Perioperative regimens for patients undergoing elective hip or knee arthroplasties.

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Perioperative regimens for patients undergoing elective hip or knee arthroplasties

Impact of nutrition and anaesthetic technique on recovery

by

Andreas Harsten

DOCTORAL DISSERTATION
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Title and subtitle: Perioperative regimens for patients undergoing elective knee or hip arthroplasties. Impact of nutrition and anaesthetic technique on recovery.

Abstract

Background: Elective knee and hip arthroplasty are common surgical procedures. Improved anaesthetic and nutritional care has the potential of increasing patient satisfaction and reducing length of hospital stay (LOS).

The overall aim of this thesis was to evaluate the effect of perioperative nutrition and different anaesthetic techniques on per- and postoperative outcome after elective total hip (THA) or total knee arthroplasties (TKA).

Methods: In this thesis prospective, randomized trials were performed in 358 patients.

Results: Patients undergoing THA received an oral carbohydrate or placebo drink in a randomized controlled trial 90 min before and 120 min after surgery. The treatment resulted in less hunger and nausea and reduced pain compared with placebo. When intrathecal anaesthesia (ITA) and traditional intra- and postoperative care was compared with general anaesthesia (GA) combined with accelerated postoperative care for TKA the LOS was reduced without adversely affecting pain or total satisfaction. TKA patients given identical perioperative treatment were randomized to either ITA or GA and GA resulted in shorter LOS, less nausea, vomiting and dizziness. GA patients also required less postoperative analgesics and had lower pain scores. Patients receiving ITA indicated that they would like to change their method of anaesthesia in the event of a subsequent operation. THA patients receiving either ITA or GA resulted in similar findings as in the TKA-study In conclusion, this thesis shows that perioperative carbohydrate administration has a limited beneficial effect on THA patients. Accelerated postoperative care and GA has favourable recovery effects when compared with ITA and traditional postoperative care. When GA was compared with ITA in a Fast-Track set-up, GA resulted in a more favourable recovery profile for patients undergoing THA or TKA. Both TKA and THA patients preferred GA in case of a future operation.

Key words: Anaesthetic techniques, dietary carbohydrates, length of hospital stay, total knee arthroplasty, total hip arthroplasty

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The cover photo shows a patient 90 minutes after his total knee arthroplasty was completed. He is walking in the PACU (postoperative anaesthesia care unit). Photo by Kjell Pantzar.

Lay-out Cover by Kjell Pantzar

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"Livet är kort, konsten lång, rätta tillfället flyktigt, erfarenheten bedräglig, omdömet svårt"

Hippocrates

To Ann-Louise, Rebecca and Jacob

Contents

List of Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Harsten A, Hjartarson H, Toksvig-Larsen S. Total hip arthroplasty and perioperative oral carbohydrate treatment. Eur J Anaesthesiol 2012; 29: 271-274.

II. Harsten A, Hjartarson H, Werner M U, Toksvig-Larsen S. General anaesthesia with multimodal principles versus intrathecal analgesia with conventional principles in total knee arthroplasty: a consecutive, randomized study. J Clin Med Res 2013; 5: 42-48

III. Harsten A, Kehlet H, Toksvig-Larsen S. Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial. Br J Anaesth 2013; 111**:** 391-399.

IV. Harsten A, Kehlet H, Ljung P, Toksvig-Larsen S. Total intravenous general anaesthesia vs. Spinal anaesthesia for total hip arthroplasty; a randomized trial. Submitted.

Abbreviations

The following abbreviations, listed in alphabetic order, are used in this thesis:

ASA class	American Society of Anesthesiologists physical status
COX-2 inhibitor	cyklooxygenase-2 inhibitor
GA	general anaesthesia
IQR	interquartile range
ITA	intrathecal anaesthesia
iv	intravenous
LIA	local infiltration analgesia
LOS	length of hospital stay
NSAID	non-steroid anti-inflammatory drug
OA	osteoarthritis
PACU	postoperative anaesthesia care unit
PCA	patient controlled analgesia
PONV	postoperative nausea and vomiting
RA	regional anaesthesia
RCT	randomized controlled trial
TCI	target controlled infusion
THA	total hip arthroplasty
TKA	total knee arthroplasty
VAS	visual analogue scale

NS	not significant

Introduction

The purpose of this thesis was to investigate if different perioperative regimens could improve patient outcome after elective THA and TKA with special focus on nutrition and anaesthetic technique. The origin of the project was a visit to dr Geselink in Gent, Belgium in 2008. He postulated that his TKA patients were mobilized within a few hours after surgery and were ready for discharge within 24 hours due to the fact that he used his own constructed patella in-place balancer. All patients received general anaesthesia with propofol and remifentanil using TCI. We hypothesized that the anaesthetic technique could be the explanation for early mobilisation and discharge. At that time there was no scientific support for our hypothesis.

This PhD project started with formulating questions for reviewing the literature. This review showed that in the area of perioperative nutrition and anaesthetic technique for patients undergoing elective THA or TKA there was a need for further studies. This was the starting point for this PhD project. At that time 85% of the Swedish TKA patients received ITA for their surgery and only 10% were anaesthetised using GA (1). Having gone through the Swedish training program in anaesthesia and intensive care medicine in the 1980s I was, like many of my colleagues, convinced that RA was beneficial to the patients and should be used whenever possible.

