge date. Preoperative education sessions can be in the form of either a group or one-to-one sessions with nurse specialists, and are supplemented by paper or media resources.

The mode of preoperative education delivery appears to be less important.(94) A recent pilot study showed that expectations for recovery after total joint arthroplasty differed significantly for the patient and the surgeon: more than 50% of patients demonstrated higher expectations of postoperative pain relief, function and well-being than their surgeon.(95) Thus, education, in addition to 'priming' the patient for early discharge, should attempt to align expectations for recovery. Specialist nurses have been utilised in co-coordinating the provision of the majority of preoperative education.(96)

Prehabilitation

The aim of prehabilitation is to optimise patients' health status preoperatively through physical exercise therapy, rendering them more resilient to the physiological stress induced by surgery.(97) This is thought to lead to improved preoperative functional capacity, which may potentially improve patient outcomes. Ditmyer et al. first reviewed prehabilitation in orthopaedic surgery and, though limited by paucity of data at the time, concluded that it was

reasonable to assume that prehabilitation improved patient outcomes. Since then, further studies have been performed investigating prehabilitation on postoperative outcomes. A recent systematic review of 12 studies (737 patients) showed no demonstrable beneficial effects of preoperative exercise on postoperative functional recovery. However, this was limited by heterogeneity and low therapeutic validity of the exercise prescription.(98)

Premedication

Postoperative pain correlates strongly with slower rehabilitation and prolonged hospitalisation.(72, 73, 85, 99) Attempts at reducing the anticipated pain of arthroplasty, particularly knee replacement, have been studied.(100, 101) Pre-emptive analgesia used in these studies includes gabapentin and COX-2 selective non-steroidal anti-inflammatories (NSAIDs). A meta-analysis failed to demonstrate any difference in pain scores postoperatively with preoperative NSAID administration, though overall analgesic consumption was reduced.(102) Despite their reputation as having detrimental effects on bone healing in animal studies (103, 104), two recent randomised, placebo-controlled trials showed that perioperative COX-2 selective NSAID use in TKA appears to be safe and to improve pain and function.(105, 106) The use of COX-2 selective NSAIDs has also been shown to reduce perioperative blood loss better than non-selective NSAIDs.(107)

Gabapentin, an analogue of gamma-aminobutyric acid, works centrally by increasing the synaptic levels of the main inhibitory neurotransmitter. Preoperative gabapentin has been studied extensively in various surgical settings and been shown to reduce pain and opioid consumption in the immediate postoperative period.(108-110) It has also been shown to reduce levels of preoperative anxiety (111, 112) in elective surgery, although not in THA.(113) One RCT in TKA demonstrated no benefit with two different doses of

preoperative gabapentin (900 mg and 1300 mg/day) in reducing acute pain. The same study reported a higher incidence of adverse events (sedation and dizziness) in the gabapentin groups ($p<0.05$), concluding that gabapentin should not be standard of care in opioid-naïve patients.(114)

PONV are significant rate-limiting factors in determining a patient's immediate postoperative recovery. Despite standardising perioperative care in THA and TKA, rates of PONV are reported to be approximately 40%–46%.(72, 89) The aetiology is multifactorial and may arise from a combination of anaesthetic agents, hypovolaemia, anaemia and excessive opioid use.

One way of addressing PONV is by the administration of preoperative dexamethasone. Perioperative glucocorticoids have been studied extensively in various elective surgeries, including elective THA.(115) Glucocorticoids appear to operate centrally by inhibiting prostaglandin and/or endogenous opioid synthesis.(116) However, of the 22 studies reviewed, only three included preoperative IV dexamethasone (4–10 mg), one of which instructed patients to take dexamethasone 10 mg the night prior to surgery.(72, 84, 85)

A lack of enthusiasm for routine preoperative glucocorticoid use may be explained by the concern over potential side effects, in particular risk for periprosthetic infection due to its anti-inflammatory effects. Though there is now an accumulating body of evidence to refute this. In THA, one double-blinded RCT demonstrated a single dose (40 mg) of dexamethasone given preoperatively had no deleterious effects on function and did not demonstrate an excess in complications, including infection and osteonecrosis of the contralateral hip, in the medium to long term (1 year).(115) Its effects on dynamic hip pain scores, in the immediate postoperative period, were superior to those receiving placebo.(101) Recent evidence suggests that high dose perioperative steroids (125mg methylprednisolone)

are effective in reducing immediate pain and achieving milestones earlier.(117) Although some large retrospective data report comparable rates of infection (high dose steroids versus none), without long term prospective studies their safety is still debatable.(118) In another placebo-controlled study, preoperative dexamethasone plus pregabalin significantly reduced the incidence of PONV compared with pregabalin alone.(119)

Nutrition

Optimising patient nutritional status should be considered part of an ERAS pathway for arthroplasty. It is of particular concern because the population receiving joint replacement surgery is generally older and more likely to have suboptimal nutrition. Poor nutrition has significant implications for postoperative recovery and prolonged convalescence. One retrospective study of 92 consecutive THA patients showed an association between low serum transferrin levels preoperatively (one measure of nutritional status) and delayed wound healing.(120) Another study demonstrated a similar correlation in patients who had suboptimal nutrition, as measured by serum albumin in patients undergoing hip surgery, with longer hospital admissions.(121)

Identifying patients at risk for malnutrition is important so that appropriate treatments can be started. The Malnutrition Universal Screening Tool (MUST) is an evidence-based, easy-to-use screening tool that identifies at-risk patients in all specialties, including orthopaedic surgery.(122, 123) The tool uses body mass index (BMI), weight loss in the preceding 6 months and, in the acute setting, a history of no nutritional intake for more than 5 days as a means to stratify risk of malnourishment and to implement treatment when indicated.(122) In the acute setting, it has been shown to identify those patients at risk of increased mortality, postoperative complications and prolonged convalescence.(124) Treatment options for optimising nutrition in patients include oral nutrition supplements and a diet of foods rich in

both macronutrients and micronutrients.(123) Assessment by a dietician, after screening for moderate- to high-risk patients using the MUST tool, should therefore be considered prior to THA and TKA for selected patients.

The use of preoperative carbohydrate drinks have been investigated to counter the catabolic demand associated with surgery. A systematic review and a Cochrane review both highlighted that compared to fasting, preoperative carbohydrate drinks were of minimal benefit in reducing adverse outcomes compared to water or placebo.(125, 126)

Intraoperative phase

Prophylactic antibiotics

Elective THA and TKA are major orthopaedic procedures that require replacement of a diseased joint with a prosthesis, and although the metalware at the time of implantation is sterile, it remains a haven for bacteria to grow when colonised. It has been well documented that administration of intraoperative prophylactic antibiotics reduces the risk of periprosthetic infection.(127-129) The American Academy of Orthopaedic Surgeons (AAOS) recommends that appropriate antibiotics be given within the hour of skin incision.(130) A prospective cohort of 1922 patients undergoing THA from 11 hospitals participated in a surgical prophylaxis project. Infection (deep and superficial) occurred in 2.6% of patients (n = 50). Those at highest risk of infection were the patients who received antibiotics after incision, had an American Society of Anaesthesiologists (ASA) score > 2 and had longer operative times.(131) The AAOS recommend that prophylactic antibiotics not be continued beyond the 24-hour postoperative period as there was no proven benefit beyond this time.(130)

Intraoperative environment

The intraoperative temperature plays a role in influencing patient core body temperature. There are four main mechanisms involved in heat loss in the operating room: radiation, convection, conduction and evaporation. Radiation and convection account for the majority of these losses in the operating room.(132) *In vitro* studies have shown temperatures below 37 degrees Celsius impair platelet function through defective thromboxane-2 (TXA2) and down regulation of glycoprotein 1b-IX complex – proteins responsible for platelet aggregation.(133)

In an RCT, Schmied et al. found that a reduction in core body temperature was associated with a higher risk of blood loss and transfusion rates in THA patients.(134) Hypothermia has also been shown to increase the risk for wound infection, delayed wound healing and prolonged hospitalisation.(135, 136) The timely use of warming blankets can prevent insensible heat loss.

Surgical approach

The anterior medial parapatellar approach is the most common approach to the knee for total joint replacement. Although the approach allows excellent exposure of the knee joint and sufficient room for cutting blocks for preparation of the bone for prosthesis, its limitation lies in the significant incision and breach of the quadriceps tendon.(137)

THA approaches are based in relation to the gluteus medius muscle. Lateral (Hardinge) and the posterior (Southern or Moore) approaches are common approaches to the hip for joint replacement, and the posterolateral approach is reported as the most common.(137) A systematic review comparing lateral and posterior approaches was performed in 2009.(138)

Only two studies measured postoperative dislocation, and no significant difference between posterior and direct lateral approaches was found.

MIS has been used in both THA and TKA with the aim of reducing the surgical insult through minimising incision length and trauma to underlying soft tissue.(137) The expectation is that this will hasten recovery and expedite discharge.

There are several forms of MIS in TKA (MIS TKA) and they are slight variations on the standard medial parapatellar approach.(137, 139) A recent systematic review reported MIS TKA to have improved immediate postoperative pain, decreased blood loss, improved short-term range of movement (ROM) and resulted in shorter hospital stay.(140) Even though MIS TKA showed significant benefits, it was also associated with higher malalignment rates and subsequent revision.(140)

MIS for the hip is largely modifications of the standard posterior, lateral and anterolateral approaches.(139) The direct anterior approach to the hip has been described and when used in selected patients hastens recovery.(141) It is favoured by some surgeons because of its anterior muscle preserving qualities, allowing for quicker recovery and reduced rates of dislocation.(142) Because this approach is yet to be widely adopted, there is a learning curve that will have to be overcome in the short term.(143, 144) Lloyd et al. attribute the benefits of MIS to the nature of the multimodal pathways that include ERAS characteristics and careful patient selection, thus making it difficult to interpret these results.(139)

Anaesthesia

There is wide variation in the type of anaesthesia used in perioperative care pathways. ERAS protocols vary in their use of anaesthesia from spinal anaesthesia (SA) alone to epidural to spinal plus general anaesthetic, along with various anaesthetic agents.(72, 75, 79, 83-85, 92)

Recommendations from a review performed by the Procedure Specific Postoperative Pain Management (PROSPECT) working group advise the use of either general anaesthesia (GA) combined with femoral nerve block or SA with local anaesthetic (LA) and spinal morphine for knee joint replacement surgery.(145)

A systematic review comparing epidural analgesia with other alternative analgesic modalities in joint replacement surgery demonstrated significantly less pain in the first 6 hours postoperatively.(146) However, after 6 hours this benefit was no longer noted. Compared with systemic analgesia, epidural analgesia exhibited higher rates of postoperative urinary retention, hypotension and itch.(146) Furthermore, many studies comparing neuraxial blockade (spinal, epidural) with GA have demonstrated benefits that go beyond providing pain relief in the postoperative period. In these studies neuraxial blockade, through either spinal or epidural analgesia, have demonstrated reductions in blood loss (147), reduced risk for VTE (148) and lower rates of blood transfusion.(148) One review by Rodgers and colleagues in 2000 proposed improved survival in patients undergoing major surgery (44 of 103 trials of orthopaedic nature, n = 3617) with neuraxial anaesthesia techniques when compared with GA.(148) Others are less convinced of its mortality benefits and question this proposition based on heterogeneity of studies, dated practices (studies included dating as far back as 1971) and studies demonstrating methodological weaknesses.(149)

Finally, the use of a tourniquet in TKA may preclude the benefits of reduced VTE since there is a brief period of blood stasis (150) – an important tenet of Virchow's thrombosis triad. In light of the nuances of each anaesthetic modality, it is important to remember that the anaesthetic technique should take into consideration the health status of the patient and safety should be a priority over analgesia.

Intravenous fluid

Intravenous fluid (IVF) administration around the time of surgery impacts clinical outcomes. Studies in abdominal surgery are conflicting: different authors have concluded that both *restrictive* and *liberal* fluid therapies around the time of surgery are beneficial in improving rates of complications.(151, 152) To that end, Holte et al. examined 48 total knee joint replacements in a randomised, double-blind study and demonstrated a significant reduction in PONV and hypercoagulability in patients randomised to *liberal* (mean 4250 ml) administration of fluid when compared with *restrictive* (mean 1740 ml) fluids.(153) Further research in this area is indicated.

Blood loss prevention

Moderate blood loss can be expected following arthroplasty and can impact on a patient's immediate postoperative recovery. Anaemia and hypovolaemia, combined with excessive opioid use, may induce unnecessary PONV, dizziness and orthostatic hypotension. Antifibrinolytics, such as TXA, have been routinely used and tested in elective arthroplasty for the past decade as a means to reduce perioperative blood loss.(84, 85, 154-158) TXA inhibits clot breakdown by reversibly binding both plasminogen and plasmin, preventing cleaving of fibrin and maintaining clot architecture.(159) Systematic reviews have concluded that when hip and knee arthroplasty are performed with perioperative TXA (10–15 mg/kg), blood loss is significantly reduced and the risk of requiring allogenic blood transfusion is decreased.(60, 61, 160) Rates of DVT and PE were reported to be similar to control groups.

Despite these findings, some surgeons continue to have concerns over its use and the potential for increasing the risk for VTE events postoperatively. A retrospective study of over 2000 hip and knee replacements examined rates of VTE on three different chemical prophylactic regimes when intraoperative TXA was used.(159) They showed no difference in VTE events in 90 days based on postoperative chemical prophylaxis type, ranging from 0.14% to 0.52% for DVT and 0.17% to 0.43% for PE.(159) Caution should be exercised in patients at high risk for VTE, however.

Surgical drains

Surgical drains are used in orthopaedic surgery to avoid developing wound haematoma and infection, and improving ROM. Coagulated blood, as in haematoma, is a prime medium for bacterial growth and hence the potential risk for infection. Surgical drains act as an egress for blood and are thought to prevent haematoma formation and allow for easier ROM. However, a systematic review and meta-analysis suggests that closed drainage systems promote blood loss and a subsequent need for blood transfusion, and show no difference in rates of infection.(161) Drains in this setting are of doubtful benefit and avoiding them should be encouraged in an ERAS setting for these reasons.

An RCT compared clamping of drains for 3 hours twice in the first postoperative day (6 hours total) and no clamping in 100 knee replacements and determined its effect on postoperative blood loss and need for transfusion. They found that the intervention group had significantly less blood loss in the first 48 hours and were 2.2 times less likely to require a blood transfusion, though this was not statistically different.(162) This may be a suitable alternative if surgeons are reluctant to abandon the use of closed drainage systems.

Periarticular anaesthetic infiltration

Postoperative pain around the surgical site impairs patient mobility, prompts excessive systemic analgesic use and may prolong hospitalisation. Five of the 22 ERAS protocols identified in the systematic review included periarticular LA as part of their analgesia regime.(73, 79, 85, 89, 92) Immediately prior to skin closure, high-volume (up to 120 ml) LA is infiltrated into the wound and surrounding tissue. The theoretical advantages are improved postoperative pain and reduced systemic analgesia requirements.

Kehlet and Andersen's recent review article concluded that there is sufficient evidence to support the use of intraoperative LA in knee joint replacements for the initial 6–12 postoperative hours, but not in hip replacements in the setting of a multimodal, opioid-sparing regime.(163) Another systematic review of LA use in knee replacement identified a mixture of high-dose ropivacaine with adrenaline and ketorolac to be the most effective technique.(164) The addition of a compression bandage in this setting has been shown to improve pain relief in the first 8 hours after knee replacement surgery.(165)

Postoperative phase

Early ambulation

Early mobilisation (< 24 hours) is a key feature of most standardised perioperative care pathways.(50, 72, 73, 75, 77-80, 82, 84, 85, 89, 91, 92) However, the nature of the surgery is an inherent barrier to this. Hence, it is imperative that interventions allow this to occur so patients can reap the benefits of early ambulation and physiotherapy. A recent review of multidisciplinary rehabilitation programmes identified early rehabilitation and clinical pathways to be a positive predictor for attaining functional milestones, shorter hospital stay, fewer postoperative complications and lower costs.(166) Early mobilisation has also been

linked to reduced rates of DVT and PE and is supported by the AAOS work group to lessen this complication.(167-169)

Rehabilitation

Rehabilitation is defined as restoration of functioning towards normality through an intervention or group of interventions.(170) An important element of restoring this level of functioning is early and aggressive postoperative physiotherapy. As mentioned, early rehabilitation correlates positively with improved outcomes after joint surgery.(166)

One pilot study demonstrated early (postoperative day 1 or 2) progressive strength training was safe and improved knee-extension strength and maximal walking speed.(171) Two systematic reviews evaluated the effectiveness of physiotherapy exercise after elective THA (172) and TKA.(173) However, the authors concluded that physical therapy had, at best, only a moderate effect on short- to moderate-term outcomes. Bandholm and Kehlet attribute this lack of significant effect to inadequate prescribing of the appropriate physiotherapy exercise "pill": *incorrect ingredients (low intensity) and/or given at the wrong time (too late).*(174) Determining the most effective method of rehabilitation remains unanswered. Further research is required to determine the appropriate intensity, frequency and modality of physiotherapy exercise.

Venous thromboembolism prophylaxis

Patients who undergo THA and TKA are at significant risk for developing VTE. This can cause significant morbidity and prolonged convalescence. Early mobilisation is a key process measure of ERAS protocols which has been shown to reduce rates of VTE.(167, 168)

The AAOS and American College Chest of Physicians (ACCP) have produced guidelines for preventing VTE disease in elective THA and TKA.(169, 175) Mechanical prophylactic measures include early mobilisation, intermittent pneumatic compression devices and thromboembolic deterrent (TED) stockings. Both guidelines recommend the use of combined mechanical and chemical prophylaxis in patients with low risk of bleeding and VTE disease. Aspirin combined with compression devices is an accepted regime when compared to other pharmacological agents.(40)

Two systematic reviews attempting to determine the safety and efficacy of various chemoprophylactic agents showed LMWH to be equivalent in reducing major VTE complications, with a more favourable side effect profile (less bleeding), to vitamin K antagonists, unfractionated heparin and direct thrombin inhibitors.(176, 177) A large, retrospective study (n = 3497) highlighted the benefits of adherence to the ACCP guideline: patients who received ACCP-recommended VTE prophylaxis were less likely to experience VTE compared with those who did not receive ACCP-recommended VTE prophylaxis.(178)

Postoperative multimodal analgesia

Opioids are very effective in controlling postoperative pain but also exhibit a side effect profile that can be counterproductive to patients' rehabilitation, including but not exclusive to nausea, vomiting, urinary retention, reduced gastrointestinal motility and obstructive sleep apnoea exacerbation, and they may cause severe respiratory depression.(69, 70) Advocates of ERAS protocols across all surgery, including THA and TKA, unanimously promote cautious use of opioids to avoid such complications.(69, 70) Gabapentinoids have been shown to reduce postoperative pain scores when compared with control groups. In addition, two systematic reviews have demonstrated that gabapentinoids have opioid-sparing effects,

thus reducing opioid-related adverse effects, including, PONV and urinary retention.(179, 180)

Discussion

ERAS pathways in elective THA and TKA have gained momentum in the past decade. Despite the increasing use of standardised perioperative care pathways, there remains considerable variation in interventions used.(50, 72-92) This is largely due to surgeon, institutional and cultural differences among centres utilising ERAS pathways. This review has sought to identify those components pertinent to an ERAS pathway in the setting of elective THA and TKA, and provides recent evidence to support their use in clinical practice.

Preoperative education and management of expectations play a vital role in enhancing patient autonomy and self-efficacy. Preoperative physical therapy has not been shown to decrease hospital stay after surgery; however, the therapeutic validity of these studies is poor. Premedication, using both COX-2 selective NSAIDs and gabapentin, has been shown to reduce postoperative opioid consumption. Additionally, preoperative corticosteroids reduce PONV. Optimising nutrition preoperatively should be a key goal for reducing postoperative morbidity. A screening tool (MUST) can be used to identify patients with suboptimal nutrition so appropriate and timely referral to a dietician can be made. Attempting to maintain core body temperature in the operating room reduces wound infection, blood loss and delayed wound healing.

Further literature is required to determine the safety and efficacy of MIS in an ERAS setting. Recommendations by the PROSPECT Working Group advocate the use of GA combined with femoral nerve block or SA with LA and spinal morphine for knee joint replacement surgery. Epidural analgesia should be avoided for the majority of cases as this has been

shown to have significant morbidity compared with other anaesthetic types. Liberal perioperative IVF administration has been shown to reduce PONV though further research is needed to strengthen this claim.

TXA and avoidance of surgical drains significantly reduces the perioperative blood loss and the likelihood for allogenic blood transfusion. High-volume LA infiltration reduces the requirement for systemic analgesia. Early ambulation and aspirin in combination with mechanical compressive devices is an appropriate VTE prophylactic measure in hip and knee arthroplasty in patients without additional risk factors for DVT or PE. Supporters of ERAS pathways unanimously advocate the use of multimodal, opioid-sparing analgesic regimes.

Interventions identified in this review have moderate evidence to support their use and have been used to design an ERAS protocol for THA and TKA (Table 3). It is important to note that ERAS has its greatest impact through the combined influence of the individual perioperative care interventions. What is less clear is the contribution of each intervention to clinical outcomes.

Table 3. A proposed ERAS protocol in elective hip and knee arthroplasty

Phase	**Perioperative care interventions**
Preoperative	Preoperative education, expectation management Discharge planning – occupational therapist, social worker Nutrition screening using the MUST tool – referral to dietician if "high" risk Premedication – COX-2 selective inhibitors, gabapentin, dexamethasone
Intraoperative	Spinal anaesthesia + regional (femoral/saphenous) block OR high-volume LA Intravenous prophylactic antibiotics – total duration 24 hours Tranexamic acid Avoiding surgical drains
Postoperative	Early ambulation Early intensive physiotherapy Aspirin, TEDS and intermittent pneumatic compression devices for VTE prophylaxis (for those without additional risks for VTE) Multimodal, opioid-sparing analgesia regime

Notes. MUST = Malnutrition Universal Screening Tool; COX-2 = cyclooxygenase-2; LA = local anaesthetic; TEDs = thromboembolic deterrent stockings; VTE = venous thromboembolism

Wellman et al. (92) and McDonald et al. (85) believed small changes in multiple areas of clinical practice made it too difficult to determine which change had the most or least significant contribution to enhancing patients' recovery. Raphael et al. (89) shared these sentiments and agreed that more research into ERAS proponents was necessary and would lead to improved patient outcomes. Isaac et al. (79) attributed their improvements in patient outcomes and reduction in LOS to modifications in surgical and anaesthetic techniques. This is in contrast to Larsen et al. (181), who kept their surgical and anaesthetic techniques the same, but attributed their improvements in LOS to nurse-led organisational changes and early, aggressive mobilisation and rehabilitation.

Both organisational and clinical changes are required to achieve enhanced recovery. However, organisational modifications are less likely to reduce pain, PONV, postural hypotension and dizziness significantly to facilitate early mobilisation and rehabilitation. Pain, dizziness and general weakness after THA and TKA were identified by Husted et al. (182) as being the main clinical reasons for being hospitalised in the first 48 hours, while nausea and vomiting, sedation and confusion delayed discharge. It is more likely that attenuating the surgical stress response and counterbalancing the effects of anaesthetic techniques allows patients to participate in their rehabilitation in the immediate postoperative period, thus increasing the chance of achieving an earlier, safer discharge.

Attempts to combine the best available evidence and come up with the "best recipe" can sometimes be hindered by conflicting evidence for different perioperative care interventions. For example, institutions that choose neuraxial anaesthesia as part of their ERAS pathway may do so for the benefits of improved pain relief, early mobilisation, reduced clot risk and

less blood loss. Although there are obvious benefits, neuraxial anaesthesia has been shown to alter thermoregulation through lowering the threshold for shivering and peripheral vasoconstriction (≈ 0.5 °C).(183) Hypothermia in patients undergoing THA increases blood loss, impairs wound healing and prolongs recovery.(134) Similarly, TXA and high-volume LAs may theoretically increase chances of morbidity. Despite the abundant evidence that TXA reduces blood loss, the most appropriate VTE prophylactic regime, in this setting, to avoid sinister clot formation remains to be determined. In the case of high-volume LA use, *in vitro* studies of ropivacaine have shown that it alters platelet function and prolongs closure time, which may lead to excessive bleeding.(184)

A limitation of the study was exclusion of acute, revision, MIS, unicompartmental knee and bilateral arthroplasty, as ERAS has been implemented in these settings. This may be justified as the protocol being implemented in Middlemore Hospital will target patients undergoing elective primary, unilateral joint replacement surgery, and in general, it is unlikely that the principles of care in these settings will differ greatly from those proposed in this review.

The information obtained from this review will act as a template to guide development of an ERAS protocol in Middlemore Hospital (Table 3). Pertinent to an ERAS pathway is the active engagement of multiple disciplines, both medical and allied health, working in close collaboration. Thus, responsibility of care has shifted from one person (the surgeon) to a team of multidisciplinary experts along the perioperative pathway.

Both organisational and clinical changes are required to achieve enhanced recovery. Clinical research is forever improving our knowledge of perioperative care interventions; however, a considerable amount of time can pass before they are accepted as standard care; in some cases as long as 17 years.(185) Here, clinical leadership and organisational restructure is paramount for driving these intended changes in a timely manner.

Conclusion

A comprehensive review of a variety of perioperative care interventions commonly used in elective THA and TKA with low to good evidence has been described in this chapter. Although the interventions have been described in isolation, it is the standardised manner in which they are delivered that reduces variation and contributes to improved clinical outcomes. Herein lies the true value of ERAS. Secondly, because of ERAS's standardised nature, any surgical outcomes measured can be done so with greater validity. The perioperative care interventions identified in this review will be used as a template to guide an ERAS protocol ready for implementation and evaluation.

Chapter 3: Perioperative care in hip and knee arthroplasty – a survey of New Zealand orthopaedic surgeons

Introduction

The evidence for ERAS protocols continues to grow, and in many centres across the world they are considered the standard of care. In the previous chapter, perioperative care interventions were identified systematically in those centres with established ERAS, fast-track or accelerated programmes specific to arthroplasty. It is important to determine which of these perioperative care interventions are, or are not, used as part of the arthroplasty surgeon's routine practice.

ERAS coordinates evidence-based perioperative care interventions to hasten recovery, and specific to elective arthroplasty, these interventions have been mentioned in the previous chapter. This survey aimed to characterise perioperative management among NZ orthopaedic surgeons across the private and public sectors as a means to assess variation and refer to surgeon readiness to adopt principles of ERAS.

Methods

An online survey (www.surveymonkey.com) was composed using 10 multiple choice questions covering surgeon's place of practice and experience (Q1 and Q2), routine perioperative surgical interventions used in hip and knee arthroplasty (THA and TKA, respectively) (Q3–9) and potential perceived barriers for ERAS implementation at their centres (Q10) (link: https://www.surveymonkey.com/s/3FRSGJW). The survey was designed by the author and scrutinised for content and face validity by three arthroplasty surgeons. The option of adding comments as free text after each question was made available. All surveys were included in the final analysis.

After obtaining ethics from the University of Auckland Human Participants Ethics Committee (Protocol 010277), the link to the survey was emailed to all current members of the New Zealand Orthopaedic Association (NZOA) for 2012–13 with a letter of endorsement by the chief executive of NZOA attached. The link to the questionnaire was sent on three separate occasions. The first on 18 October 2013; and then 1 and 2 months later. Patterns of perioperative care were characterised by level of experience (i.e., fellow, consultant < 5 years, consultant 5–10 years, consultant > 10 years) and type of funding model surgeons worked in (public/private). Results were downloaded from the website 3 months after the last response.

According to registry data for the period 2012–13, there were 198 surgeons who performed 10 or more THAs or TKAs. This would be used as the study's denominator.

Results

Fifty-three (26.8%) surgeons responded to the online survey. One responder answered Q1 and Q2 only and therefore was excluded. Fifty-two surveys were included in the final analysis. According to funding models, the majority of respondents practised in both the private and the public sectors (54.7%), followed by public hospitals (34.0%), and then private practice (18.9%). Most of the responding surgeons had > 10 years' practice as a consultant (47.2%) (Table 4).

Table 4. Proportion of respondents based on place of practice and experience as a consultant

	Public	**Private**	**Both**	
Place of practice (%)	18 (34.0)	10 (18.9)	29 (54.7)	
	Fellow	**Consultant < 5 years**	**Consultant 5–10 years**	**Consultant > 10 years**
Experience (%)	3 (5.7)	15 (28.3)	10 (18.9)	25 (47.2)

Figures 2–8 demonstrate the variation in surgical practice among surgeons concerning specific perioperative care interventions in elective THA and TKA.

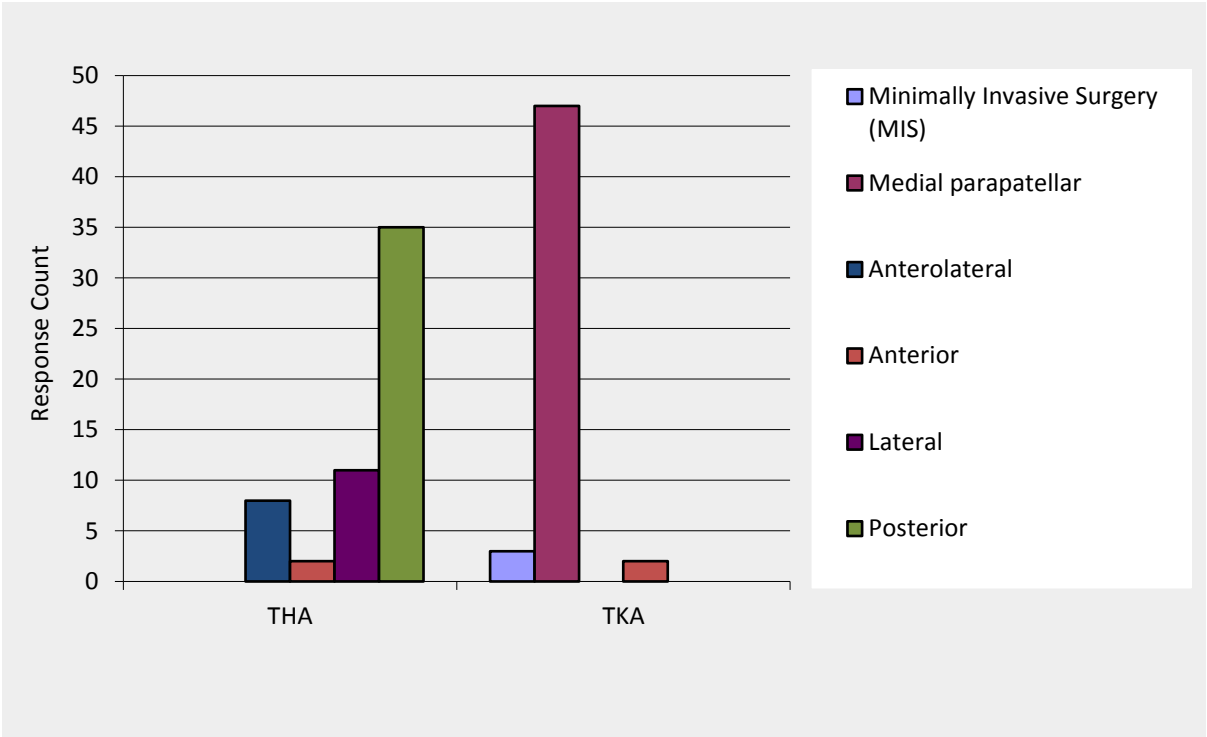


Figure 2. Surgical approach among orthopaedic surgeons (THA and TKA)

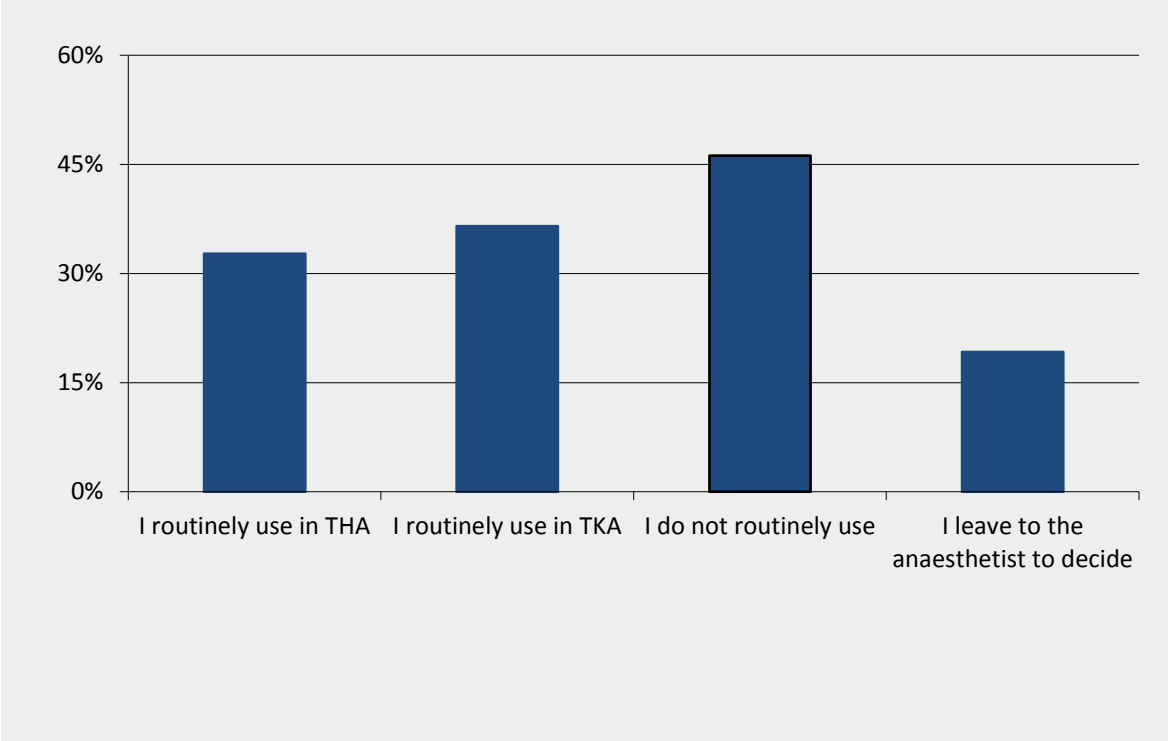


Figure 3. Tranexamic acid use among NZ orthopaedic surgeons in THA and TKA

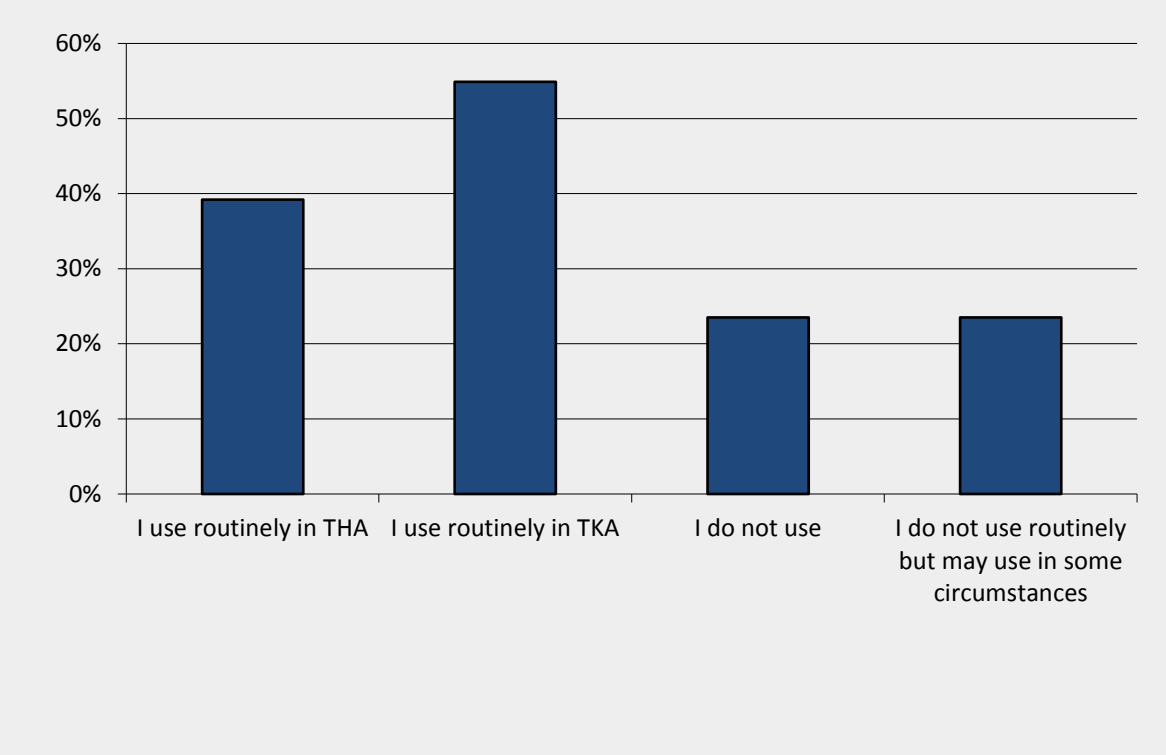


Figure 4. Surgical drain use among NZ orthopaedic surgeons in THA and TKA

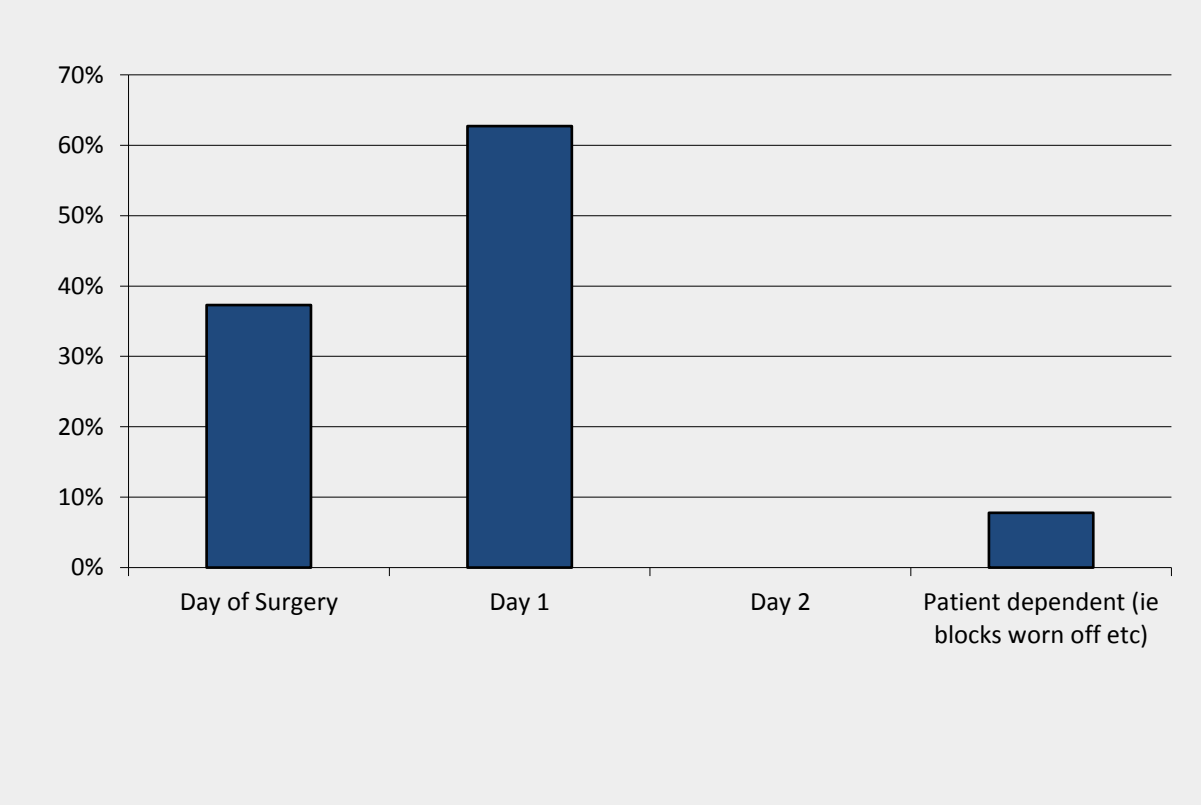


Figure 5. Instructions to mobilise among NZ orthopaedic surgeons in THA and TKA

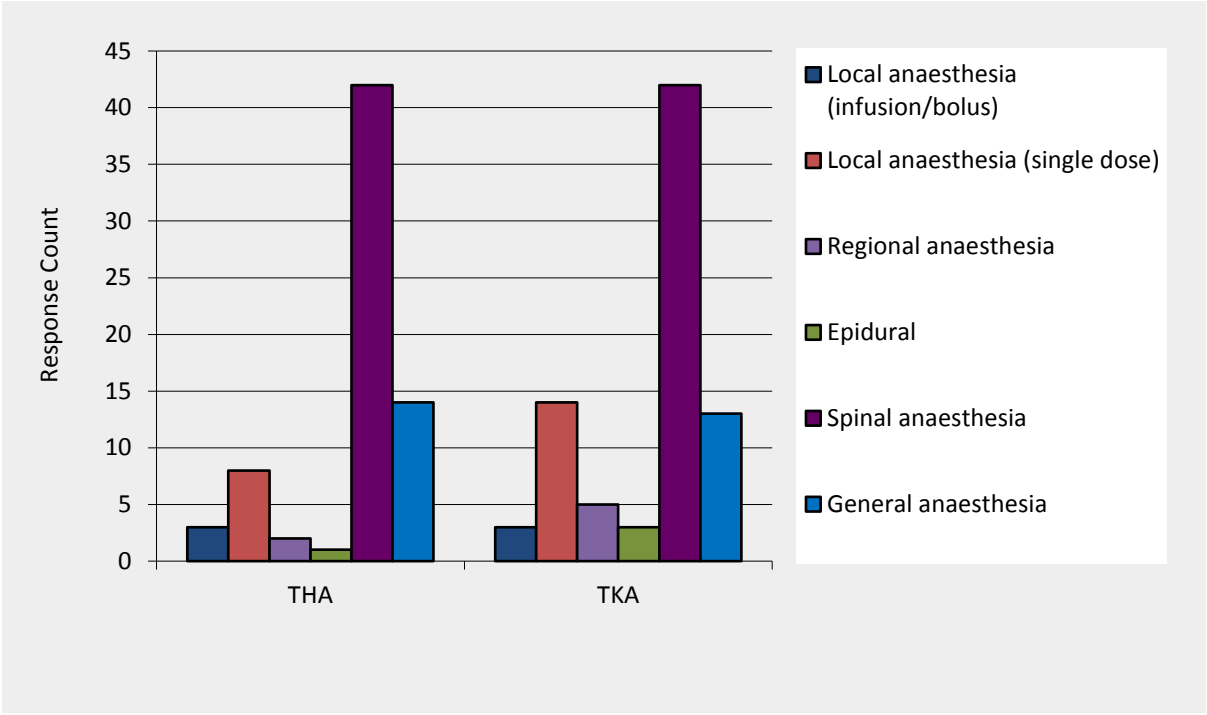


Figure 6. Preferred anaesthesia type among NZ orthopaedic surgeons for THA and TKA