General background

Osteoarthritis (OA) is the most common condition for inpatient hospital stay for adults with a considerable increase in recent years as measured as the number of stays per 10,000 population in USA. Between 1997 and 2009, osteoarthritis increased by 58 percent among adults aged 65-84 (2). THA and TKA are highly effective in patients with moderate to severe osteoarthritis (3,4). These surgical procedures are frequently performed, yielding an estimated annual number of 1.8 million procedures worldwide (5). In 2005, more than 375 00 patients underwent THA and more than 530 000 had TKA in the United States (6). In Sweden 13316 TKAs were performed in 2012 (1). Indeed, the annual number of TKA and THA is expected to surpass four million by the year 2030 (7). OA is a progressive, degenerative disorder of the joints due to loss of cartilage. Joint pain, stiffness and reduced mobility are common symptoms of OA (8). Pain is the main indication for joint replacement surgery (9). It has been shown that TKA and THA are cost-effective and improve the quality of life for the patients (10). Patients undergoing THA or TKA are approximately 70 years old and have a LOS of 5.6 days (11,12) but an increase in both younger and elderly patients is expected (1).

Approximately 30 million operations are performed every year in the United States and it accounts for an appreciable portion of the health resources (13). In recent years studies on surgical outcomes have focused on morbidity and mortality, LOS, length of time to return to full function and patient satisfaction. Many of these parameters have improved in recent years due to increased attention to factors involved in surgical technique, volume of patients undergoing a procedure at a specific site and improved organizational structure within a specific institution (14-19). Previously, anaesthesiological and surgical training was based on the guild system, where teachers passed on their own techniques and methods to their students. These approaches were generally accepted and successful by traditional standards and new doctors would usually continue using them throughout their professional life (13). The replacement of some traditional approaches in medical care with evidence-based practices has demonstrated that surgical recovery can be accelerated and convalescence decreased. This multimodal approach referred to as Fast Track was developed by professor Henrik Kehlet in Denmark (13,20,21).

Fast Track

Fast Track surgery or enhanced postoperative programmes focuses on optimization of clinical features leading to a faster recovery and hence a reduction of LOS. Initially, fast track was concentrated to patients undergoing abdominal surgery but in 1992 a study was published where THA patients had reduced convalescence and LOS due to multimodal analgesia and intensive mobilization (22). The multimodal analgesia technique includes an opioid-sparing regime with acetaminophen (paracetamol) NSAID's, and for TKA, high volume local anaesthetic intraoperative wound infiltration (23). Adding gabapentinoid and a single preoperative high-dose glucocorticoid has also been suggested (24). The development of Fast Track is based on procedure-specific analyses of various components important to enhance recovery including preoperative optimisation, intraoperative anaesthetic techniques, surgical techniques postoperative pain treatment, fluid management, use of traditional care principles and postoperative rehabilitation (23) The concept of "the pain- and risk- free operation" was born (25).

Even though we have not reached this far, we are getting closer for each year. A recent thesis investigated several of the factors important for achieving better outcome after THA and TKA (26). Predictors of length of stay, compression bandage, readmissions, thromboembolic complications, bilateral TKA, LIA to THA patients and revision TKA has been studied. However, if the anaesthetic method or technique would have any effect and if this is the case, what effect could it have in a Fast Track setup is not clear. Likewise, the clinical effect of perioperative nutrition to TKA and THA patients has not been fully analyzed.

Perioperative nutrition

In many countries overnight fasting before surgery has been a part of the standard protocol. In spite of limited scientific evidence to support this doctrine it is still a rule that is adhered to in many countries (27). However, animal studies have shown a rapid consumption of glycogen reserves during a short period of fasting (28). Overnight fasting can lead to gluconeogenesis and loss of skeletal muscle (29). Furthermore, it has been reported that mitochondrial dysfunction after a short period of fasting could cause insulin resistance (30). On the other hand an intravenous carbohydrate infusion during the night before surgery results in a decrease in insulin resistance compared to fasting (31). In addition the overall patient satisfaction improves when oral carbohydrate solutions were administered to patients preoperatively (32). In fact, oral administration results greater well-being and satisfaction among the patients compared to intravenous administration

(33). In a recent study it was shown that there was a significant but similar decrease in insulin sensitivity regardless of whether carbohydrates or water had been administered (34). The European Society of Anaesthesiology's guidelines for perioperative fasting strongly recommends preoperative feeding with clear fluids up to 2 hours before surgery (35). These guidelines include obese patients, diabetic, patients with gastro-oesophageal reflux and pregnant women not in labour. However, a recent study in THA patients failed to show any major benefits for patients given either water or a nutritional drink as compared to fasting (36)

One of the concerns of a more liberal perioperative oral administration of fluids has been whether the patients have an empty stomach or not at the time of induction of anaesthesia. Theoretically, a full stomach could increase the risk of regurgitation during anaesthesia. However, the pH and the volume of gastric content has been found to be without significant differences regardless of whether the patients fasted or drank carbohydrate solutions up to 2 hours before surgery (37). Hence the risk of aspiration would not seem to be affected by intake of oral liquids. By using spinal anaesthesia it is sometimes assumed that there is a reduced or even eliminated risk of aspiration. However, both opioids and local anaesthetics administered spinally can decrease gastric emptying (38). Although this can happen, carbohydrate solutions given orally 2 hours before surgery has no influence on the gastric emptying rate (39).