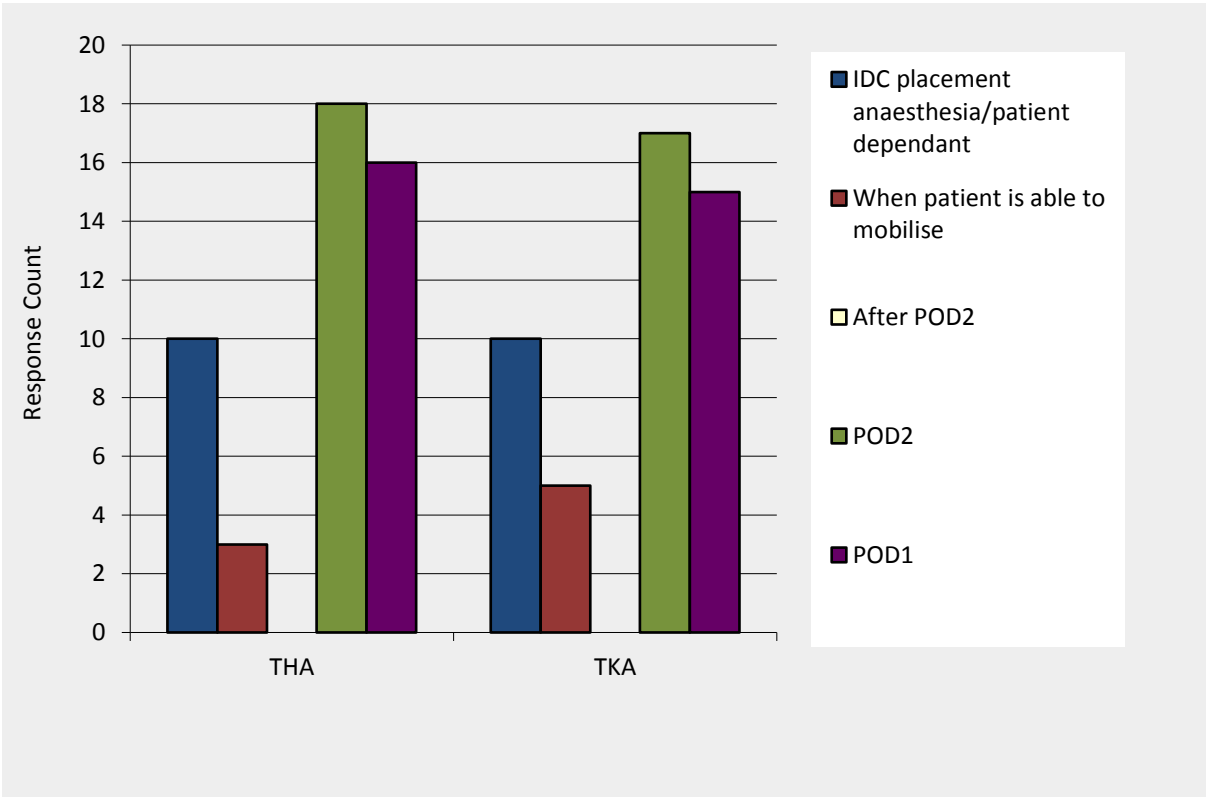


Figure 7. Indwelling catheter removal/instruction among NZ orthopaedic surgeons in THA and TKA

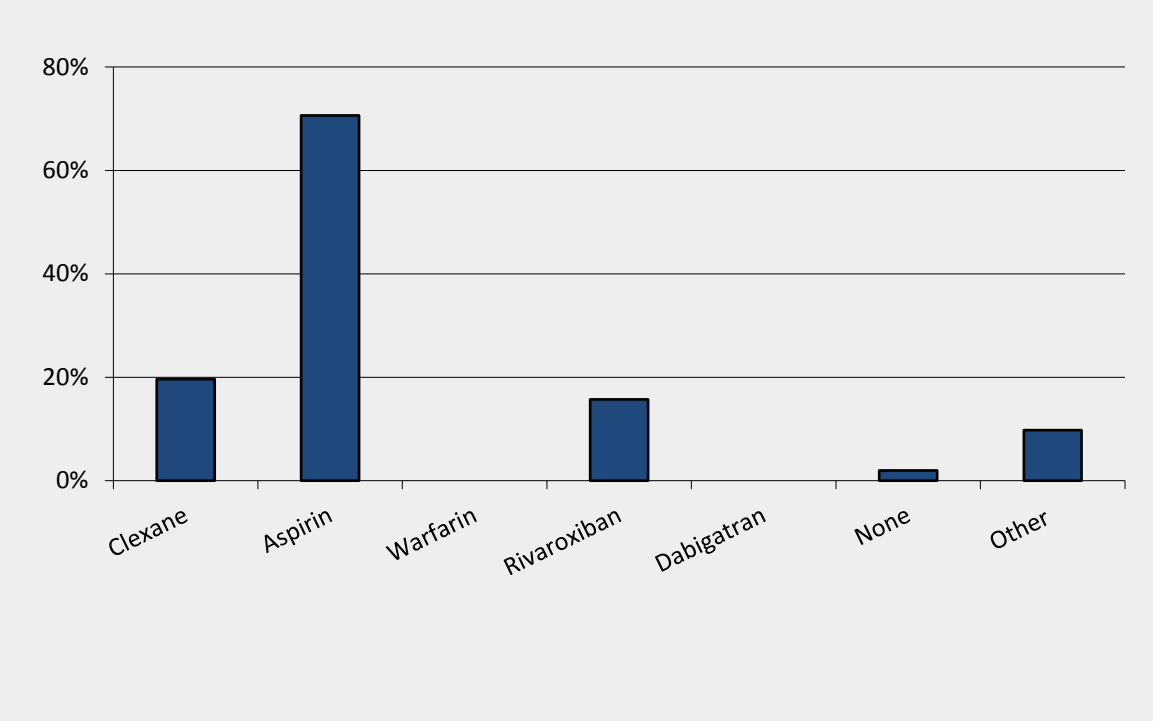


Figure 8. Pharmacological thromboprophylaxis agent of choice among NZ orthopaedic surgeons in THA and TKA

Free text responses occurred in questions asking about surgical approaches (Q3), preference for anaesthesia (Q7), instructions for indwelling catheters (IDCs) (Q8), preferred pharmacological VTE agent (Q9) and surgeon's perceived barriers to ERAS implementation (Q10).

Surgical approach

The majority of participants (62.5%) used a posterior approach to performing THA (Figure 2). Lateral and anterolateral approaches were used by 19.6% and 14.3% of surgeons. Five surgeons indicated that they used both lateral and posterior approaches for THA. Two surgeons reported using an anterior approach to the hip as their standard surgical approach for THA.

Among responders performing TKA, the surgical approach was unanimous in favour of the medial parapatellar approach (94.2%). Two surgeons specified using a sub-vastus approach for their TKA, but indicated that this was not a form of MIS.

Tranexamic acid

Almost half (46.2%) of responders reported not using TXA as a routine part of their surgical practice in this setting (Figure 3). Routine use of TXA in THA and TKA was 32.7% and 36.5%, respectively. This decision was left to the anaesthetist to decide by 19.2% of participants.

Surgical drains

Surgical drains were more commonly used for TKA 28 (54.9%) than THA 20 (39.2%). Twenty-four per cent of surgeons were selective in their use of surgical drains. No use of surgical drains was reported by 23.5% of participants (Figure 4).

Mobilisation

All surgeons encouraged mobilisation by the first postoperative day (100%), and 19 (37.3%) instructed patients to mobilise on the day of surgery (Figure 5). Four surgeons indicated that achieving this milestone would be dependent on persisting regional and neuraxial blockade.

Anaesthesia

There was a preference for SA in combination with regional blockade ± LA for patients undergoing THA (n = 34, 72.9%). A quarter of responding surgeons preferred to use GA in combination with SA ± regional blockade ± LA (Figure 6).

Anaesthesia preference for TKA was similar to that of THA. SA in combination with regional ± LA was favoured by 36 (73.5%) responders, while 10 (20.4%) preferred GA in combination with SA/regional/LA. Three (6.1%) surgeons had a preference for epidural analgesia for their TKA patients. Three surgeons indicated preference for light sedation in combination with their SA. One surgeon specified femoral nerve blockade as his choice of regional anaesthesia.

Indwelling catheter removal

When deciding to remove IDCs, removal was instructed for the first postoperative day by 34.0% and 31.9% of responders for THA and TKA, respectively (Figure 7). Instruction to remove IDCs on postoperative day 2 was preferred by 38.3% and 36.2% of responders for THA and TKA, respectively. Ten (21.3%) surgeons indicated that the decision to insert an IDC was patient and anaesthesia dependent.

Regarding postoperative instructions for IDC removal/use free text responses were varied. One surgeon indicated that the decision to remove was gender dependent (males day 1, females day 2). Two surgeons stated that IDC use was not routine for their practice. One surgeon reported removing at 48 hours if the IDC had been inserted for retention.

Venous thromboembolism pharmacological agent

Following THA and TKA, aspirin was the preferred chemoprophylactic agent by 36 (70.6%) of responders, Clexane was preferred by 10 (19.6%) of surgeons and Rivaroxaban was preferred by eight (15.7%) surgeons (Figure 8). One responder did not use any form of pharmacological prophylaxis. One surgeon preferred Dalteparin as a VTE pharmacological agent and another prescribed Dabigatran on discharge.

Adopting Enhanced Recovery After Surgery

Of 51 responders, 13 (25.5%) stated that they already follow an ERAS approach. Barriers to implementing a formalised ERAS pathway are summarised in Table 5.

Forty-seven per cent of responders indicated some form of barrier would be encountered when attempting to introduce an ERAS protocol for their arthroplasty unit. The most common barrier likely to be encountered by surgeons was the lack of “buy-in” from their colleagues (31.4%), followed by institutional barriers (25.5%). Five surgeons wrote free text about their thoughts on implementing a standardised perioperative care protocol for THA

and TKA. A common theme here was the lack of services and healthcare provision once the patient had left hospital. Three surgeons specified the lack of adequate rehabilitation and community support upon discharge, particularly if patients "live more than 3 hours from treating hospital". One surgeon had "no idea" what ERAS was.

Discussion

A nationwide survey was performed to describe several surgical practices among NZOA arthroplasty surgeons and how these aligned with or differed from the current literature and ERAS protocols. Similar surveys have been performed in colorectal surgery (186-188); however, this is the first among orthopaedic surgeons. Although the response rate was low, there was considerable variation in surgical practices among surgeons, and although many surgeons' practices aligned with the current literature, many did not.

Table 5. Perceived barriers to ERAS or similar care pathway

Responses	**Number (%)**
I already adopt such an approach	13 (25.5%)
Personal	5 (9.8%)
Institutional	13 (25.5%)
Financial	3 (5.9%)
Lack of "buy-in" from other specialties	5 (9.8%)
Lack of "buy-in" from colleagues	16 (31.4%)
I do not perceive any barriers	14 (27.5%)
Other	5 (9.8%)

The surgical approach has gained interest in enhanced recovery protocols, particularly with the introduction of the anterior approach to the hip, which boasts accelerated recovery through minimal surgical trauma.(17, 141) Although this seems reasonable and logical, there is a paucity of data supporting the idea. The increasing adoption of enhanced recovery

pathways makes it difficult to interpret any benefits of the surgical approach influencing the immediate postoperative outcomes.(139)

Despite the abundant evidence supporting the efficacy and safety of TXA in elective arthroplasty (60, 61), it is clear that TXA is not standard practice for many NZ arthroplasty surgeons (46.2%). The reason for this is unclear; however, the notion of giving an agent that maintains clot architecture through preventing its destruction can be perceived by some surgeons as unsafe. Patients are already prone to developing complications of VTE because of the inherent nature of the operation itself may make surgeons uneasy about its use in this setting. Young and Moondi surveyed centres about their practice around TXA use in both traumatic haemorrhage and elective THA and TKA. They found that 69% and 62% of responders did not routinely use TXA in trauma and elective settings, respectively.(189) The paucity of data surrounding optimal dose and regimen adds to the lack of compliance.

The topical application of TXA has appealed to surgeons because of its relatively reduced systemic absorption and maximum local effect.(190) However, its use in this manner is yet to demonstrate equal efficacy to its more established intravenous route. Soni and colleagues showed non-significant reductions in blood loss in favour of topical TXA when compared with its systemic administration.(191) In contrast, Patel et al. demonstrated less perioperative blood loss in their systemic TXA group.(192) Some may argue that this is not a surgical decision and may be left to the anaesthetist to decide. This may well be the case for the 10 surgeons (19.2%) who left this decision to the anaesthetist. Interestingly, many studies investigating TXA in arthroplasty have been published in the orthopaedic literature suggesting orthopaedic surgeons have great interest in TXA.(60, 61, 159)

Barriers to implementation of an evidence-based, standardised care pathway, as perceived by responders, varied. Interestingly, the most common barrier chosen by responders was a

lack of buy-in from colleagues (31.4%). As masters of their trade, many surgeons may perceive the idea of having to conform to a standardised, protocolised process as a threat to their surgical autonomy, irrespective of the evidence. Kahokehr and colleagues stated that "for successful implementation of ERAS the most vital ingredient is a surgeon willing to overcome traditional concepts of perioperative care".(193) In addition, the notion of "if it's not broken, then why fix it!" may contribute to this perception of their colleagues not participating in the process. For a quarter of responders an optimised, standardised perioperative care approach was standard practice. Written responses centred on patient care after discharge. Three surgeons indicated insufficient post-discharge resources, which may lead to higher readmissions.

This study was limited by a low response rate among arthroplasty surgeons in NZ. As this was an anonymous survey, it is impossible to characterise the non-responders. Likewise, it is difficult to determine whether responders practised at the same or different hospitals in NZ as other responders, which may skew response results. Both the numerator and denominator to determine the proportion of respondents may be inaccurate. The number of respondents (numerator) may not be a reflection of those surgeons who performed >10 hip/knee surgeries in the year 2013/14 as the survey was sent to all NZOA members. Statistical analysis was not performed as it was felt that there was minimal benefit in finding statistical differences between groups. The aim was to characterise current practice and any variation (or consensus) would be best depicted graphically, as shown in Figures 1 – 8. Lastly, unlike ERAS in colorectal (194), gastric (195) and pancreatic (196) surgery, there are no guidelines yet for ERAS in elective THA and TKA. Thus, there is no current gold standard. The quality of evidence supporting some care interventions covered in this survey is dubious and further research is required to cement its place in ERAS for THA and TKA.

Conclusion

This survey demonstrates that evidence-based practice among NZ orthopaedic surgeons in THA and TKA is varied, with consensus for some evidence-based care interventions but not others, indicating there is room for standardisation and implementation of evidence-based practices to improve patient outcomes. The following chapter assesses the safety and efficacy of ERAS in elective THA and TKA at one publicly funded hospital in the Auckland region.

Chapter 4: Enhanced Recovery After Surgery in elective hip and knee replacements at Counties Manukau

Introduction

ERAS programmes have successfully demonstrated benefits to the surgical patient in colorectal (197), bariatric (57) and upper gastrointestinal surgery.(99) The premise is that by attenuating the surgical insult and minimising the effects of anaesthesia to the patient, patients will avoid the immediate postoperative morbidity and hasten their recovery. ERAS programmes aim to do this through employing the best available evidence in a coordinated and standardised manner, across patients' perioperative journeys, from their first specialist consult through to discharge and follow up.

As previously mentioned, ERAS programmes have been touted as an efficient and cost-effective use of health resources.(56, 57) Similar protocols have been used for many years in elective orthopaedics under such headings as "accelerated rehabilitation", "fast-track", "clinical pathways" and "enhanced recovery", with more emphasis on recovery and rehabilitation.(76, 78, 82)

Using the outcomes of the previous two chapters, this chapter details a prospective study with the aim of evaluating the efficacy and safety of an ERAS protocol in THA and TKA in a single institution in NZ.

Methods

This study compared a prospective cohort (August–December 2013) with an historical cohort (June–August 2012). Ethical approval was obtained from the University of Auckland Human Participants Ethics Committee (Protocol 9095) and orthopaedic departmental approval was gained to proceed with prospective data collection. Over a 1-year period, important changes had been initiated using the Collaborative Breakthrough Series

methodology.(198) This improvement methodology aimed to facilitate multiple small improvements in quality of healthcare provision that rendered benefits in clinical outcomes and cost savings.

Patients

Patients in the ERAS group had their perioperative care managed according to an ERAS protocol specific to THA and TKA arthroplasty developed from the extensive review of the current literature investigating perioperative care interventions used in these settings described in Chapter 2. The final protocol was agreed upon by the multidisciplinary teams involved in delivering the protocol (surgeons, anaesthetists, nursing staff, allied health staff and managerial staff) (Table 6).

Patients undergoing elective primary THA and TKA surgery were eligible to participate in the prospective arm of the study (Figure 9). Written and verbal informed consent was gained from each patient before inclusion in the study. Exclusion criteria comprised patients undergoing bilateral joint surgery, revision surgery or unicompartmental knee replacement and inability to follow verbal or written instructions. ERAS and control group participants had their operation at the Manukau Surgery Centre (MSC), a satellite hospital where predominantly elective surgeries take place. Here, ERAS programmes for colorectal and bariatric surgeries are well established.

The control group underwent their THA or TKA while receiving standard care, which was determined by surgeons and anaesthetists as they saw fit. As in the ERAS group, surgical approach and prosthesis type were not prescribed.

Table 6. Enhanced Recovery After Surgery (ERAS) protocol for Manukau Surgery Centre

Preoperative	Preadmission clinic – appropriate medical advice given, investigations requested and patient expectations managed Group education class (Joint Camp) held weekly, 1–1.5 hours Waiting times for surgery approx 4–5 months
Intraoperative	*Premedication* Paracetamol PO 1gram +/- 100–300 mg gabapentin *Anaesthesia* Aim for regional anaesthesia (spinal or epidural) in all cases when safe and achievable +/- intrathecal morphine 100–200 mcg *Antiemetics* - Ondansetron IV 4–8 mg / Cyclizine IV 25–50 mg / Dexamethasone IV 4–8 mg Tranexamic acid IV 500–1000 mg (1 intraoperative dose), Cephazolin IV 2 g within 1 hour of incision *Other* - indwelling catheter (IDC) inserted in selected cases, avoidance of surgical drains
Postoperative	Analgesia *Non-opioid (regular for duration of admission)* Paracetamol PO 1gram, NSAIDs (Ibuprofen 1200 mg/day, Celecoxib 200–400/day), Gabapentin 200–400 mg/day *Opioid* PCA morphine/oxycodone/fentanyl if required (removed morning of 1st postoperative day) Tramadol 400 mg/day, m-Eslon 20–40 mg/day, Sevredol 10–20 mg q2h/prn, OxyContin 20–40 mg/day, OxyNorm 10–20 mg q2h/prn *Antiemetics and aperients* Regular Ondansetron 4–8 mg / Cyclizine 25–50 mg on day 1, as required thereafter Laxsol 2 tabs and Lactulose 10–20 ml twice per day *Mobility* - mobilise 4 times per day starting day 1, up to chair for all meals *Other* - Remove drains, IVL and IDC on day 1, change into usual day clothes from day 1 onwards
Discharge	Follow up call from nursing staff 24–48 hours post-discharge Family doctor follow up 10–14 days post-discharge for wound review Specialist follow up appointment 6 weeks post-discharge

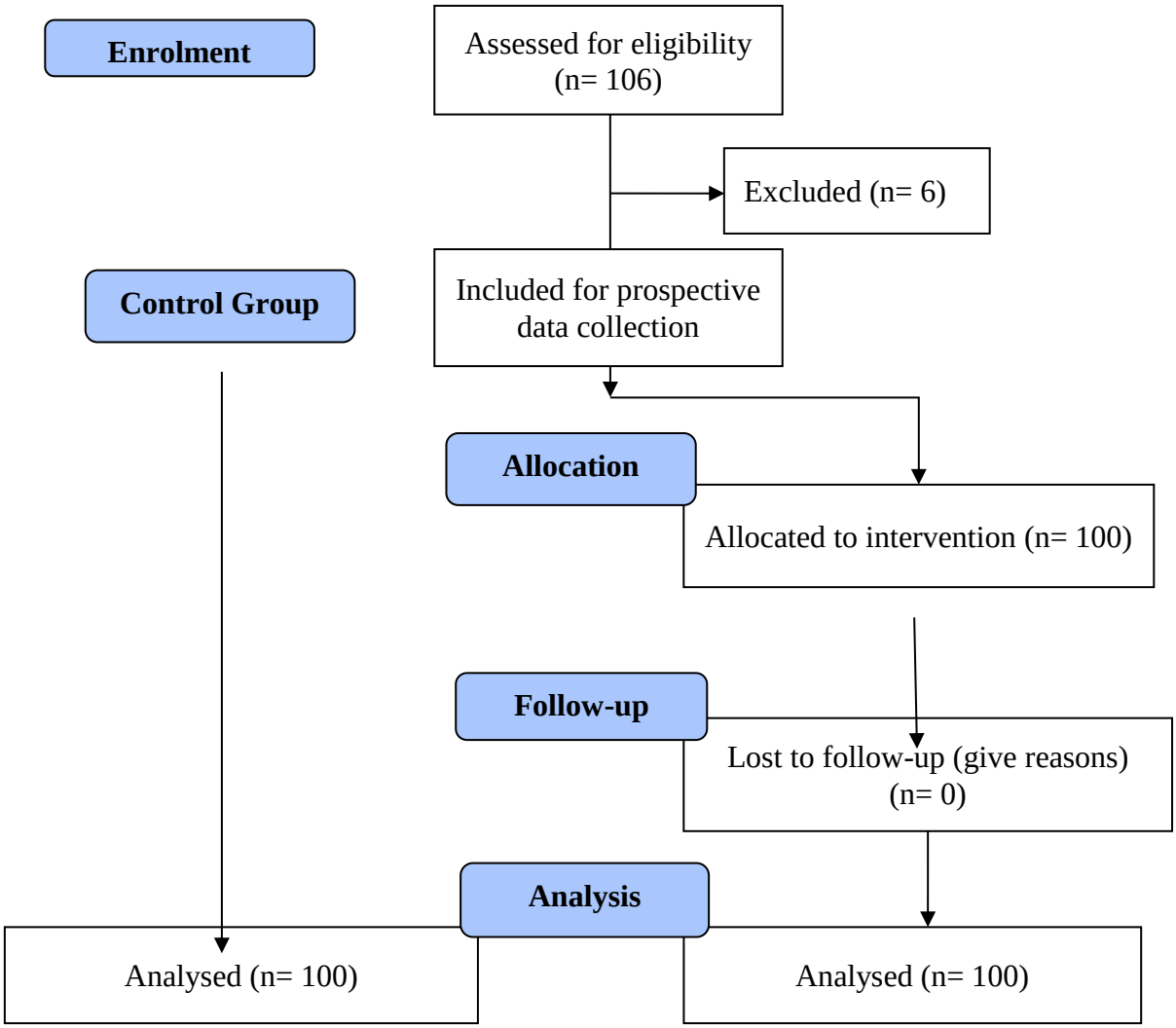


Figure 9. Flow diagram

Outcome data

Demographic data collected included age, sex, ethnicity and BMI. Preoperative comorbid status was assessed by means of ASA score, and the presence of diabetes mellitus, hypertension, hypercholesterolaemia, chronic obstructive pulmonary disease, ischaemic heart disease (IHD) and atrial fibrillation (AF). Thirty-day complication rates were recorded, including readmission rates. Total median LOS was calculated by adding readmissions lasting longer than 24 hours to the patient's index LOS.(57)

$$\text{Total median LOS} = \text{LOS}_{\text{index}} + \text{LOS}_{\text{readmission}}$$

Compliance to the protocol was also measured. Nine components of the protocol were chosen to be audited and compliance with each was deemed to be *satisfactory* if 80% or greater. Daily morphine equivalent doses (MEDDs) were recorded daily for the first 5 days (including the day of surgery) and then compared between groups.(199) All opiates administered and received by patients (systemic, oral and intrathecal) during their index admission were recorded. All analgesic medications including non-opiates have a morphine equivalent and were adjusted and collated accordingly.(200) The total cost incurred per patient was calculated by adding the cost of index LOS and any cost incurred during readmissions.(57)

$$*\text{Total cost per patient} = \text{Cost}_{\text{index}} + \text{Cost}_{\text{readmission}}$$

*costs are less the cost of prostheses

Comparative analysis was then performed to determine the cost of THA and TKA in each setting.

Statistical analysis

The primary end point was median LOS at the index admission for surgery. One year preceding the implementation of the ERAS programme at the MSC, the median LOS for our THA and TKA was 5 days, respectively. The aim of the orthopaedic department and the author was to reduce the index median LOS by at least 1 day (4 days). Using the Mann-Whitney U test and assuming alpha of 5% and statistical power of 80%, a total of 96 patients in our prospective and historical groups were required. Continuous data were analysed using Student's t-test; categorical data were analysed using Pearson's chi-square test. Statistical significance was set at 0.05. An interim power calculation was performed midway through

the study to ensure that the study continued to have adequate power. Statistical analysis was carried out using SPSS® version 21 (IBM, Armonk, New York, USA).

Results

A total of 106 patients in the ERAS group were eligible to participate in the study. Six patients declined consent to collect their data prospectively. Thus, 100 patients in each group were compared and analysed. There were no baseline differences between groups (Table 7).

A summary of postoperative complications up to 30 days is shown in Table 8. There were no statistically significant differences in complications between the two groups (p = 0.372). Ninety-eight per cent of ERAS patients were admitted on the day of surgery compared with 95% of the control group.

Morphine equivalent dosing was greater in the ERAS group on the day of surgery and the first postoperative day, especially for those undergoing TKA (POD 0: 14 mg v. 7 mg; p = 0.000, POD 1: 33 mg v. 20 mg; p = 0.000). Hereafter, MEDD was similar in the two groups. (Figure **10**)

Table 7. Baseline characteristics

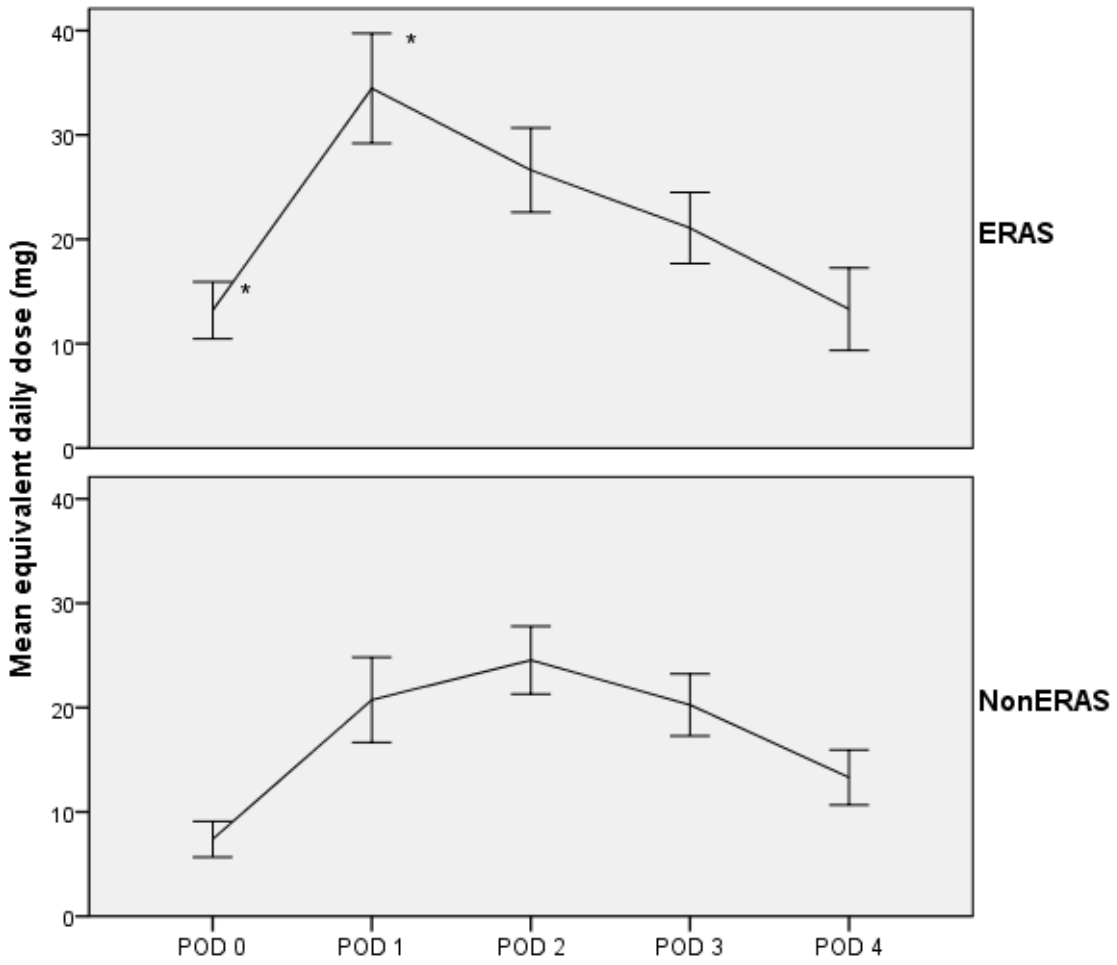
Characteristics	ERAS (n = 100)	Non ERAS (n = 100)	p-value
Operation (%)			
Hip	31	39	0.299*
Knee	69	61	
Age (mean, SD)	66.7 (9.2)	65.4 (12.5)	0.408†
Female gender (%)	53	59	0.393*
Ethnicity (%)			
European	56	63	0.721*
NZ Maori	14	8	
Pacific	15	14	
Indian/Asian	14	14	
Other	1	1	
ASA score (%)			
1	2	7	0.185*
2	67	57	
3	31	35	
4	0	1	
Diabetes (%)	23	21	0.733*
Hypertension (%)	70	66	0.544*
Cholesterol (%)	37	33	0.657*
COPD (%)	15	7	0.071*
IHD (%)	17	17	1.0*
BMI (mean, SD)	34.4 (7.0)	32.5 (6.8)	0.051†
Preop Hb (mean, SD)	137 (12.2)	139 (13.7)	0.175†

Notes. * Pearson Chi-Square Test; † Student T-test
n = number of participants included; ASA = American Society of Anaesthesiologists; COPD = chronic obstructive pulmonary disease; IHD = ischaemic heart disease; BMI = body mass index; Hb = haemoglobin.

Table 8. Length of stay, readmissions and 30-day complications

Outcomes	ERAS (n = 100)	Non ERAS (n = 100)	p-value
Index median LOS (IQR)	4 (2)	5 (2)	0.000†
Hip	4 (2)	5 (2)	0.000†
Knee	4 (1)	5 (3)	0.000†
Readmission (%)	8	14	0.258*
Hip	1	3	0.424*
Knee	7	11	0.194*
Total median LOS (IQR)	4 (2)	5 (2)	0.000†
Hip	4 (2)	5 (3)	0.000†
Knee	4 (2.5)	5 (2)	0.001†
Complications (%)	13	18	0.372*
Hip			
Symptomatic DVT/PE	0	1	ns
Wound infection	1	2	ns
Deep infection	0	0	-
Return to theatre	0	0	-
Medical (MI/CVA/Pneumonia/UTI)	0	2	ns
Dislocation	1	0	ns
Knee			
Symptomatic DVT/PE	1	4	ns
Wound infection	8	6	ns
Deep infection	0	0	-
Return to theatre	0	1	ns
Medical (MI/CVA/Pneumonia/UTI)	2	2	ns

Notes. † Mann-Whitney U Test; * Pearson Chi-Square Test
n = number of participants included; LOS = Length of stay; IQR = Inter-quartile range; ns = not statistically significant



Notes. *indicates $p < 0.05$ between groups
POD = postoperative day 0–4

Figure 10. Morphine equivalents daily dose for the first five days index admission (ERAS versus Non ERAS)

The ERAS group demonstrated significant differences in index median LOS and total median LOS (Table 8). One year post-implementation of the ERAS protocol, the median LOS for patients undergoing primary THA and TKA was reduced by 1 day (4 days; $p < 0.001$). There were fewer readmissions in the ERAS group but this failed to reach statistical significance (8 v. 14; $p = 0.258$). Seven readmissions occurred in TKA (1 urinary tract infection, 4 superficial wound infections requiring intravenous [IV] antibiotics, 1 gout flare, 1 episode of acute heart failure), and a single readmission occurred in THA (superficial wound infection treated with short course of IV antibiotics). The total median LOS was

significantly different between the two groups (5 days control v. 4 days ERAS; $p < 0.001$). No deaths occurred in either group (30-day follow up).

In-hospital costs calculated combined index admission costs with the readmission costs. The mean cost analysis demonstrated ERAS in both THA and TKA to be less costly than patients who had their operation prior to implementation of the new protocol, but this failed to reach statistical significance (Table 9).

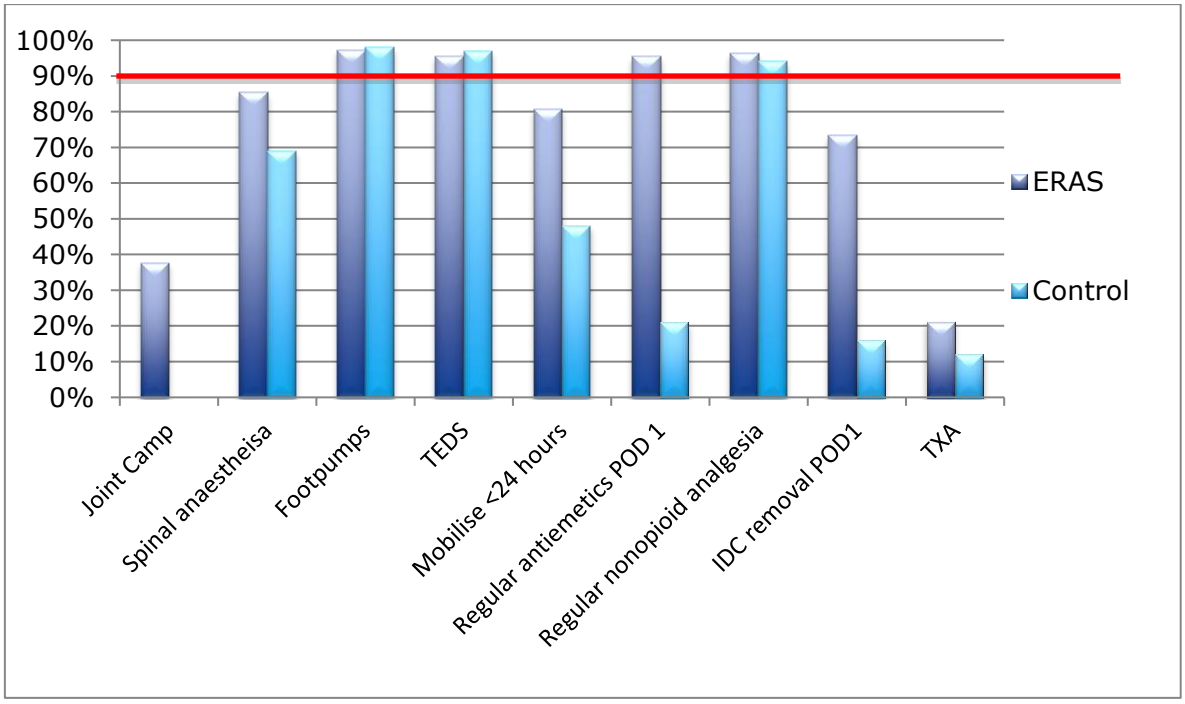
Table 9. Cost of index admission and readmission in 30 days (less implant cost)

Cost (NZD) ***Index admission + readmission***	**ERAS (per patient)**	**Non ERAS (per patient)**	**p-value**
Hip	10,638.66	13,216.89	0.057
Knee	11,804.80	12,045.35	0.326
Combined	11,439.65	12,502.25	0.119

Nine components of the ERAS protocol were used to evaluate compliance. The same components were audited for the control group to identify any crossover between the two groups. Eighty per cent was set as the threshold for achieving *satisfactory* compliance to each perioperative care intervention chosen to be audited.

Figure 11. demonstrates the percentage of patients in the two groups who completed each component. The ERAS group fell short of achieving *satisfactory* compliance in three of the perioperative care components (Joint Camp attendance, IDC removal day 1 and IV TXA use). In the beginning, Joint Camp was optional and was only established in the later stages of the implementation period. With experience, it was realised that this was an important component of the programme and it was made "compulsory". Despite TXA use failing to achieve satisfactory compliance in the ERAS group, this was almost double (21% v. 12%) that of the control group.

Early mobilisation (< 24 hours) was achieved in 88% of patients in the ERAS group. Eighty-one per cent of those patients mobilising early were successfully discharged within 4 days.



Notes. TEDS = thromboembolic deterrent stockings; POD = postoperative day; IDC = indwelling catheter; TXA = tranexamic acid

Figure 11. Compliance to ERAS protocol

Discussion

Patients undergoing THA and TKA within ERAS had a significant reduction in LOS compared with those patients who had their operation managed as per their surgeon's and anaesthetist's instruction. Importantly, the reduction in LOS did not result in higher rates of readmission. The mean in-hospital costs for THA and TKA in the ERAS group showed a trend to be less costly compared with the control group, thus supporting the increasing evidence that such protocols are cost-effective.(52, 201)

Studies evaluating enhanced recovery programmes for elective THA and TKA have achieved similar reductions in LOS without compromising patient safety.(84, 85, 90)

Arthroplasty units choosing to establish an ERAS protocol in their institution have been instigated by champions within their departments or have been guided by national governments to replicate benefits seen in other centres with established enhanced recovery programmes. McDonald and colleagues (85) demonstrated significant reductions in LOS and transfusion rates ($p < 0.001$ and $p < 0.001$, respectively). Their programme was modelled on a Danish protocol and supported by the institute's clinical governance guidelines. In Scotland in 2009, a national steering group was instructed to support implementation and auditing of each hospital's ERAS protocol. Scott and colleagues (90) reported reductions in median length of hospital admissions of 1 day across 22 Scottish orthopaedic units over 1 year.

The implementation of the ERAS protocol is often met with some resistance, and gaining traction can be difficult.(193) At MSC, the ERAS protocol was composed first by performing an extensive review of the literature detailing commonly used components of ERAS used in joint arthroplasty. The Collaborative Breakthrough Series model for improvement provided a framework to introduce these changes "to bridge the gap of what we *know* and what we *do".*(198) Larsen et al. also used this method of implementation for their accelerated perioperative care and rehabilitation intervention for their THA and TKA patients.(50) Researchers demonstrated large reductions in LOS. The additional benefits of this implementation method have resulted in sustainable change with minimal additional resource requirements. Thus, the set-up of an ERAS programme can be slow in its initial stages, but how each centre decides to roll it out is dependent on departmental policy and the willingness of individuals responsible for change.(193, 202)

The primary outcome measure for this study was LOS following THA and TKA. LOS has previously been used to evaluate the efficacy of ERAS in other surgical specialties, including

bariatric and colorectal surgery.(57, 203) Of importance, the present study demonstrated reductions in hospital stay without an increase in postoperative morbidity and readmissions. A common misconception of ERAS is that reductions in LOS are likely to be offset by a higher readmission rate negating these observed gains. As with Lemanu et al., index LOS was combined with any readmission in 30 days LOS (total LOS) in an attempt to address this issue, and similarly to Lemanu et al. this study demonstrated no increase in readmissions or median total LOS when compared with control or historical groups.

Furthermore, rates of complications were lower in patients who had their THA and TKA in an ERAS setting. Although these group differences were not statistically significantly different, it highlighted that the true value of ERAS lies in its ability to reduce perioperative morbidity.(57, 204) This has important implications in long-term survival: one study reported a 69% survival reduction (18.4 to 5.6 years) in patients experiencing a complication within 30 days of major surgery.(205) In the present study this difference may well be understated as the control group's data were recorded retrospectively, leaving them prone to under-reporting of both major and minor complications and also this was a secondary outcome that the study was not powered for.

Early mobilisation has been shown across several specialties to correlate with a shorter LOS and therefore reduced in-hospital resource utilisation.(206-208) The current study showed similar results: 81% of those mobilising early (< 24 hours) were discharged successfully in 4 days or less. To successfully achieve this milestone, patients must be both educated and physically and cognitively able to do so. This expectation was made explicit at every point of contact made with the patients prior to their surgery. The ability to mobilise requires several important functions to be in check, including adequate analgesia, sequelae of postoperative anaemia, dizziness and PONV. Enabling early mobilisation should act as a

key performance indicator of ERAS protocols. This simple outcome measure captures all of the aforementioned proponents of care to be targeted in the perioperative and immediate postoperative periods, again highlighting the value of ERAS programmes.

An integral aspect of ERAS is its opioid-sparing analgesic regime. In this study morphine equivalents were measured during the index admission to assess morphine consumption. For day of surgery and postoperative day 1, morphine consumption was significantly higher in the ERAS group than in the control group for the same periods. Certainly, joint replacement surgery can be very painful, particularly TKA.(209) This is in contrast to a study of colorectal patients in a tertiary centre in the USA that showed after successful implementation of their ERAS programme improved pain scores in the first 48 hours despite taking less opioid both during and after surgery (ERAS MEDD: 143 mg versus preERAS MEDD: 241.2 mg; $p < 0.001$).(210)

Even with spinal analgesia used to facilitate early mobilisation, patients continue to experience severe pain in the immediate postoperative period. It is difficult to say with certainty why such large differences in opioid consumption have occurred. One possible reason is that ERAS attempts to employ early and aggressive mobilisation, which may result in pain during this early mobility. Another factor contributing to these findings may be that nursing staff are aware of early mobility of patients as part of the ERAS programme and anticipate patients being sore and therefore offer or administer analgesia prior to mobilisation. Pain scores were not captured and therefore it was not possible to correlate consumption with pain severity. These findings demonstrate an area where anaesthetic modalities can be targeted to attenuate opioid consumption, and therefore its sequelae, but continue to facilitate aggressive, earlier mobilisation. This is especially true for TKA.

Audit of and compliance to the ERAS programme are important aspects of evaluation of a standardised pathway in surgery.(211) The impact of process standardisation and adherence to evidence-based processes cannot be overstated. The standardised nature of a pathway such as ERAS in lower limb arthroplasty has resulted in improved clinical outcomes and shorter length of hospital stays, independent of surgeon and hospital volume.(71) Those centres with greatest compliance to their respective ERAS programmes demonstrate greater reductions in LOS.(211) This study has replicated these benefits seen in larger centres. However, compliance with several audited components of the MSC protocol failed to reach satisfactory levels.

The slow uptake of TXA use in THA and TKA may be explained by surgeons' cautious attitudes towards using an anti-clot degradation agent in this setting. These attitudes are reflected in TXA practices in the UK, where only 38% of centres routinely use TXA in arthroplasty.(189) This may be reasonable considering that questions remain over the optimal regime, including appropriate dose, route and timing. What is less well understood, however, is the impact each component has on producing reductions in LOS and perioperative morbidity.(52) More research into ascertaining which ERAS components lead to the greatest gains are required as those responsible for policy making and resource allocation are likely to have an invested interest in these findings.(52)

One of the main limitations of this study was its non-randomised study design comparing a retrospective cohort to a prospective cohort. However, baseline differences failed to demonstrate any significant differences in age, gender, ASA scores, preoperative haemoglobin (Hb) or preoperative comorbidities. Furthermore, performing an RCT would leave the study at risk of inadequate blinding and therefore subsequent performance bias. These important limitations have been encountered in previous RCTs investigating

ERAS.(57, 212) Costs reported in this study are from a payer's perspective only and although the method of calculating the costs was not a validated one described in the literature it was performed in the same way for each of the patients enrolled. Studies performing economic evaluations of ERAS or fast-track programmes report in-hospital costs, but often fail to report costs from a societal perspective. That is, once discharged, the cost of caregiver burden, loss of income as a result of convalescing and loss of sleep when recovering at home.(52) Capturing these costs was beyond the scope of this study.

Conclusion

In conclusion, an orthopaedic-specific ERAS programme in THA and TKA is effective in reducing hospital stay without compromising the quality of healthcare provision. Readmission rates were similar in both groups. This ERAS programme allows testing of an intervention in THA or TKA patients as part of an RCT.

Chapter 5: Efficacy and safety of systemic and topical tranexamic acid in arthroplasty: A systematic review

Introduction

Postoperative anaemia following elective arthroplasty can lead to prolonged hospital stay and delays in rehabilitation, and is often poorly tolerated in patients with cardiovascular disease.(42) TXA in arthroplasty is used by many orthopaedic surgeons to reduce perioperative blood loss and subsequent transfusion of blood products in elective THA and TKA. Several reviews have shown systemic TXA (sTXA) significantly reduces blood loss and transfusion rates when compared with placebo, without an increased risk for VTE.(60-62)

The CRASH-2 study, with over 20,000 randomised trauma patients, has also confirmed the efficacy and safety of TXA in this setting, particularly when given early.(213) The evidence for its use to date is overwhelming and, when not contraindicated, should be employed by all arthroplasty units as part of their standard practice. However, despite the convincing evidence for its use in arthroplasty, some surgeons remain cautious over its safety profile when given systemically. TXA is a synthetic derivative of lysine, which is responsible for binding reversibly to plasminogen, effectively inhibiting clot degradation.(59) Although this is not clot promoting, inhibiting clot breakdown theoretically may increase the likelihood of clot formation. This is of real concern for surgeons in patients who have had previous VTE. For this reason, some surgeons have utilised TXA as a topical application directly into the surgical field to reduce systemic absorption and avoid VTE.(63, 64)

TXA administered topically in TKA has also been reported to reduce swelling, which may give the advantage of earlier mobility and less pain.(66) In cardiac surgery, TXA has been

touted not only as having blood-conserving properties via the coagulation pathway but also as reducing inflammation via attenuation of the pro-inflammatory cascade.(214, 215)

Based on this rationale, this appears to be a sensible and reasonable route of administration for TXA in this population. However, there is conflicting evidence on whether this route of administration is as effective as systemic administration.(65, 192) The purpose, therefore, of this study is to systematically review the literature to answer two important clinical questions:

1. Does topical TXA (tTXA) demonstrate an efficacy and safety profile equivalent to that of its systemic administration in elective arthroplasty?
2. Does tTXA have any additional benefits or risks over sTXA in arthroplasty?