The integrity of the small intestine is maintained leading to reduced bacterial translocation in animals fed with carbohydrate compared to fasting (40). Consequently, overnight fasting before surgery could lead to ischemic-reperfusion injury of the small intestine.

Nutritional support for the elderly patient could perhaps also improve their immune function and therefore reduce the risk of infection (41). At the same time it is appropriate to point out that a recent study in THA patients showed reduced postoperative complications in patients with preoperative insulin resistance (42).

A majority of the clinical trials in the area of perioperative carbohydrate nutrition have been performed on patients undergoing abdominal, thoracic, vascular or endocrine surgery. In a recent meta-analysis it was shown that carbohydrate treatment may be associated with reduced LOS in patients undergoing major abdominal surgery but not for orthopaedic procedures (43). One of the few studies on orthopaedic patients included 15 patients undergoing THA and showed improved glucose uptake in peripheral tissues (44)

Method of anaesthesia

General anaesthesia was introduced in the mid 1800s when ether was used as an inhalation anaesthetic (45). In 1898 August Bier in Germany started using ITA (45). During the first decades of the 20th century i.v. anaesthetics were being ntroduced as a number of barbiturates became available (45). TCI became possible in 1981 when computerized pharmacokinetic model-driven continuous infusions were described (46).

RA is the most prevalent method used for anaesthesia in high-volume hip- and knee replacement centres (47). Meta-analyses have shown that regional anaesthesia can reduce the risk of thromboembolic complications and the need for blood transfusions and slightly reduce the duration of surgery (6). A recent retrospective analyses of short-term complications in GA vs. ITA for TKA showed less than 1% difference in the occurrence of several complications and the clinical importance of these differences is likely to be low (48). Despite a low rate of adverse effects and superior postoperative analgesia for RA, there are disadvantages like failed segmental blockade, the necessity of an indwelling urethral catheter and potentially serious complications (haemorrhage, infection) (49-51). A large Swedish retrospective study showed surprisingly many complications following RA (52). Permanent neurological damage was observed in 0.06‰ and spinal haematoma was significantly more common in patients undergoing TKA compared with an obstetric population (1:3600 vs. 1:200 000) (52). In a prospective study major complications were found in 7:100 000 patients where central neuraxial blocks were used (53). Failure rate with ITA or epidural analgesia has been reported to be in the area of 5-20% and RA is commonly associated with excessive motor block (51,54).

The PROSPECT working group (procedure specific postoperative pain management) recommended either general anaesthesia with a peripheral nerve block or ITA with local anaesthetics and an opioid for patients undergoing THA or TKA (55,56). Furthermore, this should be combined with paracetamol and NSAID.

RA has been reported to reduce pain and morphine consumption among patients receiving RA compared to GA (49,50). However, most of the studies included in this review and the PROSPECT recommendations were done before the introduction of the LIA technique (57). The term “pre-emptive analgesia” was launched by Wall in a landmark editorial in 1988 (58). It was thought that by administering preoperative analgesia a pre-emptive effect on pain could occur. More recent work on preventive analgesia has also noted the “protective” effect of opioids and other analgesics such as N-methyl D-aspartate receptor antagonists on pain control beyond the clinically expected duration of these drugs (59).

The entire 1998 April supplement of the journal Anaesthesia was devoted to a review of the development of TCI from 1981 with computer-controlled infusion pumps (60). The TCI technique makes it easy to titrate the depth of anaesthesia, shows the calculated concentration in plasma and at the effect site and compensates for any interruption of the i.v. infusion (60)

The advantages of using TCI for maintenance have been demonstrated in several studies. These have shown the early recovery associated with the use of this method (61-64). The advantages are particularly apparent in surgery of short to intermediate duration (62,63). TCI is well tolerated with rapid and clear headed emergence (65). The TCI technique using propofol and remifentanil wears off rapidly after the infusions have been terminated and hence an alternative method of providing postoperative analgesia is required such as LIA (66,67).

When ITA is used for TKA various combinations of drugs have been used. Adding an opioid to the local anaesthetic is common and morphine is frequently used (55,56). The analgesic effect of ITA with morphine as well as the α_2-adrenegic agonist clonidine is well described (68,69). Unfortunately, both drugs are limited by their negative side effects such as respiratory depression, pruritus and hypotension (68,70-72). Many of the earlier studies comparing GA with RA for TKA or THA did not use TCI as the GA method.

LIA

The infiltration analgesia technique for THA and TKA was developed by Bianconi et al. and Kerr et al. and based on a systematic infiltration of a mixture consisting of ketorolac, ropivacaine and epinephrine into the surrounding tissues around the surgical field (57,73). LIA has been widely used since 2008 in connection with TKA and it is more simple to perform compared with other RA techniques (74). Initially the LIA technique was described using an intraoperative injection and placement of an epidural catheter allowing top-up doses (57). In connection with TKA LIA is recommended but only as a single shot treatment and not by using a catheter which would allow subsequent injections (74). Whether adding NSAIDs to the LIA solution would improve the analgesic effect remains unclear since NSAIDs provide analgesia regardless of given locally or systematically (74,75). Furthermore, the systemic concentration of NSAID (ketorolac) has been shown to be surprisingly high when it is administered together with local anaesthetics as LIA (76). In connection with THA, intraoperative LIA administration may not be effective or required when a multimodal opioid-sparing regimen is used (NSAID, paracetamol, gabapentin) (77). In a recent study it was also showed that LIA provided no additional analgesic benefit among THA patients being anaesthetized using GA (78) On the other hand LIA may be effective when compared with intrathecal morphine for THA patients (79).

Indwelling urinary catheter

Postoperative urinary retention is defined as the sudden inability to pass any urine, despite a full bladder (80). It is well known that TKA and THA patients have an increased risk of urinary retention (81). Old age, male sex, surgery in the pelvic area, spinal anaesthesia, opioids and a history of urinary tract problems are well known risk factors for postoperative urinary retention (82-86). Urinary catheterisation is the main risk factor for nosocomial urinary tract infection (87). The frequency of these infections among THA patients is reported to be 2-16% (83,88). Clean intermittent catheterisation has been shown to produce a lower risk of developing bacteriuria compared to indwelling urinary catheters (89). Using clean intermittent catheterisation instead of indwelling urinary catheters requires that ultrasound bladder scans are done on a regular basis in order to avoid over distension of the bladder (89). In a recent randomized, prospective study it was shown that indwelling urinary catheters were not required for patients undergoing THA (90)

Dizziness

Orthostatic intolerance and dizziness following THA has been reported to be as high as 42% at 6 hrs and 19% at 24 hrs after surgery (91). It is together with pain and general weakness the main clinical reasons for delayed discharge from hospital after THA or TKA (92). Dizziness can hinder early physical therapy, which is the most important factor for successful postoperative rehabilitation (92). Dizziness caused by orthostatic intolerance is not affected by correction of functional hypovolemia. Instead it has been postulated that a dysregulation of vasomotor tone could explain orthostatic intolerance (93).

Length of hospital stay

LOS after TKA or THA has been reported to be 6-12 days in the United Kingdom, Germany and Demark (92,94). However, in the last decade the use of the Fast Track methodology has reduced LOS to about 2-4 days (24,57,94-96). Having well-defined functional discharge criteria is important in order to ensure a safe discharge and facilitates comparison of LOS in different studies. Using the Fast Track concept the following functional discharge criteria have been used: independent ability to get dressed, to get in and out of bed, to sit and rise from a chair/toilet, mobilization with crutches. In addition, sufficient oral pain treatment, having trained in walking stairs, ability to flex knee to at least 70° and acceptance to being discharged have been used (92).

Using these functional criteria recent research has shown that a LOS of approximately 24 hrs is achievable for THA (97). One should keep in mind that fulfilling the discharge criteria is not the same as actually being discharged. Logistical reasons such as waiting for physiotherapy or postoperative x-ray and patient related factors such as a feeling of general insecurity delays the actual time of discharge (92).

Fast Track THA and TKA with LOS ≤ 4 days and discharge to home, and not to rehabilitation units, is feasible and safe even in older patients with comorbidities (98). Furthermore, LOS among smokers and alcohol users have not been shown to be increased in Fast Track THA or TKA (99).

Postoperative pain

Postoperative pain relief is a prerequisite for fast track surgery with early mobilization (100,101). Multimodal, opioid sparing analgesia has been shown to reduce nausea, vomiting and sedation (102). NSAID, COX-2 inhibitors, ketamine, gabapentin and LIA have all been demonstrated to be effective (103,104). High volume infiltration of local anaesthetics was introduced in 2008 and has shown to be effective and more simple compared with many other regional anaesthetic techniques (57,74). However, LIA seems to be more effective in TKA as compared to THA (74,77,78).

Despite numerous publications the degree of pain following many types of surgery in everyday clinical practice has been unknown until recently. In a large prospective cohort study, 179 surgical procedures were compared. According to pain scores the operations were ranked and among the 40 with highest pain scores 22 were orthopaedic operations. TKA and THA were ranked 53 and 82 where 1 was the most painful and 179 the least painful. Interestingly, both these procedures were associated with the same peak pain scores regardless of the operations were performed under GA or RA (105). Even though excellent long-term functional outcomes have been reported following TKA and THA, pain can still be severe in the early postoperative phase after TKA (106). Studies have also suggested that poor pain control after knee replacement is associated with development of chronic pain although our understanding of this area is in its beginning (107,108)

Postoperative nausea and vomiting

PONV following THA or TKA has a reported incidence of 20 to 83% (109-111). Opioids and anaesthetic drugs are frequently associated with PONV (112-115). Vasopressin and serotonin are likely to be involved in the development of PONV (116). Apart from patient discomfort PONV can cause immobilisation, potentially increasing the risk of thromboembolic disease, interfere with physiotherapy and delay discharge (117-119). Avoidance of PONV is essential for fast track surgery with speedy recovery and shorter LOS.

Major complications

Major complications, such as death or serious cardiovascular morbidity are rare during or after THA and TKA regardless of whether GA or RA is used. In the MASTER study 915 patients were randomized to receive RA and GA or GA only. There were no differences in deaths or major postsurgical morbidity apart from a reduction in respiratory failure in the RA group (120). In a recent review of a large dataset including 400 000 patients, major in-hospital morbidity and thirty-day mortality was reduced among those receiving RA (121). In contrast to this the POISE trial showed that patients at high risk of cardiovascular morbidity, RA was associated with an increased risk of adverse cardiovascular outcome (122).