Methods

A comprehensive review of the literature was performed in accordance with methods outlined in the PRISMA statement (Figure 12). Online databases (Medline, PubMed, Embase and Web of Science) were searched from inception to 31 July 2014. After excluding duplicates and studies by title and abstract, remaining full text articles were hand searched for relevance to the systematic review. A combination of key terms was used to allow for a thorough review (Table 10). The remaining articles' reference lists were then manually searched for any additional eligible articles. During the write-up of the review, an additional journal article that met inclusion and exclusion criteria was published after the search in August 2014.(191) This article was included for review and its reference list failed to identify any additional papers.

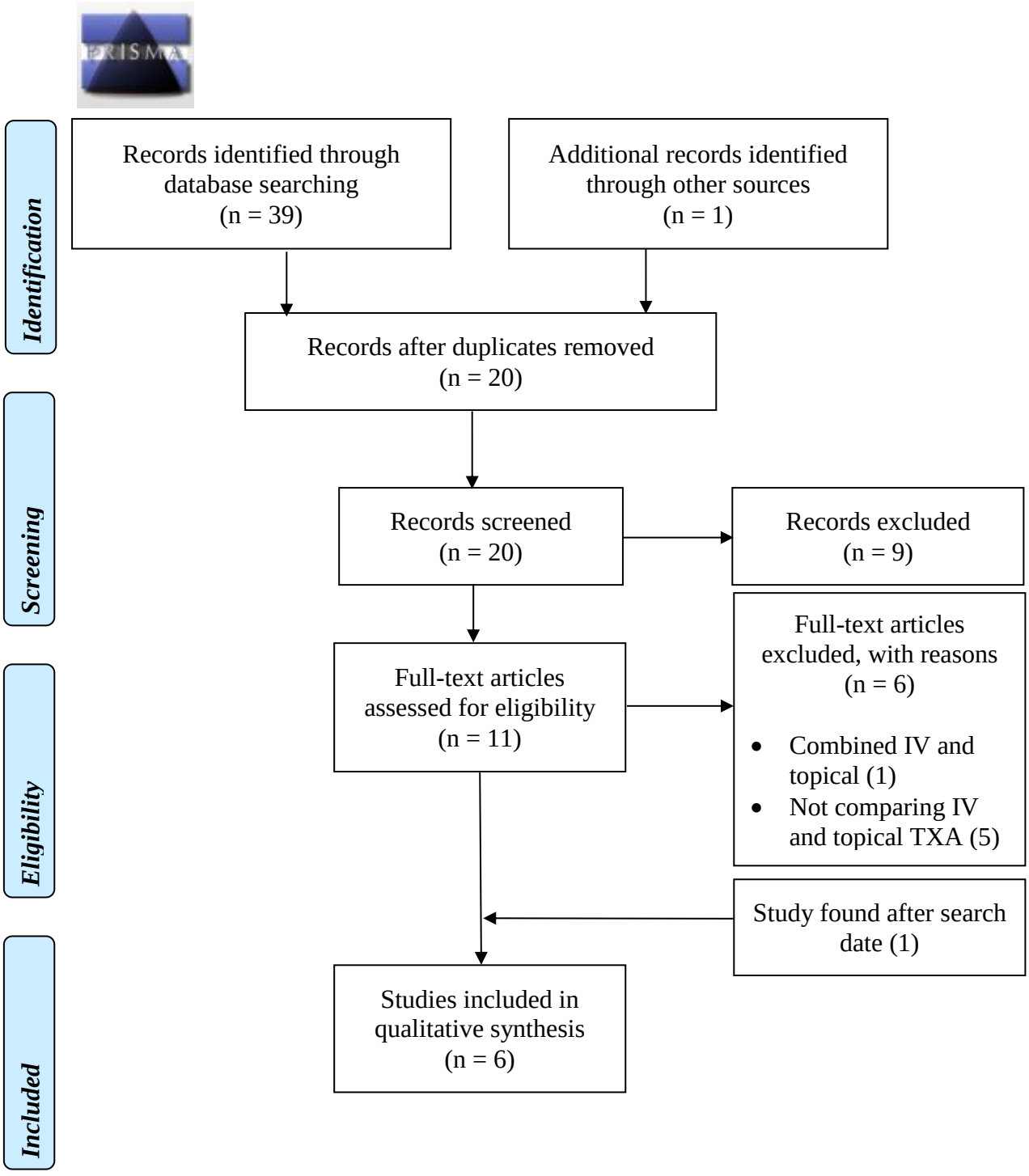


Figure 12. PRISMA flow diagram

Table 10. Key search terms combined with "AND"

Search terms	
Medline (3) Embase (4)	Orthopaedic$ OR Arthroplasty OR joint replacement OR total hip arthroplasty OR total knee arthroplasty
PubMed (16) Web of Science (16)	Topical tranexamic acid OR periarticular tranexamic acid OR pericapsular tranexamic acid OR intraarticular tranexamic acid
	Intravenous tranexamic acid OR IV tranexamic acid OR systemic tranexamic acid

Note. Numbers in parentheses are articles found in each online database

All studies investigating and comparing sTXA and tTXA in the setting of THA or TKA were included for review. No restrictions on study design were used to determine article eligibility. Non-English articles were excluded from the study.

Study information was extracted and recorded in Microsoft Excel spreadsheets predesigned by the author. Any missing data that the author thought were important for the review were sought by contacting the corresponding authors of the studies. If there was no response from the corresponding authors of the respective studies, then the specific data were recorded in tables as "not reported".

The quality of studies included for review were assessed using the Physiotherapy Evidence-Based Database (PEDro) scale.(216) The PEDro scale assesses the methodological quality of clinical trials using an 11-item questionnaire. Questions 2–9 assess a study's internal validity. Items 10 and 11 determine whether there is sufficient statistical information to make the results interpretable. An additional item (Item 1) relates to the external validity of the trial. When assessing the methodological quality of randomised studies, PEDro offers scores to allocation concealment, intention-to-treat analyses and follow up, which are all important parameters for enhancing the internal validity of trials. Allocation concealment has been identified as an important measure of internal validity of a study and when not used can have

large influences on the effect estimate of an intervention.(217) The PEDro scale accounts for these methodological aspects, which are not accounted for by other quality assessment tools like the Jadad scale, and hence the decision to use the PEDro scale tool to assess the quality of included studies.

Outcomes

Primary outcomes measures used in studies included transfusion rates, perioperative blood loss (direct and indirect) and postoperative Hb reduction. Secondary outcomes recorded in studies included VTE and other complications. Functional outcomes including ROM, Oxford hip and knee, Short-Form Health Survey (SF-36/12) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores were also sought.

Results

Six studies met criteria to be included in the study for review.(63-65, 191, 192, 218) Five of the six studies investigated TXA in TKA and the remaining study in THA. A total of 2469 patients underwent 2669 TKA and a total of 1494 patients received 1595 THA. A summary of the efficacy and safety of each included study is shown in Table 11.

Table 11. Summary of studies, effect estimates and quality

Author (year)	Study design	Surgery type	Case number			Efficacy (systemic-topical)†			Safety (systemic/topical)		PEDro score
			IV	Topical	Placebo	Transfusion rates (%)	Hb reduction (g/dL)	Blood loss (ml)	DVT (count)	PE (count)	
Seo et al. **(65)** (2013)	RCT	TKA	50	50	50	14*	−0.2	102*	0/3	0/0	6
Wind et al. **(64)** (2013)	Retrospective audit	TKA	330	130	1839	0.3	N/A	N/A	7/2	1/1	3
Hedge et al. **(218)** (2013)	Prospective non-randomised trial	Computer-assisted BTKA	30	30	30	23*	0.66	N/A	0/0	0/0	4
Patel et al. **(192)** (2014)	RCT	TKA	42	47	N/A	−2.1	−0.36	−71.5	0/0	0/0	8
Wind et al. **(63)** (2014)	Retrospective audit	THA	478	70	1047	−8.5	N/A	N/A	0/0	1/0	3
Soni et al. **(191)** (2014)	RCT	TKA	30	30	N/A	−3.3	0.21	23	0/0	0/0	5

Notes. IV = intravenous; Hb = haemoglobin; DVT = deep vein thrombosis; PE = pulmonary embolus; RCT = randomised controlled trial; PEDro = Physiotherapy Evidence-Based Database; TKA = total knee arthroplasty; BKTA = bilateral total knee arthroplasty; THA = total hip arthroplasty
N/A = not applicable; †Efficacy is calculated by the equation systemic outcome measure *minus* topical outcome measure. *Comparisons with $p < 0.05$

The quality score of the trials, based on the PEDro scale, ranged from 3 to 8 out of a possible 11. Two studies were large retrospective audits (63, 64) , one study was a prospective non-randomised trial that recruited patients consecutively (218) and three studies were RCTs.(65, 191, 192)

Blood loss

Three of six studies comparing sTXA and tTXA reported on blood loss.(65, 191, 192) Seo et al. reported significant reductions in perioperative blood loss via two surgical drains in the tTXA group when compared with those patients receiving sTXA. Soni et al. reported non-significant reductions in perioperative blood loss in favour of the tTXA group. Conversely, Patel et al. reported less perioperative blood loss in the sTXA group. Of note, all studies describe different doses and regimens of TXA for their respective systemic and topical groups (Table 12).

Transfusion rates

Transfusions of packed red blood cells (PRBCs) were measured in all included studies. Two studies reported significant reductions in transfusion rate in groups given TXA topically compared with groups who were administered sTXA.(65, 218) Three studies demonstrated non-significant reductions in transfusions in groups given IV TXA when compared with its local application.(63, 191, 192)

Venous thromboembolic events

All studies included in the review reported on rates of VTE. No significant differences between systemic and topical administration groups were found for VTE. In one institute, TKA overall appeared to have higher rates of DVT than THA, irrespective of the route of TXA administration.(63, 64)

Table 12. Summary of tranexamic administration and potential confounders

Author (year)	Tranexamic acid administration, timing and method of delivery		Tourniquet used	Drains used (n)	Transfusion trigger	VTE prophylaxis used
	Systemic	Topical				
Seo et al. **(65)** (2013)	1.5 g in 100 ml of saline administered immediately after closing wound	1.5 g in 100 ml of saline direct into the knee joint cavity while closing	Yes	Yes (2)	Hb < 8.0 g/dL or Hb < 10.0 g/dL + anaemic symptoms	Not reported
Wind et al. **(64)** (2013)	2 perioperative doses (each 1 g): • Within 1 hour of incision • At commencement of wound closure	1 g placed into the knee joint and the capsule closed	Not reported	Yes*	Hb < 8.0 g/dL	Warfarin
Hedge et al. **(218)** (2013)	10 ml (1 g) 20 minutes prior to tourniquet inflation	10 ml (1 g) immediately after wound closure	Yes	No	Hb < 7.0 g/dL or Hb < 9.0 g/dL + cardiac disease Signs of hypoxia or haemodynamic instability	Not reported
Patel et al. **(192)** (2014)	10 mg/kg dose given 10 minutes prior to tourniquet deflation	2.0 g in 100 ml of normal saline injected into the surgical site and bathed in the solution for 2 minutes prior to tourniquet release	Yes	Yes (2)	Hb < 8.0 g/dL + symptoms[α]	LMWH
Wind et al. **(63)** (2014)	2 perioperative doses (each 1 g): • Within 1 hour of incision • At commencement of wound closure	1 g placed into the hip joint and the capsule closed	N/A	Yes*	Hb < 8.0 g/dL	Warfarin
Soni et al. **(191)** (2014)	3 perioperative doses each 10 mg/kg at: • 20 minutes before tourniquet application • 15 minutes prior to tourniquet deflation • 3 hours after intraoperative dose	3 g diluted in 100 ml normal saline applied locally after cementing the implant and before tourniquet release. At least 5 minutes of contact time.	Yes	Yes (2)	Hb < 8.0 g/dL	LMWH

Notes. VTE = venous thromboembolism; LMWH = low molecular weight heparin; N/A = not applicable
*Tourniquet clamped for 30 minutes postoperatively in the topical TXA group. [α]Symptoms defined as syncope, light-headedness, short of breath, fatigue, palpitations

Complications

Studies reported on new onset of AF (65), wound complications including infection (192, 218), revision surgery (192) and mortality.(65) Two cases of new onset AF occurred in the study of Seo et al., one in each of the topical and placebo groups.(65) No statistically significant differences in reported complications were found in any of the included studies.

Functional outcomes

One RCT recruited 150 patients, allocated to three groups, and reported on range of motion at follow up of 2 months.(65) The average ROM in each group was 2.6–123.3 degrees (IV), 2.5–120.4 degrees (topical) and 2.9–124.1 degrees (placebo). There was no statistically significant difference between groups for this outcome at this time point.

Discussion

Systemic TXA has for the past decade been the gold standard for many arthroplasty centres around the world as an integral blood-conserving measure.(219, 220) However, debate surrounding the optimal regimen for TXA in elective arthroplasty continues to fuel research in orthopaedic surgery.(221) Researchers have investigated tTXA in arthroplasty as a way of not only reducing blood loss but also minimising risk for sinister clot formation in a group of patients inherently at risk for DVT and PE. This route appeals to many surgeons as its local administration direct to the intended site of action is easy to administer and is associated with minimal systemic absorption.(222)

Few studies have compared sTXA and tTXA, and at a glance it appears the two routes for a given dose may demonstrate equivalent efficacy and safety profiles. Two studies reported significantly lower transfusion rates in sTXA groups compared with tTXA (65, 218); one of these studies reported significantly less blood loss when TXA was given directly into and around the joint replacement.(65)

Interest in topical application of TXA is increasing, with recent studies investigating its efficacy in knee and hip arthroplasty surgery.(223-225) However, most of the studies described in these reviews were superiority studies that compare against placebo. In light of the evidence for sTXA, the topical application of this drug should in fact be compared with the IV route, at least as a third arm of future trials. Ensuring that topical administration is as efficacious as its more widely accepted systemic route should first be an ethical consideration that investigators address. Failing to ensure equivalence (or non-inferiority) may place patients in future trials at risk of increased blood loss, increased transfusions and delays in rehabilitation when applied topically. Lack of equivalent efficacy may well be a possibility, especially when surgeons' protocols for administering sTXA are sometimes instructed to be given prior to skin incision and tourniquet inflation.(63, 64, 191, 192, 218) This may reduce intraoperative bleeding further, especially when a tourniquet is omitted, which tTXA may not influence because of its application towards the end of the surgery.

Two studies administering preoperative sTXA reported conflicting findings with respect to transfusion requirements. Hedge et al. found significant reductions in transfusion rates favouring tTXA. Soni et al. demonstrated non-significant reductions in transfusion rates favouring the sTXA group. Uncertainty around the optimal regimen is compounded from these findings. However, a previous study has identified the importance of timing of tTXA on influencing blood loss.(226) The authors found significant reductions in both drain loss and total blood loss in the regimens of preoperative and intraoperative (POIO) dose group ($p = 0.023$ and $p = 0.02$, respectively), and the preoperative, intraoperative and postoperative (POIOPO) dose groups ($p = 0.000$ and $p = 0.001$, respectively). Groups that lacked a preoperative dose demonstrated greater drain losses and total blood losses overall.(226)

Two systematic reviews of TXA in the setting of hip (61) and knee (60) joint replacement surgery demonstrated reduced blood loss and an equivalent safety profile when compared with placebo. A majority of studies included for both reviews used LMWH as their venous thromboembolic prophylactic agent. The external validity of these reviews is questioned when attempting to apply these findings to centres that use agents other than LMWH. Two studies reported using LMWH for the duration of admission to 14 days (191, 192), another two used warfarin (63, 64) and in the remaining two studies an agent was not specified.(65, 218) It is unclear what influence, if any, different VTE chemoprophylactic agents may have on the incidence of DVT and PE in the setting of TXA use.

The ACCP and AAOS recommend, in combination with mechanical devices, that all chemoprophylactic agents include low dose aspirin as the appropriate DVT prophylaxis.(227) The inclusion of aspirin in the most recent AAOS and ACCP guidelines for DVT prophylaxis was born from concern by surgeons regarding the increased risk of wound problems through excessive bleeding from other agents.(228)

No prospective study has yet addressed the safety of TXA, irrespective of route, when aspirin alone is used as part of the surgeon's DVT prophylaxis. In one retrospective study of 2046 patients undergoing elective arthroplasty, agents including aspirin alone, dalteparin and dose-adjusted warfarin were found to have similar rates of symptomatic VTE.(159) Future studies should report DVT chemoprophylactic agents when investigating TXA.

In an RCT of patients undergoing TKA, Ishida et al. found that tTXA reduces swelling at 1 and 2 weeks postoperatively ($p < 0.05$) when compared with placebo. The authors of this study claim the reduction in swelling is attributable to lowering the hidden blood loss that may occur via extravasation in surrounding soft tissue. However, they did not measure this in the immediate postoperative period. Doing so would have allowed the investigators to

correlate this to early ROM and pain scores. As a result, the author recommends the measurement of early postoperative pain scores, swelling and ROM in future trials examining tTXA in TKA.

Recently, TXA has been investigated for its anti-inflammatory effects in cardiopulmonary surgery.(215) Although the coagulation and inflammatory cascades have been typically taught in isolation, they are interlinked, particularly when endothelial injury occurs. Pro-inflammatory cytokines are released in response to injury, and at the same time, endothelial injury activates the coagulation cascade.(215, 229) IV TXA decreases markers of inflammation in cardiac surgery.(229) In addition to less blood extravasation to the surrounding soft tissue, reduction in postoperative knee swelling may be the consequence of TXA exhibiting anti-inflammatory properties. However, these anti-inflammatory effects have yet to be demonstrated in an orthopaedic setting.

Limitations

Several limitations in conducting and reporting of this review are acknowledged. Two of the six included studies were retrospective audits and any interpretation of significant findings should be done so with caution. Heterogeneity of studies at both patient and study levels adds to the lack of generalisability of findings and precluded meta-analysis. Important differences in dosage and timing of systemic administration of TXA were noticeably variable between studies. Doses of TXA in all studies ranged from 1 g as a single dose to 10 mg/kg given at three different points in time. This undoubtedly has significant influences on the variability in effect sizes reported. Only published data were included in the review.(230) A recent review reported doses of > 2 g given topically demonstrated greater reductions in transfusion rates for total knee joint surgery when compared with lesser doses.(231) Secondly, drains were used in all but one study, which has been suggested as a

mechanism for increasing blood loss in THA and TKA.(232, 233) For these reasons and the small number of included randomised studies an informed decision was made to not perform a quantitative analysis.

Conclusion

Topical TXA in hip and knee arthroplasty appears to show similar reductions in blood loss and transfusion rates and comparable rates of VTE to those of sTXA. The next chapter is a study that addresses some of the issues encountered in this chapter and fills in the identified gaps that affect the validity of the included studies.

Chapter 6: Tranexamic acid in knee surgery – a prospective, multicentred, randomised controlled trial

As mentioned in the previous chapter, the optimum regime for TXA administration remains uncertain. The purpose of this study was to assess whether tTXA has similar efficacy to sTXA in reducing blood loss in knee joint replacement surgery when compared with placebo.

Methods

The research reported here is in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.(234) Ethical approval was obtained from the New Zealand National Health and Disability Ethics Committee (HDEC) (13/CEN/101). The trial was registered at ClinicalTrials.gov (NCT02278263).

Study design

A double-blinded, placebo, multicentred RCT was performed investigating the efficacy of topical and systemic routes of a single intraoperative dose (1.5 g) of TXA with three prospective groups running in parallel. The sTXA, tTXA and placebo arms were weighted with a 2:2:1 allocation ratio, respectively.

Participants

From July 2014 to November 2015 patients were recruited from five hospitals in NZ after study approval at each centre. Patients older than 18 years undergoing primary unilateral TKA were eligible to participate in the study. Patients were excluded if they had a history or risk of thrombosis, had active thromboembolic disease, refused blood products, had known hypersensitivity to TXA or any of its ingredients, had complex hematologic disorders requiring manipulation, were pregnant or lactating women, had taken anticoagulant therapy

within 5 days of surgery (warfarin, Dabigatran, heparin, Rivaroxaban) or had severe renal failure (eGFR < 29).

Standard surgical protocol

Surgery was performed as per each surgeon's routine practice with standardisation of potential confounders (Table 13). All patients received a midline incision with a medial parapatellar approach using standard haemostasis techniques. Both conventional and computer-navigated knee arthroplasty was performed. The patellar was selectively resurfaced as per surgeon preference. All components were cemented. All patients received aspirin 150–300 mg/day for 6 weeks following surgery, as agreed upon by all surgeons. When an intramedullary jig was used, this was plugged with either bone or cement. All but one surgeon used cruciate-retaining implants; the single surgeon used posterior substituting TKAs. Trainee registrars were involved in some of the enrolled surgeries.

Table 13. Surgical protocol pertaining to primary outcome

Standardised aspects of surgery
Tourniquet inflation to 250–300 mmHg immediately prior to skin incision
No surgical drains
No adrenaline used as part of high-volume local anaesthetic
Tourniquet deflated while crepe bandage being applied
Aspirin 150–300 mg orally for 6 weeks
All but a single surgeon used cruciate-retaining implants. The single surgeon used a posterior stabilised implant.

Anaesthetic protocol

SA was performed, with or without IV sedation. All patients received high-volume LA (ropivacaine 0.2% diluted in 100–200 ml) to the periarticular tissue.

Postoperative management

Patients were managed according to the hospitals' respective routine postoperative protocols, or ERAS pathways. Although there were slight inter-centre differences with

respect to their protocols, each patient was managed according to their standardised, perioperative protocol.

Treatment protocol

Once the arthrotomy was closed, the study drug was injected intraarticularly, followed by standard closure in layers with absorbable sutures or clips to skin. At the same time the intraarticular study drug was injected, the anaesthetist administered the IV study medication. The interventions for each group are summarised in Table 14. Study drug preparation was performed on the day of surgery by the theatre nurses and attending anaesthetist. After allocation, the intraarticular syringe was prepared by the circulating and scrub nurses. This was done in the sterile pre-scrub area concealed from the surgeon.