Mortality and serious morbidity such as pneumonia, pulmonary embolus or myocardial infarction has been shown to be less frequent if the surgery is performed by surgeons or hospitals with greater volumes of THA or TKA (123,124)

Aims of the thesis

The overall aim of this PhD project was to evaluate different regimens for patients undergoing THA or TKA with special focus on perioperative nutrition and anaesthesia technique

Specific aims were:

I. To determine if perioperative oral administration of a carbohydrate solution reduces discomfort in elective THA patients.

II. To compare if GA combined with intraoperative glucocorticoids, exclusion of intraoperative tourniquet, indwelling urethral catheter and an accelerated postoperative care regimen with standardized traditional intra- and postoperative care including ITA for TKA patients reduces pain and LOS.

III. To compare the influence of GA or ITA on the need for postoperative hospitalization and early comfort in patients undergoing fast track TKA.

IV. To compare the influence of GA or ITA on LOS, pain and patient comfort for patients undergoing fast track THA.

Patients and methods

Overview of the four studies

Study	I	II	III	IV
Design	RCT (double blind)	RCT, consecutive randomized	RCT consecutive randomized	RCT, consecutive randomized
Participants (n)	n = 60	n = 60	n = 120	n = 118
Data collection	Study protocol, telephone interviews	Study protocol	Study protocol, telephone interviews	Study protocol, telephone interviews
Data analysis	Mann-Whitney U-test, Student's T-test	Mann-Whitney U-test, Student's T-test	Mann-Whitney U-test, Student's T-test, Chi-square test	Mann-Whitney U-test, Student's T-test, Chi-square test

Setting

The setting for the studies was the department of orthopaedic surgery at Hässleholm hospital, Sweden. The patients came from the primary catchment area but there were also patients that had been referred to Hässleholm hospital from other areas in Sweden. The main reason for referral was that the waiting period was too long at other hospitals and according to the health care guarantee, patients are free to choose another hospital if surgery cannot be provided within 90 days. The Department of orthopaedic surgery consisted of one ward, six operating theatres, one PACU and an outpatient clinic. Our hospital performed 1496 primary and revision TKA and THA in 2012. In 2013 there was a reduction in the number hospital beds designated for elective orthopaedic surgery from 38 to 28.

Sample

Study I

Patients with OA scheduled for THA were consecutively included after the preoperative visit to the anaesthetist between September 2009 and March 2010. Exclusion criteria were obesity (BMI > 35 kg m^{-2}), diabetes mellitus, prior hip surgery to the same hip, ongoing infection, immunological deficiency, ASA physical status IV or higher and age < 50 or > 80 years. 60 patients were included (Figure 1.).

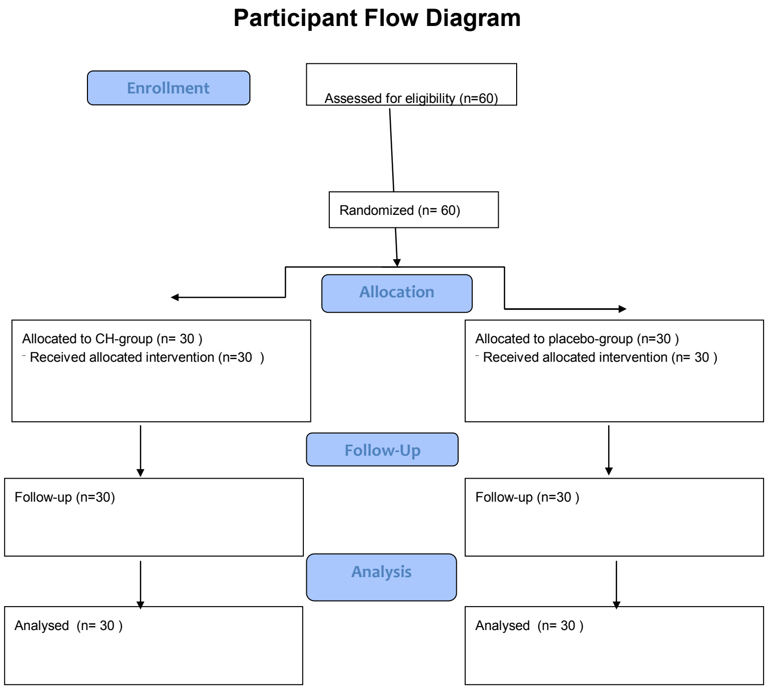

Figure 1. Flow chart of patients in Study I. CH = carbohydrate group.

Study II

Patients with OA scheduled for TKA were eligible for participation in the study. Patients were recruited between September 2008 and May 2009. Sixty-one consecutive patients were assessed for eligibility by two orthopaedic surgeons and 60 were included after the preoperative visit by the anaesthetist (Figure 2.). Exclusion criteria were obesity (BMI > 35 kg m^{-2}), prior major surgery to the ipsilateral knee, ongoing infection, immunological deficiency, ASA physical status IV or higher.