Table 14. Summary of intervention groups

Group	Intervention
A	*Intraarticular*:* 20 ml of normal saline intraarticularly after implantation of prosthesis and closure of arthrotomy followed by standard closure *Intravenous:* administration of 20 ml of normal saline intravenously at the same time prior to release of tourniquet
B	*Intraarticular*:* 1.5 g TXA in 20 ml intraarticularly after implantation of prosthesis and closure of arthrotomy followed by standard closure *Intravenous:* administration of 20 ml of normal saline (in a 20 ml syringe) intravenously at the same time prior to release of tourniquet
C	*Intraarticular*:* 20 ml of normal saline intraarticularly after implantation of prosthesis and closure of arthrotomy followed by standard closure *Intravenous:* administration of 1.5 g TXA intravenously at the same time prior to release of tourniquet

Notes. TXA = tranexamic acid
*all intraarticular study drugs were administered using a single 20 ml syringe via a 20 gauge hypodermic needle

The dose of TXA decided upon was based on findings in Chapter 5. Pantelli et al. (2013) demonstrated reduced requirements for allogenic transfusion with doses of ≥ 2 g given topically.(231) Given the theoretical risk of VTE and in the setting of less aggressive chemoprophylaxis (i.e., aspirin), the author felt cautious giving these doses intravenously

and deemed them too high for this route; hence, a single dose of 1.5 g (both systemic and topical) was chosen.

Outcomes

Primary outcomes

The primary outcome measure was estimated blood loss (EBL) as calculated from the difference between preoperative Hb and final Hb prior to discharge or day 3 at the latest. The EBL was calculated according to the formula described by Good et al. (235) The loss of Hb (in grams) was then estimated according to the formula:

$$Hb_{loss} = BV \times (Hb_i - Hb_e) \times 0.001 + Hb_t$$

where Hb_{loss} (g) is the amount of Hb lost, Hb_i (g/L) the Hb concentration before surgery, Hb_e (g/L) is the Hb_e concentration on the third day after surgery (or if discharged prior to day 3, then day of discharge Hb was used), and Hb_t (g) is the total amount of allogeneic Hb transfused; and BV (ml) is the estimated blood volume based on Nadler's formula, which attempts to adjust for patient gender, weight and height.(236) A unit of banked blood was considered to contain a minimum of 40 g Hb (*Blood component datasheet, NZBS*). All units of blood were processed and stored in a nationally standardised manner. The blood loss (ml) was related to the patient's preoperative Hb value (g/L):

$$\text{Estimated Blood Loss} = 1000 \times Hb_{loss} / Hb_i$$

The criteria for transfusion of blood products was a haemoglobin < 80 g/L, or a haemoglobin < 100 g/L in a patient with IHD or with symptomatic anaemia. IVFs in the perioperative period were also measured to account for any differences in haemodilution effect on Hb recordings between the three groups.

Secondary outcomes

Functional measurements using patient self-reported questionnaires (Short-Form 12 survey and Oxford Knee Scores) were performed preoperatively and at 6 weeks after surgery. Transfusion rates, median LOS and 30-day readmissions and complications were also measured. Important complications captured included symptomatic DVT, PE and infection. ROM, both passive and active, was measured as a surrogate for postoperative swelling. These measurements were performed by the physiotherapy teams on days 1–3 and recorded once each day. Measurements were taken with patients in a seated position using a goniometer.

Sample size

PROC POWER procedure (c) (2002–2010 by SAS Institute Inc., Cary, NC, USA.) was used to estimate the sample size required where analysis of variance was used as the analysis method. The sample size estimation used the means (standard deviations) of blood loss from the publication of Seo et al., who reported the mean blood loss for systemic, topical and placebo groups as 528 ml, 426 ml and 833 ml, respectively.(65) Assuming a common standard deviation of 412 ml, to detect a difference of 300 ml (approx. 1 unit of suspended red blood cells) of blood loss between the two treatment arms (sTXA and tTXA) and the placebo group, a sample size of 125 participants is required to be adequately powered. A statistical analysis would be performed using the contrast method in analysis of variance, given a statistical power of 0.85, and type I error of 0.05.

The sample size was increased by 15% to allow for expected dropouts. Therefore, a minimum of 147 patients was required for the study. An intention-to-treat analysis was used to compare the study groups.

Randomisation

Sequence generation

Sequence generation was performed by an independent biostatistician. The sequence was then assigned to pre-templated group instructions for placebo, intraarticular and systemic groups with a ratio of 1:2:2, respectively. These were then block randomised into three groups and distributed to the five different centres.

Allocation concealment

Pre-packaged A4 envelopes with consent forms, questionnaires and a postoperative record template were kept in a box in the preoperative areas. In the same A4 envelope, another smaller (letter-sized) envelope could be found with the patient's group allocation and corresponding instructions. Upon recruitment and prior to the patient entering the operative theatre, the smaller envelope containing the group allocation would then be revealed to the theatre nursing staff aware of the study protocol.

After assignment to interventions, patients, surgeons and outcome assessors remained blinded to group allocations. Group allocation envelopes were stored in a secure place on the ward with an identification sticker attached until the completion of the study.

Statistical analysis

Primary outcome: Estimate blood loss

An analysis of variance (ANOVA) was used to assess associations between covariates (including centre) and EBL. One-way ANOVA was then used to assess whether there were significant differences in EBL between the three groups.

Secondary outcomes

Repeated measure mixed effect models were used for assessing the repeated measures of functional measurements (SF-12, Oxford Knee Scores and ROM) between groups, adjusted for baseline level, and covariates specified.

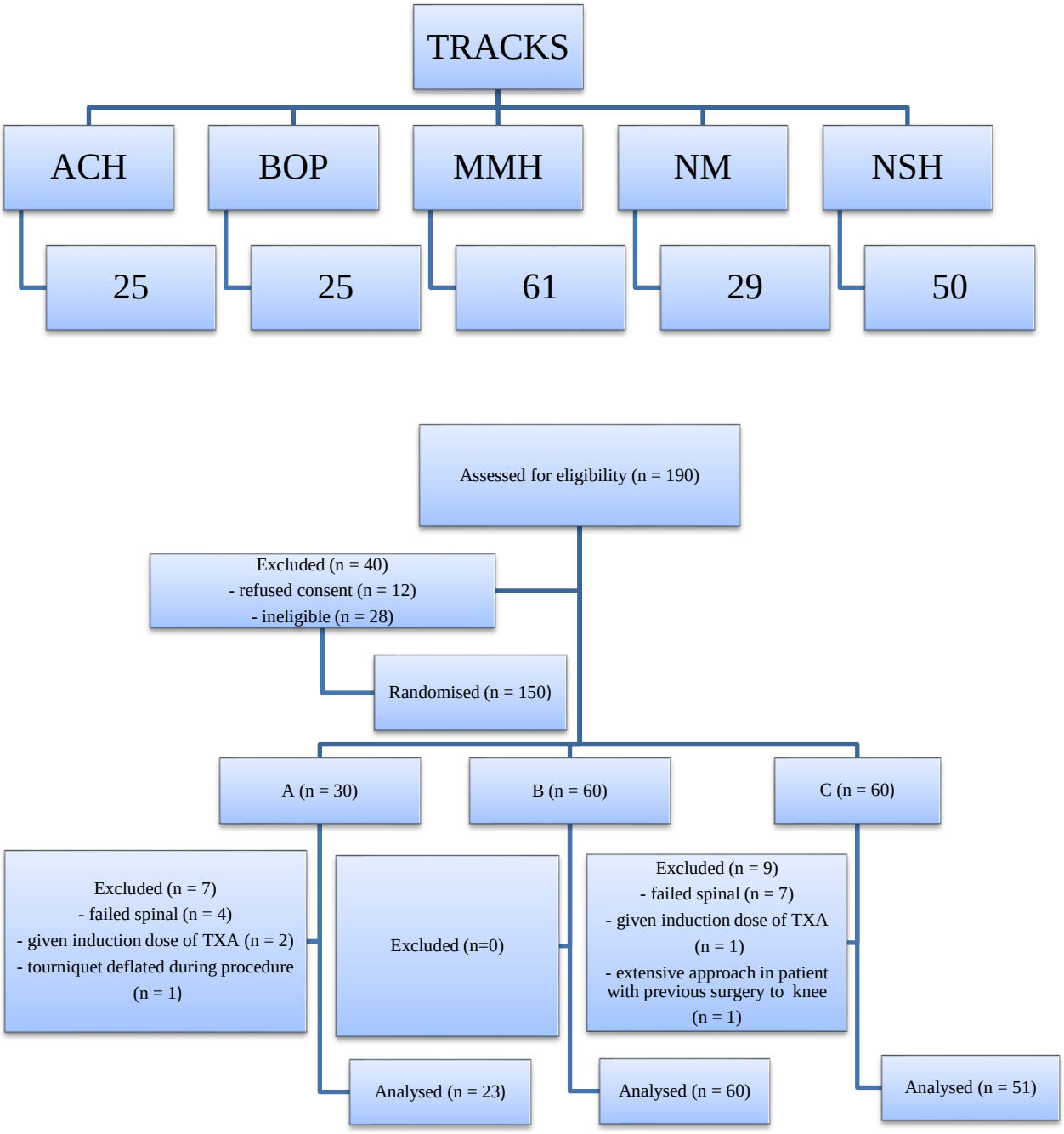
Secondary outcomes of binary variables, including 30-day complications and readmissions (yes/no), transfusion (yes/no) and mobilise day of surgery (yes/no), were analysed using logistic regression. Simple and multiple logistic regressions were applied to these two binary variables for the assessment of the interventions.

Results

For each group the numbers of participants who were randomised, received their intended treatment and were analysed are shown in the participant flow diagram (Figure 13).

Recruitment

Patient recruitment began in July 2014 and was completed in November 2015 after the final patient (n = 150) was recruited. Table 15 shows baseline demographics and clinical characteristics for each group. The placebo group (A) demonstrated a mildly skewed gender distribution favouring females.



Notes. ACH = Auckland City Hospital; BOP = Bay of Plenty DHB; MMH = Middlemore Hospital; NM = Nelson Marlborough District Health Board; NSH = North Shore Hospital

Figure 13. CONSORT flow diagram

Table 15. Baseline demographics and clinical characteristics for each group

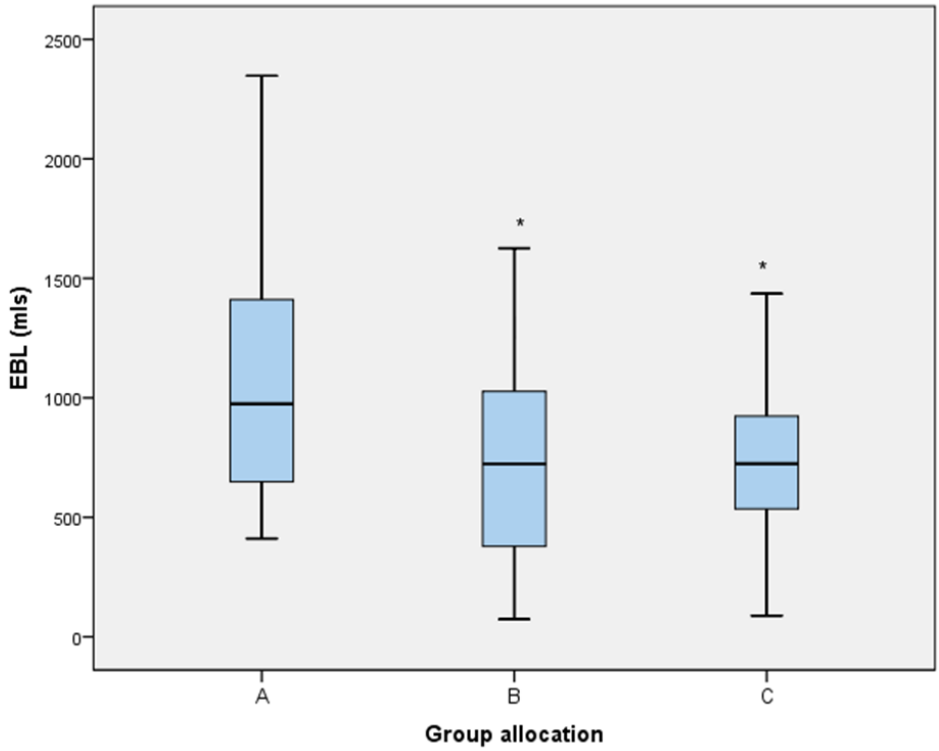
	A (n = 23)	**B (n = 60)**	**C (n = 51)**
Age (years)	70 (7.6)	70 (8.5)	71 (8.6)
Gender (M:F)	4:19	28:32	27:24
BMI (kg/h^2)	32.3 (6.6)	31.2 (5.5)	31.2 (5.5)
Preop Hb (g/L)	135 (12)	139 (12)	138 (11)
Number of days Hb taken prior to surgery	28 (34)	39 (40)	28 (34)
ASA (1:2:3)	4:15:4	4:48:8	10:28:13
Comorbidities			
T2DM (%)	17	23	10
HTN (%)	52	60	57
CHOL (%)	17	28	29
COPD (%)	0	10	14
IHD (%)	0	7	8
By centre			
ACH	4	7	7
BOP	5	9	6
MMH	8	19	18
NM	1	11	6
NSH	5	15	14

Notes. Numbers shown in parentheses represent +/- 1 standard deviations
BMI = body mass index; Hb = haemoglobin; ASA = American Society of Anaesthesiologists physical status score; T2DM = type 2 diabetes mellitus; HTN = hypertension; CHOL = cholesterol; COPD = chronic obstructive pulmonary disease; IHD = ischaemic heart disease; ACH = Auckland City Hospital; BOP = Bay of Plenty District Health Board; MMH = Middlemore Hospital; NM = Nelson Marlborough District Health Board; NSH = North Shore Hospital

EBL was significantly lower in those patients receiving TXA either systemically or topically compared with the placebo group ($p = 0.001$ and $p = 0.0003$, respectively) and this is illustrated in tween the two treatment groups.

The tTXA and sTXA groups had EBLs of 723 ml (95% confidence interval [CI]: 620–826) and 749 ml (95% CI: 637–860), respectively. The placebo group had mean EBLs of 1090 ml

(95% CI: 923–1257). No statistical differences were demonstrated between the two treatment groups.



Note. *p < 0.05 (compared with group A)

Figure 14. Boxchart: Unadjusted estimated blood loss (EBL) in each group (A, B and C)

Two patients developed symptomatic PE in the tTXA group and one in the sTXA group. All three were treated with warfarin for 6–9 months postoperatively. None of the patients in the placebo group developed symptomatic DVT or PE.

The placebo group received more allogenic blood transfusions than the other two treatment groups but this was not statistically significant (p = 0.060) (Table 16). Two patients in the placebo group received on average 2.5 units, one patient in the tTXA group received a blood transfusion and none were received in the sTXA group. Of note, the one tTXA patient who received blood failed to meet the transfusion criteria stipulated in the study. The patient was transfused based solely on the clinical acumen of the attending anaesthetist. Perioperative

IVFs were similar across the three groups (p = 0.380). No differences in postoperative ROM were observed between groups at any of the time points measured (Table 17). Surgical times for groups A, B and C were 86, 82 and 82 minutes, respectively. Superficial wound infection occurred in one, two and four patients in groups A, B and C, respectively. All were treated with a combination of IV and oral antibiotics and the infections resolved over time. One patient developed a large haemarthrosis that required close observation and did not require further surgical intervention.

Table 16. Secondary outcomes

Outcomes	**A**	**B**	**C**	**p-value**
Mobilised day of surgery (Y:N)	7:14	32:27	26:24	0.211
Perioperative fluids ml (CI 95%)	1765 (1320–2209)	1613 (1455–1770)	1807 (1581–2033)	0.380
Transfused (Y:N)	2:21	1:59	0:51	0.060
Average no. units	2.5	1	-	-
Length of stay (IQR)	4 (3–5)	4 (3–4)	4 (3–5)	0.431
Complications (30 days)				0.759
DVT	0	0	0	
PE	0	2	1	
Superficial wound infection	1	2	4	
Haemarthrosis	0	0	1	

Sensitivity analysis

Three patients in the placebo group were noted to have > 2000 ml of blood loss. As part of a sensitivity analysis, these patients were excluded to determine the effect this had on overall EBL. A significant difference in blood loss remained between the tTXA and placebo groups

(723 ml v. 917 ml; p = 0.0406) but statistical difference was lost between the systemic and placebo groups (749 ml v. 917 ml; p = 0.0812).

Table 17. Range of movement for days 1, 2 and 3

Range of movement	**A**		**B**		**C**	
	Ext	Flex	Ext	Flex	Ext	Flex
Day 1						
Active	12 (13)	57 (23)	8 (8)	65 (18)	10 (13)	58 (16)
Passive	3 (5)	65 (28)	5 (5)	74 (15)	7 (11)	68 (15)
Day 2						
Active	11 (16)	71 (15)	7 (8)	75 (14)	7 (9)	72 (16)
Passive	2 (3)	76 (15)	7 (11)	81 (13)	5 (6)	80 (13)
Day 3						
Active	9 (17)	75 (11)	5 (7)	82 (12)	5 (7)	78 (16)
Passive	1 (2)	82 (13)	2 (4)	87 (11)	4 (7)	87 (13)

Note. Numbers in parentheses represent +/- 1 standard deviations

Discussion

TXA has been shown to reduce perioperative blood loss and the need for allogenic blood transfusion in the setting of THA and TKA.(60-64) Although we have replicated these findings, to our knowledge, this is the first multicentred RCT investigating TXA in elective knee arthroplasty.

Interest in topical application of TXA is increasing and recent studies have investigated its efficacy in knee and hip arthroplasty surgery.(223-225) Most of the studies described in these reviews were superiority studies only. In the current study and in light of the evidence for sTXA, the topical application of TXA was compared with its more established IV route and placebo. This is the first study to compare topical and sTXA using a control group across multiple centres.

The primary outcome measure was EBL.(235) This indirect method of measuring blood loss was necessary as we did not use surgical drains and this precluded direct measurement. Authors have demonstrated hidden losses in TKA (an additional 50% blood volume as measured in surgical drains) even with the use of surgical drains and therefore their use significantly underestimates total losses.(237) Similarly, surgical drains have also been shown to increase blood loss.(238)

On average, we demonstrated approximately 300 ml less blood loss in patients receiving TXA irrespective of administrative route compared with those patients who did not receive TXA. This roughly equates to a single unit of allogenic blood (usually > 300 ml). As part of our sensitivity analysis, three patients in the placebo group who had greater than 2000 ml of EBL were excluded. This sub-analysis again demonstrated significant differences in blood loss between the tTXA and placebo groups, but not the sTXA and placebo groups. Given this finding, topical application is an excellent alternative route for delivering TXA and may even be superior for all patients undergoing knee replacement, including those at high risk of cardiac and thromboembolic events. In a single-centred study investigating tTXA, the authors reported similar findings and conclusions. Seo et al. investigated IV and intraarticular TXA using a similar protocol with the same dose (1.5 g) used in our current study and showed similar reductions in blood loss when compared with placebo (305 ml and 407 ml, respectively).(65)

Wong et al. investigated the use of 1.5 g and 3.0 g of tTXA in TKA, and demonstrated significant reductions in blood loss when compared with placebo.(225) Total perioperative blood loss (based on postoperative Hb drop) was higher than that seen with the current study. Interestingly, a dose response relationship was not identified between the two treatment groups (1.5 g: 1295 ml [1167–1422] v. 3.0 g: 1208 ml [1078–1339]). Despite the lack of

EBL difference between the two doses, no patient in the higher dose group received allogenic blood transfusion, whereas 13% (4 of 31) of patients who received the lower dose required transfusion. This outcome was not replicated in our study.

The current study's VTE chemoprophylactic agent of choice was aspirin 100–150 mg per day for 6 weeks, which in conjunction with mechanical devices and early mobilisation is an appropriate form of VTE prophylaxis as recommended by the ACCP and AAOS expert groups. Although the current study was not powered to detect differences in rates of DVT and PE, our findings may be useful in a meta-analysis investigating TXA's safety profile in the setting of aspirin alone. To our knowledge, no other study has investigated TXA in the setting of TKA when aspirin alone is used as part of VTE chemoprophylaxis. In one retrospective study of 2046 patients undergoing elective arthroplasty, agents including aspirin alone, dalteparin and dose-adjusted warfarin were found to have similar rates of symptomatic VTE.(159)

There are several limitations to the current study. First, the efficacy of tTXA in particular relies largely on watertight closure of the arthrotomy wound and leaching of the study drug may have occurred. The observed blood loss in the current study, therefore, may be underestimated. The findings of three symptomatic PEs in the two treatment groups and none in the placebo group are interesting. This finding was not statistically significant; however, the study was underpowered to draw any meaningful conclusions with regard to safety. The method of EBL is indirect and to be calculated requires a preoperative Hb and serial postoperative Hb levels. Preoperative Hb levels were on average taken 32 days prior to surgery and not on the day of surgery, and may be inaccurate.

Conclusion

This study has shown that tTXA (1.5 g) effectively reduces blood loss without an increase in complications, and may negate the concerns about the use of IV TXA. On average, TXA reduces blood loss by approximately 300 ml, which equates to a single unit of blood. Its safety profile in the setting of aspirin as the chemoprophylactic agent of choice remains unclear and should be further investigated with larger prospective trials.

Chapter 7: Discussion

Summary of results

Patients presenting for elective THA and TKA are generally older and harbour more chronic conditions, placing them at increased risk for postoperative complications, prolonged convalescence and mortality.(35, 36) As a result, this presents health providers and those responsible for policy making with a difficult predicament. *How do we get these patients through their surgeries safely so they may ultimately regain function and independence?* This thesis has attempted to address the surgical morbidity associated with these surgeries by standardising and optimising perioperative care, and at the same time, restructure current resources in a manner that does not add expense to the ever-scarce health budget dollars.