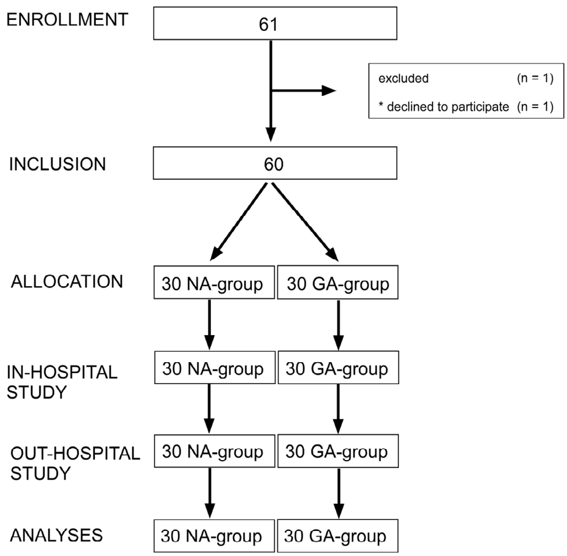

Figure 2. Participant flow diagram Study II. NA = neraxial anaesthesia.

Study III

Patients with OA scheduled for TKA were eligible for participation. 124 consecutive patients were assessed by two orthopaedic surgeons between September 2011 and June 2012. 120 were enrolled after the preoperative visit to the anaesthetist. Exclusion criteria were previous major knee surgery to the same knee, obesity (BMI > 35 kg m^{-2}), rheumatoid arthritis, immunological deficiency, allergy to any of the drugs used, inability to understand the given information, ASA status IV or higher, age < 46 or > 84. Patients were also excluded if they were taking opioids or if they had a history of stroke or psychiatric disease that could affect the perception of pain (Fig 3).

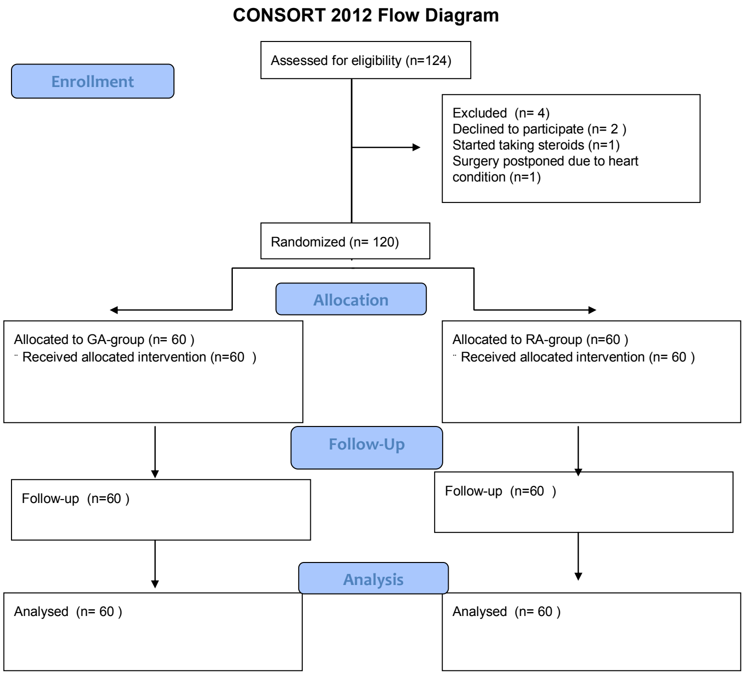

Figure 3. Participants Flow diagram Study III.

Study IV

Patients with OA scheduled for THA were eligible for participation. 124 consecutive patients were assessed by four orthopaedic surgeons between January 2013 and May 2013. 120 were enrolled after the preoperative visit to the anaesthetist and 118 received their allocated treatment. Exclusion criteria were prior surgery to the same hip, ASA status > III, obesity (BMI > 35 kg m^{-2}), rheumatoid arthritis, immunological depression, allergy to any of the drugs used, age < 46 or > 84. Patients were also excluded if they had a neurological or psychiatric disease that potentially could affect the perception of pain or if they were taking opioids (Fig 4).

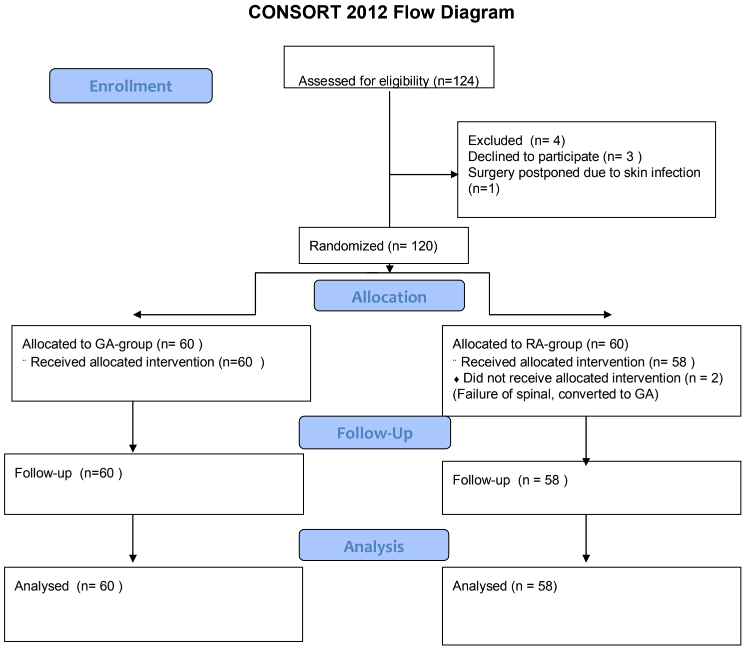

Figure 4. Participants Flow Diagram Study IV.