Unlike ERAS in colorectal and bariatric surgeries in Australasia, ERAS in orthopaedics is less established and details surrounding which care interventions to be included in such a programme are not well-defined. Chapter 2 reviewed those interventions commonly used in ERAS programmes in the setting of elective THA and TKA. Perioperative care interventions used in elective lower limb arthroplasty had poor to good evidence to support their use. However, a common theme in these studies is the standardised manner in which these interventions were delivered. Advocates of ERAS support the idea of standardisation and are often quoted as saying that ERAS has its greatest impact through the combined influence of all the perioperative care interventions.(56, 193)

Chapter 3 was a survey-based study that captured a snapshot of perioperative care practices among NZ arthroplasty surgeons in 2013–14. Considerable variation among arthroplasty surgeons for some evidence-based care interventions existed and for others (i.e., use of aspirin, surgical approach and mobilisation day) surgeons demonstrated a consensus. Hence, this study highlighted there was scope for standardisation and implementation of an ERAS

programme. Chapter 4 evaluated the efficacy and safety of an orthopaedic-specific ERAS programme at a large public hospital in NZ. ERAS reduced LOS by 1 day, which is similar to other enhanced recovery studies in orthopaedics observed elsewhere in the world.(90, 202, 210) LOS was used as a surrogate for enhanced and hastened patient recovery and is often prone to criticism as it fails to capture the patients' experience of their surgery. Important and relevant clinical endpoints are those patient-reported outcomes that, to a larger extent, have guided healthcare service delivery and should continue to do so. Surgical recovery scores have been validated in colorectal, bariatric surgeries and in patients who have had surgical procedures under GA.(239, 240)

One principle employed by ERAS is adopting a multimodal, opioid-sparing analgesic regime that aims to avoid opioid-derived side effects, which are numerous and can often contribute to postoperative morbidity and prolong convalescence. An interesting finding that emerged from Chapter 4 is the higher opioid administration in the ERAS group for the day of surgery and first postoperative day (POD 0: 14 mg v. 7 mg, $p = 0.001$; POD 1: 33 mg v. 20 mg, $p = 0.001$). Without having captured pain scores, it is difficult to correlate this with patients' experiences. It may be presumptive, but because of earlier and more aggressive rehabilitation, nursing staff may anticipate higher pain levels experienced by patients and therefore offer stronger pain relief to see them through their early rehabilitation.

Readmission rates and complications were lower in the ERAS group than in their historical control group. There was also a reduction in direct costs associated with those patients managed according to ERAS protocol. Audit of the respective components of the pathway showed that despite the overwhelming evidence for TXA in elective THA and TKA, its use continued to be low among those patients managed as per the ERAS programme. This is likely a reflection of lack of knowledge and a prevailing theoretical risk of sinister clot

development among arthroplasty surgeons at MSC – a sentiment shared by UK arthroplasty units.(189)

Local infiltration of TXA in a handful of studies showed promise as a means to reduce perioperative blood loss and as an alternative to administering the drug systemically.(64, 65, 191, 192, 218) Chapter 5 assessed those studies, comparing local TXA with the more established IV route. Few studies were identified though the two routes demonstrated differences in rates of blood transfusion, often favouring the topical groups; and differences in blood volume losses, with two favouring topical and another favouring its systemic administration. Considerable heterogeneity exists among these studies, making its interpretation less definitive.

Chapter 6 assessed the efficacy of TXA via both IV and topical routes when compared with a placebo. This study found that giving the study drug, irrespective of route, reduced blood loss significantly when compared with placebo. Excluding those patients who had greater than 2000 ml of blood loss, those patients in the tTXA group continued to have significantly less blood loss than the placebo group (723 ml v. 917 ml; $p = 0.0406$), but statistical significance was lost between the systemic and placebo groups (749 ml v. 917 ml; $p = 0.0812$). The absolute difference between treatment and placebo groups was a minimum of 300 ml, which in all involved hospitals equates to approximately a unit of PRBCs. Seo et al. found similar reductions with the same protocol.(65) Hence, this protocol is both simple to use (single intraoperative dose) and clinically useful.

Future directions

Although this thesis has answered clinically important questions, it has also prompted others that remain unanswered.

Delivery of an optimised, standardised care pathway that utilises evidence-based care interventions such as ERAS has been shown to reduce LOS and reduce direct costs. Process standardisation has been shown to strongly correlate with improved quality and efficiency of care, independent of both surgeon and hospital volume.(71) What is less clear is the extent to which each of the care interventions contributes to the overall outcome, and whether these interventions should be weighted differently. In the current fiscal environment, this is an important question that health providers and funders may ask in order to allocate resource judiciously.(241) Similarly, if a reduction in LOS means there is more capacity to perform more surgeries then resource allocation needs to be discussed at a managerial level and higher. The implications from this reduction in day stay means funding agencies should entertain the notion of increasing surgical staff and associated resource, keeping in mind the longer term benefits.

Nevertheless, economic evaluations of care interventions, including ERAS as a whole, are seldom reported and when they do occur are primarily from a payer's perspective. As mentioned, postoperative function and QoL scores (societal perspective) are an important aspect of the effectiveness of an intervention, and without capturing this crucial data, it is impossible to report on *actual* cost-effectiveness of the health intervention. Mutually exclusive interventions can be compared by using cost-effectiveness analysis and the resulting unit being the incremental cost-effectiveness ratio. This is a useful way of informing providers of the average cost to be sustained to achieve an additional success of one intervention over another.(242)

Furthermore, less is known about how sustainable these gains in reductions in LOS and cost are in the medium to long term. All prospective studies evaluating ERAS are prone to a Hawthorne-like effect, suggesting these benefits may not be maintained into the distant

future. A retrospective study at 5 years post-implementation of the standardised protocol is likely to answer this question. One such study in colonic surgery across 10 different hospitals evaluating ERAS 3–5 years after its implementation demonstrated a non-significant increase in LOS (5.25 v. 6.0 days; $p = 0.052$) and a drop in protocol adherence (75% to 67%; $p = 0.32$).(243) If observed in orthopaedics, this would highlight the importance of audit, which has been identified as a key component to ERAS programmes.

The parenteral preparation of TXA is inexpensive (NZD 5.50 per 500mg vial). However, there is some evidence to suggest that the oral preparation is equally effective at reducing blood loss in the arthroplasty setting and is a fraction of the cost (NZD 0.20 per 500mg tablet), thus potentiating cost savings even further.(244, 245)

ERAS protocols encourage an opioid-sparing analgesic regime to reduce the side effects of these medications which can often lead to increased morbidity and delay recovery. Chapter 4 demonstrated higher opioid equivalent consumption during the first 24-48 hours after surgery. Local anaesthesia can give reliable pain relief; however, their duration is variable owing to their pharmacokinetic properties. Ropivacaine given locally can give reliable sensory blockade for up to 15 hours and adding adrenaline does not prolong its duration.(246) Thus, a window of opportunity presents itself to potentially prolong the effects of the local analgesia beyond 15 hours and keep patients sufficiently comfortable. The merits of achieving sustained pain relief beyond this time are obvious, especially in the first 24-48 hours, a time when patients are at most risk for developing clots and chest complications (i.e. chest infections). Liposomal bupivacaine has been heralded as a novel way of prolonging the duration of local anaesthesia through encapsulating the medication to increase its residence time at the intended site of action.(247) Despite initial testing of the formulation showing great promise, these results are yet to be reliably replicated in

orthopaedic clinical studies.(248-250) In light of this, the author has developed a special interest in this area and has taken a different approach to addressing this problem by collaborating with experts responsible for developing and formulating delivery systems of medications. Using surgical drain fluid taken from THA and TKA patients, the author has characterised the physiochemical properties of this fluid over time as a surrogate for the surgical milieu around the recently inserted implants.(unpublished data) Using this information a delivery system for LA that provides sustained analgesia can be designed and formulated with the potential for utilising the surgical environment to its advantage.

Although ERAS has been observed to be beneficial for all key stakeholders (i.e., patients, the surgical team, ward staff and policy makers), the adoption of its principles may be met with some resistance. In Chapter 3, the final question in the survey asked respondents about their perceived barriers to implementing ERAS in their departments as a means to determine surgeon readiness for adopting ERAS principles. Thirty-two per cent of surgeons reported that the most common barrier to implementing such a pathway was lack of "buy-in" from their own colleagues, whereas, for a quarter of responders an optimised, standardised perioperative care approach was standard practice. Two recent qualitative studies using semi-structured interviews reported lack of resource, poor communication and collaboration, resistance to change and patient factors as being the most commonly cited barriers for ERAS implementation and function. (251, 252) Addressing these issues upfront can hasten the implementation process and lead to a more seamless transition. Further exploration of surgeons' perceptions of these barriers to ERAS implementation is warranted given the profuse evidence heralding its merits.

The demand for acute orthopaedic surgery in NZ is much greater than those experienced by other surgical specialties. Acute surgeries take priority and can often overwhelm the local

resources that see patients waiting for their acute operations for many days. This forces service managers to cancel elective lists to relieve the pressure induced by the acute work load which has historically seen orthopaedics struggle to meet the Ministry's elective waiting times, including those waiting for THA and TKA. The 2012/13 NZ health budget allocation identified key areas to be addressed and at the top of the list for *'actions and priorities'* was increasing the number of elective operations by an average of 4,000 per year, to ensure patients wait no longer than 4 months for their surgery and for patient referrals to specialists are seen within 4 months in the public sector.(54) An expert advisory group assembled to support the Ministry's stance on tackling these priorities. These included orthopaedic surgeons, anaesthetists, orthopaedic nursing staff, physiotherapists and occupational therapists. Some of which were from Middlemore Hospital who had established experience in ERAS (Chapter 4). The expert advisory group recommended ERAS as a means of addressing waiting times and increasing elective surgical throughput, simultaneously enhancing the quality of patient care and improving clinical outcomes. Chapter 3 highlighted there was scope to implement ERAS on a national scale as variation in perioperative care practices among NZ arthroplasty surgeons existed. Therefore, using the experience gained in Chapter 4, the methods and outcomes have performed as a template and a source of learning for other orthopaedic departments around the country as a guide for ERAS implementation and evaluation.

Since the writing of this thesis the Ministry of Health developed the National Orthopaedic ERAS Collaborative that was rolled out and implemented across 17 other District Health Boards shortly after implementation of the ERAS protocol described and evaluated in Chapter 4. Using similar methodologies, the collaborative was able to achieve great gains in reduction in average LOS for both THAs and TKAs (THA: 5.1 v. 4.3 days; TKA: 5.4 v. 4.5 days), though the same could not be said for neck of femur fracture patients.(253) The

authors report that neck of femur fracture patients are highly variable and generally more comorbid than their elective counterparts making clinical outcomes less predictable. NZD1.3 million was allocated to the collaborative and DHBs were given a fixed sum to implement ERAS principles where they thought was important or considered missing as part of their pathway. Cost savings calculations based on LOS and PRBC reductions for the period 2013-2014 showed monetary savings of NZD1.80 million and NZD515,607, respectively.

Unquestionably, TXA has been proven to be effective in reducing perioperative blood loss in elective TKA However, the question remains over its safety profile when less aggressive chemoprophylactic agents are used. In 2014, Poeran et al. highlighted TXA's safety in a large population based study, reporting similar rates of DVT and PE to placebo. Although the use of chemoprophylaxis is reported in this study, it fails to stratify these outcomes based on type of chemoprophylactic agent used.(254) Conversely, the Pulmonary Embolism Prevention (PEP) trial of the mid-1990s showed that aspirin (160 mg) significantly reduced DVT and PE in hip fracture patients; however, the use of TXA to reduce perioperative blood loss is not mentioned, which can be significant in this cohort of surgical patients.(255) Larger studies investigating the safety of TXA in the setting of aspirin are warranted.

The optimum regimen for TXA remains unanswered and the benefits of dosage and route of delivery needs to be optimised, without placing patients at increased risk of VTE. Maniar et al. investigated 5 different regimes of TXA (10 mg/kg) administration to determine which was most effective. They found those patients enrolled into regimes which included a preoperative dose (before skin incision) demonstrated significantly smaller drain and total blood losses than the placebo group whereas those patients who did not receive a preoperative dose had less blood loss compared to the control group but failed to reach statistical significance.(226) Several studies have suggested that the effective therapeutic

level of TXA ranges from 5-15 mg/L.(256, 257) Another important factor to take into account is the fibrinolytic response to trauma. Its response is biphasic with a *hyperfibrinolytic* state occurring in the first few hours followed by a hypofibrinolytic state which is reported to peak at approximately 24 hours. With this in mind it is important to have a regime that achieves effective therapeutic levels long enough to target the initial hyperfibrinolytic state but then to be subtherapeutic later. However, it is not clear when this fibrinolytic transition occurs. Benoni showed that 71% of total blood losses in patients undergoing knee arthroplasty occurred within the first 8 hours.(258) Hence, their rationale for a two injection technique; a bolus of 10 mg/k at induction followed by a short infusion of the same dose 3 hours later. Chapter 6 investigated two routes of administration of TXA as a single intraoperative dose demonstrating similar blood conserving properties. Adding a preoperative dose to this regime may have potentially reduced blood losses further, however at the cost of potentially increasing the theoretical risk of VTE with cumulative doses.

An alternative method, not yet investigated in this setting, is the intraosseous (IO) route. Recently, IO administration of prophylactic antibiotics has been shown to achieve higher local tissue levels of cephazolin at all time points when compared to the more routine IV route prior to TKA.(259) A single animal study, using a swine model, showed similar pharmacokinetic profiles with IO and IV administration of TXA with similar concentrations observed from the end of the infusion onwards. Taking into account the findings of Maniar's study and the tissue levels that one can achieve with IO administration of antibiotics, one may postulate that IO administration of TXA given at the beginning of TKA surgery may demonstrate even greater blood conserving properties than when given topically or systemically. Furthermore, potentially negating the need for repeated doses in the intraoperative and postoperative periods which can be tedious and time consuming.

Conclusion

From this thesis the following conclusions can be drawn.

An orthopaedic-specific ERAS programme for THA and TKA reduces LOS, reduces perioperative costs and is sustainable in the short to medium term. A reduction in LOS is not offset by an increase in readmission rates or their duration.

A single 1.5 g dose of TXA significantly reduces perioperative blood loss in elective TKA and is equally efficacious when given intravenously or topically. Therefore, surgeons can administer their TXA paying little attention to its route.

Appendices

Appendix A – Chapter 2 consent form

South Auckland Clinical School, PO Box 93311, Otahuhu Auckland, NZ

Principal Investigator: Mr Jacob Munro

Department of Surgery, University of Auckland

Room 12.096, 12th floor Support Building

Auckland City Hospital, Grafton

Ph: (09) 923 2861

Fax: (09) 367 7159

CONSENT FORM

ERAS in elective hip and knee arthroplasty – a nationwide survey

I have read and I understand the information sheet dated 01/08/13 for volunteers taking part in the study designed to evaluate hip and knee arthroplasty surgeon's current surgical practices. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I understand that taking part in this study is voluntary (surgeon choice) and that participants may withdraw from the study at any time and this will in no way affect their future affiliation with the organisation.

I understand that their participation in this study is confidential and if information they have provided is reported/published, this will be done in a way that does not identify them as its source.

I know who to contact if I have any questions about the study.

I wish to receive a copy of the results YES/NO

Date

Signature

Full names of Researchers:

Mr Jacob Munro

Dr Marinus Stowers

Contact Phone Number for researchers:

Dr Marinus Stowers (09) 276 0044 ext. 2219 or msto062@aucklanduni.ac.nz

Project explained by

Project role

Signature

Date

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE for (3) years, Reference Number 010277

Appendix B – Chapter 2 participant information sheet

South Auckland Clinical School, PO Box 93311, Otahuhu Auckland, NZ

Participant Information Sheet

Principal Investigator: Mr Jacob Munro

Department of Surgery, University of Auckland

Room 12.096, 12th floor Support Building

Auckland City Hospital, Grafton

Ph: (09) 923 2861

Fax: (09) 367 7159

Introduction

Participants are invited to take part in an anonymous online survey. The survey is 10 questions long and will take no longer than 2-3 minutes. Their participation is entirely voluntary (their choice). They do not have to take part in this study and if they choose not to take part this will not affect their current affiliation to New Zealand Orthopaedic Association (NZOA).

About the study

Enhanced Recovery After Surgery (ERAS) pathways have gained momentum over the last decade and are increasingly popular among health boards as they are perceived as an efficient use of resources. Implementation of ERAS programs are challenging and this is in part due to regional, institutional and clinician preferences.

Surveys in Europe and North America have demonstrated these challenges documenting the relatively slow change of surgical practice towards evidence based care. Reasons for this are varied but include, lack of awareness of evidence-based ERAS data, lack of agreement with the data (i.e. difficult to accept) or lack of belief that ERAS can be done in their own institution.

This project aims to summarise current surgical practices among arthroplasty surgeons in NZ as no such study has been done previously. Summarising the extent of variation in surgical practices in NZ will then allow us to compare this with current evidence based care surrounding specific perioperative care interventions. Identifying major discrepancies between current practice and the current literature will then allow the researchers to investigate reasons for why these may fail to align.

Risks

We do not anticipate any additional risks to participants.

Participation

Participation is entirely voluntary (their choice). Participants do not have to take part in this study. If you agree to participate please click the link below as pasted in your email and you will be directed to the survey. Your consent is implied by completion and submission of the survey.

General

Further information regarding this study can be obtained from Mr Jacob Munro or Dr Marinus Stowers.

Mr Jacob Munro	Dr Marinus Stowers
Department of Surgery	Department of Surgery
University of Auckland	University of Auckland
Ph: (09) 923 2861	276 0044 ext. 2219
Fax: (09) 367 7159	msto062@aucklanduni.ac.nz

There will be no costs or payments to you in order to participate in this study.

Confidentiality

No material which could personally identify the participant will be used in any reports on this study. Names or any other personally identifying information will not be used in reports or publications resulting from this study. Participants will not be able to withdraw their data because we will not know who submitted the responses. Data will be electronically stored and deleted after 1 year.

Results

The final results of the research will not be known until November 2013. At the conclusion of the study, results will be published as a journal article and be made available by mail to those who request them. However, if they are not sure about whether you have requested the study results, you can Dr Marinus Stowers, 276 0044 ext. 2219 or msto062@aucklanduni.ac.nz

For any concerns regarding ethical issues you may contact the Chair, The University of Auckland Human Participants Ethics Committee, The University of Auckland, Research Office, Private Bag 92019, Auckland 1142. Telephone 09 373-7599 ext. 87830/83761. Email: humanethics@auckland.ac.nz

Statement of Ethical Approval: APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE for (3) years, Reference Number 010277

Appendix C – Online Enhanced Recovery After Surgery survey

Enhanced Recovery After Surgery (ERAS) in Hip and Knee Arthroplasty

ERAS in Hip and Knee Arthroplasty

Enhanced Recovery After Surgery (ERAS) or 'fast-track' surgery is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. It works by attenuating the proinflammatory response associated with surgery and its implementation also standardises perioperative care and reduces variation in patient management.

ERAS programs have already been successfully established in adult colorectal and bariatric surgery although implementation has been challenging, in part due to regional, institutional and clinician preferences. This survey aims to summarise arthroplasty surgical practices in New Zealand and how this compares to currently available scientific evidence supporting specific perioperative care interventions.

This survey is anonymous and we appreciate your time for completing it.

*

1. What is your place of practice?

☐ Public Hospital

☐ Private Practice

☐ Both Public and Private

*

2. What is your current position?

○ Consultant <5 years

○ Consultant 5-10 years

○ Consultant >10 years

ERAS in Hip and Knee Arthroplasty

You will now be asked a series of questions surrounding your surgical practice in hip and knee arthroplasty.

For adults having primary, elective hip or knee arthroplasty...

3. What surgical approach(es) do you regularly use for ...

	Posterior	Lateral	Anterior	Anterolateral	Medial parapatellar	Minimally Invasive Surgery (MIS)
Hip	☐	☐	☐	☐	☐	☐
Knee	☐	☐		☐	☐	☐

If MIS (please specify)

4. Choose the option(s) that apply to your surgical practice when it comes to the use of tranexamic acid?

☐ I routinely use in hip arthroplasty

☐ I routinely use in knee arthroplasty

☐ I do not routinely use

☐ I leave to the anaesthetist to decide

ERAS in Hip and Knee Arthroplasty

For adults having primary, elective hip or knee arthroplasty...

5. Choose the option(s) that apply to your surgical practice when it comes to the use of surgical drains

- ☐ I use routinely in hip arthroplasty
- ☐ I use routinely in knee arthroplasty
- ☐ I do not use
- ☐ I do not use routinely but may use in some circumstances

6. When do you encourage patients to first mobilise?

- ☐ Day of Surgery
- ☐ Day 1
- ☐ Day 2
- ☐ Patient dependent (i.e. blocks worn off etc.)

ERAS in Hip and Knee Arthroplasty

For adults undergoing primary, elective hip or knee arthroplasty...

7. What is your preferred combination of anaesthesia for hip and knee arthroplasty? (choose as applicable)

	General anaesthesia	Spinal anaesthesia	Epidural	Regional anaesthesia	Local anaesthesia (single dose)	Local anaesthesia (infusion/bolus)
Hip	☐	☐	☐	☐	☐	☐
Knee	☐	☐	☐	☐	☐	☐

Other (please specify)

ERAS in Hip and Knee Arthroplasty

For adults having primary, elective hip or knee arthroplasty...

8. When do you use an indwelling catheter?

- ☐ For Hip
- ☐ For Knee
- ☐ For Hip and Knee
- ☐ Depends on anaesthesia used
- ☐ Attempt to avoid IDC whenever possible

9. In a patient with no additional risk factors for VTE, what is your preferred pharmacological thromboprophylaxis agent?

- ☐ Clexane
- ☐ Aspirin
- ☐ Warfarin
- ☐ Rivaroxaban
- ☐ Dabigatran
- ☐ No pharmacological thromboprophylaxis
- ☐ Other (please specify)

10. What barriers do you envisage in attempting to adopt a standardised perioperative care approach, such as an ERAS program, in to your practice?

- [ ] I already adopt such an approach
- [ ] Personal
- [ ] Institutional
- [ ] Financial
- [ ] Lack of 'buy in' from other specialties
- [ ] Lack of 'buy in' from colleagues
- [ ] I do not perceive any barriers
- [ ] Other (please specify)

Appendix D – Chapter 4 consent form

South Auckland Clinical School, PO Box 93311, Otahuhu Auckland, NZ

Principal Investigator: Mr Jacob Munro

Department of Surgery, University of Auckland

Room 12.096, 12th floor Support Building

Auckland City Hospital, Grafton

Ph: (09) 923 2861

Fax: (09) 367 7159

CONSENT FORM

ERAS in elective hip and knee arthroplasty study

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Spanish	Me gustaría que haya un intérprete	Sí	Pas
French	Je souhaite avoir un interprète	Oui	Pas
	Other languages to be added following consultation with relevant communities.		

I have read and I understand the information sheet dated 01/09/13 for volunteers taking part in the study designed to assess whether a care pathway improves outcomes following total knee/hip joint replacement. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care/continuing health care.