Procedures

The patients were informed and asked whether they would like to participate in the studies when they visited the orthopaedic surgeon and the anaesthetist prior to surgery. Generally, this visit took place 1-3 weeks before the operation. If they were included, a signed informed consent was obtained. Randomization was performed by an employee not involved in the studies, who prepared non-transparent, sealed envelopes each containing a slip of paper with a computer generated description of which group the patient should be allocated to (study group or control). In **study I** two nurses who were not otherwise involved in the study administered the oral solutions. Patients and all other care providers were blinded to group allocation. In **study II – IV** subjects and investigating doctors were blinded to treatment group until 1 h before surgery. After that, both subjects and personnel in the operation theatre were, for obvious reasons, aware of the method of anaesthesia being used. Once the subjects left the operating theatre, staff responsible for monitoring and assessing home readiness were blinded as to treatment group.

In **study I** premedication consisted of celecoxib 200 mg, paracetamol 1g, midazolam 2.5 mg and morphine 10 mg orally. No glucose containing solutions were permitted and anaesthesia consisted of ITA with bupivacaine 15 mg, fentanyl 25 µg and clonidine 30 µg. Patients were randomized to either an oral carbohydrate solution or flavoured water. Four hundred ml of either solution was taken orally 90 min before induction of anaesthesia and again 2 hrs after the end of surgery. In all patients surgery started before noon.

In **study II** premedication was midazolam 2.5 mg, paracetamol 2g, meclizine 10 mg, celecoxib 200 mg and oxycodone 10 mg. Patients were randomized to either the study group or control group. In the study group anaesthesia consisted of GA with TCI using propofol and remifentanil. Endotracheal intubation was facilitated by succinylcholine and the mechanical ventilation with oxygen and air aimed at endtidal CO_2 of 4.5 kPa. The study group also received betamethasone 4 mg during surgery and at the end of surgery a mixture of ropivacaine 250 mg and epinephrine 0.3 mg (total volume 100 ml) was injected in the tissues in the peri-surgical area. The mixture was injected using a systematic technique ensuring uniform delivery to all tissues incised, handled or instrumented during the procedure. It was divided into three equally large volumes and the first third was injected into the posterior joint capsule and both collateral ligaments after the bone cuts had been performed. After the insertion of the prosthesis another third was injected along the borders of and into the capsule and the cut quadriceps tendon, infra-patellar ligament, possible remnants of the fat pat, crusiate ligaments and the soft tissues surrounding the joint. The last third was infiltrated into the subcutaneous tissues before wound closure. Approximately 20 min before the end of anaesthesia an i.v. bolus dose of 7.5-10 mg of oxycodone was given. The study group did neither receive an indwelling urethral catheter nor a thigh tourniquet. Bladder scans were done every second hour during the first 24 hrs postoperatively. If the bladder contained > 400 ml an intermittent catheterization was done. Mobilisation was started within 2 hrs of arrival to PACU.

The control group received ITA consisting of bupivacaine 12.5 – 15 mg, morphine 0.1 mg and clonidine 30 µg. At the end of surgery a mixture of ropivacaine 110 mg, epinephrine 0.5 mg and morphine 10 mg (total volume 21 ml) was injected into the peri-surgical area as described above. This group also had an indwelling urethral catheter inserted prior to surgery and a tourniquet around the thigh was used during surgery. Mobilization started on the day after surgery. The urethral catheter used in this group was removed the day after surgery and a urine sample was taken for urine bacterial analyses.

Both groups were given intermittent doses of oxycodone 2-8 mg i.v. as rescue medication. Patients complaining of PONV were given ondansetron 4 mg i.v.

1 h before surgery the patients in **study III** and **study IV** received celecoxib 400 mg, paracetamol 1 g and thereafter 12-hourly (celecoxib 200 mg) and 6-hourly

(paracetamol 1 g). No subjects received an indwelling urinary catheter before surgery and a thigh tourniquet was not used. Patients in the control group received ITA consisting of bupivacaine 5 mg/ml, 3 ml. Subjects in the study group were anaesthetized using TCI with propofol and remifentanil. Rocuronium bromide was used to facilitate intubation. Ventilation was with oxygen/air targeting an endtidal CO_2 of 4.5 kPa. At the end of surgery glycopyrronium 0.5 mg and neostigmine 2.5 mg was given i.v. and a bolus dose of oxycodone 10 mg was also given 20 minutes before end of surgery.

All subjects in **study III** received LIA in the perisurgical area consisting of 150 ml of ropivacaine (0.2%) with epinephrine (10 µg ml^{-1}). A Cryo-bandage (Iceband, Nordic Medical Supply A/S, Denmark) was in **study III** applied directly after surgery and remained in place for 24 h. In **study VI** no LIA was used.

The differences in premedication between the studies represent the development from an older, more comprehensive strategy towards an opioid-sparing, technique and are in line with the Fast Track methodology.