I have had this project explained to me by _____.

I understand that my participation in this study is confidential and if information I provide is reported/published, this will be done in a way that does not identify me as its source.

I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I know who to contact if I have any side effects to the study.

I know who to contact if I have any questions about the study.

I know that I may withdraw from the study at any time during the study period of 12 months; and I do not need to give a reason for my withdrawal.

I know that data collected will be stored securely for 10 years and then destroyed in a confidential manner.

I agree to an approved auditor appointed by either the ethics committee, or the regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

I wish to receive a copy of the results YES/NO

Alternatively "I would like the researcher to discuss the outcomes of the study with me". YES/NO

I _____(full name) hereby consent to take part in this study.

If you would like to be sent a copy of the results, please include your contact details here:

Date

Signature

Full names of Researchers:

Mr Jacob Munro

Mr Brendan Coleman

Dr Daniel Lemanu

Dr Marinus Stowers

Contact Phone Number for researchers:

Dr Marinus Stowers (09) 276 0044 ext. 2219 or msto062@aucklanduni.ac.nz

Project explained by

Project role

Signature

Date

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE for (3) years, Reference Number 9095

Appendix E – Chapter 4 participant information sheet

South Auckland Clinical School, PO Box 93311, Otahuhu Auckland, NZ

Participant Information Sheet

Principal Investigator: Mr Jacob Munro

Department of Surgery, University of Auckland

Room 12.096, 12th floor Support Building

Auckland City Hospital, Grafton

Ph: (09) 923 2861

Fax: (09) 367 7159

Introduction

You are invited to take part in a clinical research study. Your participation is entirely voluntary (your choice). You do not have to take part in this study and if you choose not to take part this will not affect any future care or treatment.

About the study

Successful outcome from surgery is dependent on many factors. Most doctors agree that successful surgery is a combination of excellent care before, during and after surgery. As knowledge about the human body increases, we have developed many strategies to enhance recovery after surgery.

One way to improve recovery after surgery is to provide the best possible care around the actual operation and to ensure that this is done consistently for every patient. This can be achieved using protocols and checklists that care-givers can follow. We and other doctors internationally have trialled this for other operations such as weight loss procedures and bowel operations with great success. We have now designed such a checklist to be used for patients having a hip or knee replacement, and the Orthopaedic Department here at Counties Manukau District Health Board have recently started using it.

We are inviting you to participate in our study. We wish to investigate whether this care pathway for total hip and knee replacements decreases complications, hastens the speed of recovery and determine its effect on function in the long term.

We are planning to invite 100 patients who are going to have either total hip or total knee replacement to take part in this study. If you agree, we would like to monitor your progress and ask you to fill in a questionnaire at 6 months after your operation.

Your participation in this study will not affect the standard of care you receive in any way, and is no different to those patients not participating in the study. Taking part or not taking part in the study will not change any healthcare you receive in future.

During your stay in hospital, we will record data from the patient notes regarding how long you stay in hospital and whether you experience any complications. Before your operation we will also ask you to complete a questionnaire with regards to your pain and function.

Risks

We do not anticipate any additional risks to you, except the ones already mentioned to you surrounding the time of your operation.

Participation

Your participation is entirely voluntary (your choice). You do not have to take part in this study. This will not affect your treatment in any way. If you do agree to take part you are free to withdraw from the study within 12 months from enrolling in the study, without having to give a reason and this will in no way affect your continuing health care.

General

Further information regarding this study can be obtained from Mr Jacob Munro or Dr Marinus Stowers.

Mr Jacob Munro

Department of Surgery

University of Auckland

Ph: (09) 923 2861

Fax: (09) 367 7159

Dr Marinus Stowers

Department of Surgery

University of Auckland

276 0044 ext. 2219

msto062@aucklanduni.ac.nz

An interpreter will be provided if you would like one. You may have a friend, family, or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require.

There will be no costs or payments to you in order to participate in this study.

Advocacy

If you have any queries or concerns regarding your rights as a participant in this research study, you can contact an independent Health and Disability Advocate. This is a free service provided under the Health & Disability Commissioner Act:

Telephone (NZ wide): 0800 555 050

Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)

Email: advocacy@hdc.org.nz

Confidentiality

No material which could personally identify you will be used in any reports on this study. Your hospital records are confidential. Your name or any other personally identifying information will not be used in reports or publications resulting from this study. The information about your medical history and medications required to interpret the research results will be identified using a code to ensure your confidentiality. Written and electronic data will be stored and safeguarded in locked cupboards and computerised password protected files. Data collected will be kept for 10 years and will be destroyed in a safe and confidential manner.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

Results

The final results of the research will not be known until January 2015. At the conclusion of the study, results will be published as a journal article and be made available by mail to those who have requested this on the consent form. However, if you are not sure about whether you have requested the study results, you can contact Dr Marinus Stowers, 276 0044 ext. 2219 or msto062@aucklanduni.ac.nz

For any concerns regarding ethical issues you may contact the Chair, The University of Auckland Human Participants Ethics Committee, The University of Auckland, Research Office, Private Bag 92019, Auckland 1142. Telephone 09 373-7599 ext. 87830/83761. Email: humanethics@auckland.ac.nz

Statement of Ethical Approval: APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE for (3) years, Reference Number 9095

Appendix F – Chapter 6 consent form

Consent Form

Tranexamic acid in Total Knee Joint Surgery

– a Randomized Controlled Trial

If you need an INTERPRETER, please tell us.
If you are unable to provide interpreters for the study, please clearly state this in the Participant Information Sheet

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature:	Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature:	Date:

Appendix G – Chapter 6 participant information sheet

Participant Information Sheet

Study title: **Tranexamic acid in Total Knee Joint Surgery – a Randomized Controlled Trial**

Locality: **Counties Manukau/Auckland City Hospital/North Shore Hospital/Tauranga Hospital/Nelson Hospital**

Lead investigators for locality: **Dr Marinus Stowers, Dr Jacob Munro**

Contact phone number: **(09) 276 0044 ext. 2219**

You are invited to take part in a study on **the use of tranexamic acid in knee joint replacement surgery**. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can withdraw from study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what will happen after the study ends. We will go through this information with you and answer any questions you may have. **You do not have to decide today whether or not you will participate in this study**. Before you decide you may want to talk about the study with other people, such as family, whanau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 7 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine whether **tranexamic acid**, which is a medication, **used to prevent excessive bleeding**, can help reduce blood loss in people who undergo knee joint replacement surgery. We would also like to determine whether we can give this medication intravenously (directly in to the veins) or whether it is just as effective to give it topically (directly in to the knee joint). This study will help us determine whether tranexamic acid may benefit patients undergoing knee replacement surgery. The potential benefits may include reduced bleeding during and after surgery, reduced use of blood transfusions, faster recovery time following surgery and shorter stays in hospital.

There are studies which show the benefits of tranexamic acid in reducing blood loss, not only in orthopaedic surgery, but also in other types of surgery. The use of tranexamic acid

is not routine amongst orthopaedic surgeons. It is unknown whether topical use is better than intravenous use or vice versa.

With this study, it is important that both tranexamic acid (real medication) and placebo (fake medication) are used, and that they are given to participants in a random fashion without the participant or the investigators knowing who received which one. In this way we are able to then determine whether tranexamic acid has a real and true effect over and above that which might happen by coincidence or chance. Note that if you choose to participate in the study you are four times as likely to receive the study drug (either through the veins or directly into the joint) than the placebo (fake medication).

There is no external funding source for this study as costs are already included in your usual patient care through the public health system. The investigators are all health practitioners, including orthopaedic surgeons and anaesthetists, who work for the Counties Manukau District Health Board and may be contacted through the Middlemore Hospital switchboard.

The study has ethics approval from the Health and Disability Ethics Committee.

WHO PAYS FOR THE STUDY?

We would like you to participate as you are undergoing a knee joint replacement and it is in this setting we would like to determine whether tranexamic acid can be helpful.

If you choose to participate we will ask you some standard medical questions to ensure you are suitable from a medical point of view to be involved in the trial. Health information will be collected directly from you at the time that you are assessed for knee joint replacement surgery and from your medical records.

You will undergo a normal preoperative assessment as part of our standard care for patients undergoing knee joint replacement. On the day of your surgery you will require a spinal anaesthetic with sedation; if you were unable to undergo a spinal anaesthetic then you would need to be excluded from the trial. You will then undergo your knee joint replacement surgery as per usual practice. Once the knee joint prosthesis has been inserted, study medication will be given both intravenously and topically into the knee joint prior to closure of the skin incision. You will have been randomised in to one of three groups: you will have received either 1) tranexamic acid intravenously and placebo topically (into the joint) 2) tranexamic acid topically (into the joint) and placebo intravenously or 3) placebo intravenously and topically.

Following your surgery, all aspects of normal postoperative care will be administered. Routine blood tests to measure your haemoglobin will be checked on days 1, 2 and 3 after your surgery. Following discharge from hospital, you will be followed up in clinic at the normal periods of 6 weeks and 6 months. No further participation will be required 1 year after your surgery. There will be absolutely no difference in your clinical care whether or not you choose to be involved in this study.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF TRANEXAMIC ACID USE?

The possible direct benefits of this study include reduced blood loss during and after surgery. This may lead to lower use of blood transfusion products, lower risk of wound complications, quicker rehabilitation time and therefore shorter stays in hospital leading to an overall better clinical outcome.

Side effects may include may include nausea, vomiting and diarrhoea however this is more likely if taken orally which is not the case in this study.

Although clinical studies show no significant increase in blood clotting problems with tranexamic acid, the risk of blood clotting complications cannot be ruled out. Participants with a history or risk of blood clots or active blood clotting disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis will not be suitable for the study. Should a blood clotting complication arise this will be managed as per standard clinical practice which may include the use of blood thinning medications.

Tranexamic acid will not be given to participants with acquired disturbances of colour vision and if disturbances of colour vision arise during the trial then the participant will be referred to an ophthalmologist for further care. Patients with previous subarachnoid haemorrhage should not be given tranexamic acid as experience indicates that cerebral oedema and cerebral infarction can result and these patients will not be included in the trial.

The investigators, in conjunction with the operating surgeon, will be wholly responsible for the clinical care of the patient during the course of the study, unless that care requires other specialist input. In that case, appropriate transfer to other specialist services will be facilitated.

WHO PAYS FOR THE STUDY?

The participant will not incur any costs during the trial. All hospital and clinic visits will be part of the normal routine care for knee joint replacement surgery and therefore no additional costs will be incurred whether you choose to be involved in the trial or not.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC and if your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Your participation in this trial is completely voluntary. You are free to decline to participate or to withdraw from the trial at any time and this will have no effect on your clinical care or your future clinical care or right to health care.

You have the right to access any medical information collected about you as part of the study.

You will be informed of any new information about adverse or beneficial effects related to the study that becomes available during the study that may have an impact on your health

All information about you will be collected and stored securely within hospital databases and any data analysis will only be performed by the investigators involved in the study. All other medical data relevant to your surgery will only be accessed by health practitioners involved in your clinical care.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

The results of the trial will be analysed and if there is a significant benefit then the study medication can be used in future knee replacement surgery if the surgeon deems it appropriate.

The study data will be stored securely on hospital grounds by the investigators for no longer than 5 years at which point will be destroyed according to standard hospital protocols.

No biological specimens will be stored for future use.

The study findings will be communicated back to participants in summary form and also published in the appropriate research journals in its entirety. We would expect that this may take approximately 2 years.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr Marinus Stowers, Dr Jacob Munro

Middlemore Hospital & Manukau Surgery Centre, Counties Manukau District Health Board

(09) 276 0044 ext. 2219

marinus.stowers@middlemore.co.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@hdc.org.nz

For Maori health support please contact :

Karla Rika-Heke
Email: karla.rika-heke@middlemore.co.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS

Email: hdecs@moh.govt.nz

Appendix H – Chapter 6 eligibility screen form

Tranexamic Acid in Total Knee Joint Replacement Surgery

Are you eligible to participate in this study? (tick 'yes' or 'no')

	Yes	No
In the past, have you had a blood clot develop as a result of surgery or spontaneously?	☐	☐
Are you currently being treated for active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis?	☐	☐
Have you suffered from a subarachnoid haemorrhage (type of stroke) in the past?	☐	☐
Do you have a known allergy to tranexamic acid or any of its ingredients?	☐	☐
Do you have a problem with receiving blood products/transfusion (if required)?	☐	☐
Do you have colour blindness?	☐	☐
Do you have a blood condition that might prevent you from participating in the study? (i.e. haemophilia etc.)	☐	☐
Do you have a condition where your blood tends to clot?	☐	☐
Female specific: Are you pregnant or breast feeding?	☐	☐
Do you have any kidney conditions?	☐	☐

If you have answered 'no' to **all** questions then you may be eligible to participate in the study.

If you have answered 'yes' to **only a few** questions you may still be eligible to participate.

Appendix I – Chapter 6 postoperative outcome record template

Tranexamic Acid in Knee Joint Surgery – a Randomised Controlled Trial

Postoperative record

Patient Sticker

Patient demographics

(Scrub nurse to fill in please)

Age	
Date of birth	
Ethnicity	
ASA score	
Date of surgery	
Diagnosis	
Height	
Weight	

Postoperative Day 0 (Day of Surgery)

Pain scores	3 hours post op		6 hours post op	
(using numeric rating scale: 0 = pain free; 10 = severe pain)	Active	At rest	Active	At rest
Did the patient stand or mobilise to chair prior to 2400hrs?	Y		N	
Fluids given during surgery in mls				
Complications ?				
Transfusion? **Number of units?**				
Comments				

Postoperative Day 1

ROM	Morning		Afternoon		
	Active	Passive	Active	Passive	
Did the patient stand or mobilise to chair prior to 2400hrs?	Y		N		Stood/ mobilised yesterday
Wound site (e.g. oozy, dry)					
Complications ?					
Transfusion? **Number of units?**					
Comments					

Postoperative Day 2

ROM	Morning		Afternoon		
	Active	Passive	Active	Passive	
Did the patient stand or mobilise to chair prior to 2400hrs?	Y		N		Stood /mobilised yesterday
Wound site (e.g. oozy, dry)					
Complications?					
Transfusion? **Number of units?**					
Comments					

Postoperative Day 3

ROM	Morning		Afternoon		
	Active	Passive	Active	Passive	
Did the patient stand or mobilise to chair prior to 2400hrs?	Y		N		Stood/ mobilised yesterday
Wound site (e.g. oozy, dry)					
Complications ?					
Transfusion? Number of units?					
Comments					
Total intravenous fluids (including intraoperative)					

Appendix J – Chapter 6 group allocation instructions

TRACKS Study: Group Allocation Protocol at time of surgery

Circulating nurse:

- Select a sealed allocation envelope from the supply and place a patient's identification sticker on the envelope.
- Without letting the surgeon see, open the envelope to see which study arm the patient is assigned to.
- Show the scrub nurse and anaesthetist the group the patient has been allocated to and assist the scrub nurse and anaesthetist to prepare the appropriate study medications based on the patient's group allocation. The instructions are inside the envelope.
- Please record the patient's envelope group allocation (i.e. A, B or C) in their clinical notes at the bottom of the operation note. For example write; **TXA Study – Group A/B/C.**
- Please refold the paper so that the group allocation is hidden and the Group allocation with the attached patient identification sticker is on the outside. Seal with tape and file in the patient's clinical notes.

Surgeon:

- Administer the study medication intra-articularly after partial closure of the arthrotomy.
- Inform the anaesthetist when you are administering the study medication, so they can also simultaneously administer their study medication.
- Please **dictate the patient's group allocation (A, B or C)** in the operation note. This is vital to determine each group allocations.
- For post-op instructions:
    - Hb is must be checked daily for three days.
    - Aspirin 100mg daily and foot pump as DVT prophylaxis

Appendix K – Chapter 6 Enhanced Recovery After Surgery protocols for each hospital

Comparison of each centre's ERAS protocols

	Auckland	Tauranga	Middlemore	Nelson	North Shore
Preoperative	Group education classes held within 4 weeks of surgery date	Education and exercise classes within 6 weeks of surgery	Attend group education session 1-2 weeks prior to surgery Discharge planning starts	Patient given Hip or Knee education booklet once placed on waiting list. ERAS pathway discussed Discharge planning commenced	Group education classes held within 4 weeks of surgery
Perioperative					
Day of surgery	Same day admission when possible Carbohydrate drink Premedication with Paracetamol 1-1.5g +/- Gabapentin 600mg	Same day admission Normal diet until 6 hours before anaesthesia Carbohydrate drink (Nutricia) to finish 2 hours before anaesthesia (excl diabetics) Mark surgical site and ensure consent signed and dated	Same day admission Premedication with paracetamol 1g, +/- gabapentin 200-400mg	No food with 6 hours of surgery, clear fluids until 2 hours prior to surgery	Same day admission Paracetamol 1g +/- Etoricoxib 60-120mg **OR** Naproxen 500mg *plus* omeprazole 20mg **OR** Gabapentin 300-600mg Normal diet until 6 hours before anaesthesia, clear oral fluids 2 hours before anaesthesia

In theatre	No routine indwelling catheters Confirm with surgeon the use of high volume local anaesthesia Spinal anaesthesia +/- sedation/GA Avoid intrathecal morphine Cephazolin 2g for most patients Dexamethasone 8mg during surgery Tranexamic acid 1.5-2g prior to tourniquet release IV fluids to replace losses Avoid epidural and conventional femoral nerve blocks	Indwelling catheter if appropriate Spinal anaesthesia recommended, with local anaesthetic periarticular infiltration Ropivacaine (2mg/kg) Avoid surgical drain use	Indwelling catheter if appropriate Spinal anaesthesia recommended, with local anaesthetic periarticular infiltration with or without adrenaline Use of TXA encouraged Avoid surgical drain use	Indwelling catheter if appropriate Spinal and regional anaesthesia encouraged High volume local analgesia recommended TXA encouraged Surgical drain avoidance	No routine urinary catheters Single shot spinal anaesthesia with Bupivacaine 0.5% heavy or plain, no routine intrathecal opioid. Sedation with propofol TCI 0.5-2mcg/ml OR midazolam 0.5-5mg if required. Antibiotics administered is weight dependent (1g, 2g, or 3g if <50kg, 50-120kg, or >120kg, respectively) Tranexamic acid 1-2g Dexamethasone 0.1mg/kg during operation Local anaesthetic infiltration with 200mls of Ropivacaine 2mg/ml

	Auckland	Tauranga	Middlemore	Nelson	North Shore
Postoperative					
Day of surgery	IV antibiotics x 3 doses	IV antibiotics x 3 doses Aspirin and foot pumps (if high risk then follow VTE algorithm) Oral intake encouraged 3-4 hours post op Early mobilisation – day of surgery if surgery done in the morning	IV antibiotics x 3 doses Aspirin and foot pumps (if high risk then follow VTE algorithm) Early mobilisation – day of surgery if surgery done in the morning	2 postop doses of IV antibiotics Aim for oral fluid intake of >500mls Stop IV fluids once patient has achieved this Offer sandwich 4 hours post op Bed exercises started Mobilise out of bed as soon as stable and block worn off	IV antibiotics x 3 doses 1-3g Enoxaparin 40mg **OR** Rivaroxaban 10mg **OR** Dabigatran 220mg **OR** Aspirin 75-150mg.

	Auckland	Tauranga	Middlemore	Nelson	North Shore
Analgesia and antiemetics	Regular paracetamol and NSAID. Consider Celebrex if GI upset with NSAIDs Gabapentin 300mg tds for 4 doses on ward Rescue medication: OxyNorm 5-10mg 2hrly OR PCA fentanyl No routine postoperative IV fluids.	Standardised analgesic and antiemetic regime	Standardised analgesic and antiemetic regime Aperients started	Pain control with oral regime, maximise opioid sparing analgesia	Regular paracetamol 1g 6-8 hrly, Etoricoxib 60-120mg daily, **OR** Naproxen 0.5-1g *plus* omeprazole 20mg daily **OR** m-Eslon 10-20mg 12hrly, **OR** if patients >80 years OxyCodone CR 5-20mg Rescue medication: sevredol 10-20mg, OxyNorm 5-10mg, tramadol SR 100mg Standardised antiemetic and aperient regime
Day 1	Removal IDC at 0600hrs Hb check – transfuse <80g/L, consider in those with <100g/L and symptomatic Debulk dressing Continue physiotherapy and rehabilitation	Removal IDC at 0600hrs Hb check – transfuse <80g/L, consider in those with <100g/L and symptomatic Debulk dressing Continue physiotherapy and rehabilitation	Removal IDC at 0600hrs Hb check – transfuse <80g/L, consider in those with <100g/L and symptomatic Debulk dressing Remove lines if not indicated Continue physiotherapy and rehabilitation	Remove IDC at 0800hours Hb check Standard physiotherapy rehabilitation regime commence	Hb check – transfuse <80g/L, consider in those with <100g/L and symptomatic
Day 2	Continue Physio and transition to normal clothes	Xray Regular analgesia and antiemetics Continue physiotherapy	Recheck Hb (same transfusion triggers as day 1) Continue physiotherapy Change into usual clothes	Normal diet and fluid target of 1500-2000mls, encouraging high fibre diet	Normal diet and fluid target of 1500-2000mls, encouraging high fibre diet

	Auckland	Tauranga	Middlemore	Nelson	North Shore
Criteria for discharge	Independent walking with aid Independent on and off bed Independent on stairs Adequate home support/s	Get in and out of bed independently Walk unsupervised with walking aid Manage stairs safely if applicable Perform exercise programme independently Pain well managed on oral analgesia Home support is in place for discharge	Medically stable Wound satisfactory Able to ambulate with walking aids Climb 5 steps with crutches TKA – bend to 90 degrees Pain well controlled Home supports in place	Independent walking with aid Independent on and off bed Independent on stairs Adequate home support/s	Medically stable Wound satisfactory Able to ambulate with walking aids Climb 5 steps with crutches TKA – bend to 90 degrees Pain well controlled Home supports in place
Follow up		Nurse calls patient at 48 hours after discharge Clips, if any, out at 10-12 days Follow up at 6 weeks Further follow up at 1 year or as required.	Follow up phone call with predesigned follow up questionnaire Outpatient follow up at 6 weeks, then as required thereafter	Nurse calls within 48 hours of discharge Wound check by GP Follow up at 6 weeks, then as required thereafter	Nurse calls within 48 hours of discharge Wound check by GP Follow up at 6 weeks, then as required thereafter

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