Outcome measures and assessments

Pain

The patients scored their pain using a 100 mm visual analogue scale (0 = no pain, 100 = worst imaginable pain). Pain was recorded at rest in **study I** and **II**. In **study III** and **IV** pain was registered at rest, with 45° knee flexion, with the knee strait and 45° hip flexion and after walking 5 meters. Pain was also evaluated by recording the amount and the time of postoperative pain treatment. In **study III** and **IV** this was done by registering the number of doses and amount of analgesia delivered via a PCA device. We also monitored requested but not administered PCA doses and the time for these doses.

Discomfort

Patients scored their subjective sense of discomfort using a 100 visual analogue scale (0 = no symptoms, 100 = worst symptoms imaginable). Anxiety, hunger, nausea, thirst tiredness and headache was assessed in **study I**. In **study III** and **IV** dizziness and PONV was recorded.

Anaesthesia satisfaction

Global satisfaction with the anaesthesia received was assessed using a 100 mm visual analogue scale (0 = least possible satisfaction, 100 = best possible satisfaction). In **study III** and **IV** subjects were asked 6 months after the operation what type of anaesthesia they would prefer in case of a subsequent TKA or THA (GA or ITA).

Cognitive function

The Short Portable Mental State Questionnaire (SPMSQ was used to assess the patients' cognitive function in **study I**.

LOS

LOS was defined as the time from the end of surgery until actual discharge in **study I** and **II**. In **study III** and **IV** LOS was defined as the time from end of surgery until the subjects met the discharge criteria from the ward: (i) able to get in and out of bed, (ii) able to get dressed, (iii) able to sit down in a chair and get up again, (iv) able to walk 50 m with or without walking aids (crutches, etc.), (v) able to flex the knee to ≥ 70°, (vi) able to walk stairs, (vii) pain manageable with oral analgesics and (viii) acceptance to be discharged.

Discharge from PACU

Discharge criteria from PACU were: (i) sufficient level of consciousness (aroused by verbal stimuli), (ii) able to maintain a free airway, (iii) adequate breathing with $SaO_2 > 94\%$ when administering a maximum of 5 litre min^{-1} O_2 nasally, (iv) mild or no PONV (VAS < 30 mm), (v) pain control adequate (VAS ≤ 30 mm at rest). In **study III** and **IV** discharge criteria from PACU to the ward were assessed every 15 minutes until obtained.

Intraoperative blood loss

In **study III** the intraoperative blood loss was calculated by increase of weight of gauze and draping sheets together with the content in the surgical suction bottle corrected for irrigation fluid volume. In **study IV** calculation of blood was similar with the exception of that draping sheets were not included in the measurement. In **study II** blood loss was roughly estimated by visual estimation of blood content in gauze and suction bottle.

Blood samples

Venous blood samples were analysed for plasma concentration of haemoglobin, glucose, albumin and creatinine.

Sample size and statistical analyses

Sample size was determined using PS Power and Sample Size Program for PC version 3.034 by William D. Dupont and Walton D. Plummer. (http://biostat.mc.vanderbilt.edu/PowerSampleSize). Pain was the primary outcome used in **study I** and **II**. Data from previous randomized clinical trials indicated that 28 patients were needed in each group to demonstrate a 30 % difference in pain score with a significance of 0.05 and a power of 0.80 (125). To compensate for drop outs, 30 patients were included in each group.

For statistical analysis SPSS 17.0 (SPSS, Chicago, USA) was used in **study I-III.** In **study I** Mann-Whitney U-test was used when analysing pain and discomfort scores, hospital stay and SPMSQ. Student's T-test was used for analysing demographic and blood sample data. $P < 0.05$ was considered to indicate statistical significance. Data was presented as mean (±SD) except for pain scores where median (IQR, [25-75% interquartil range was used]).

In **study II** data-distribution was tested for normality with Shapiro-Wilks test and residual plots. According to data-distribution either Student's-t test for un-paired data or Mann-Whitney U-test was used. Data are presented as mean (± SD) or median (IQR). A *P*-value < 0.05 was considered to indicate statistical significance.

In **study III** power and sample size calculation was done with the same program as above. We planned a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous pilot study at Hässleholm Hospital the response within each subject group was 72 hrs with standard deviation of 42. If the true difference between experimental and control means was 24 hrs, we would need to study 49 experimental subjects and 49 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. To compensate for drop outs we decided to include 124 patients. Data are presented as mean (± SD) or median (IQR). A *P*-value < 0.05 was assigned statistical significance.

Sample size for **study IV** was calculated using the same method as described above. LOS was the primary outcome used. We planned a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. Results from a previous study indicated that we would need 49 patients in each group to be able to reject the null hypothesis that the population means of the experimental and control groups were equal with probability (power) 0.8 (126). The type I error probability associated with testing of this null hypothesis is 0.05. To compensate for dropouts we included 120 patients.

Data analyses were performed using SPSS version 20.0 (SPSS, Chicago, USA). Data distribution was tested for normality with Sharpio-Wilks test and residual plots. According to data distribution either Student's-t test for unpaired data or Mann-Whitney U-test was used. Chi Square test was used for binary data. Data are presented as mean (± SD) or median (IQR). A *P*-value < 0.05 was considered to indicate statistical significance.

Summary of main results

Study I

"Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomized, double-blind, controlled trial".

Sixty patients received their allocated intervention. Baseline patient characteristics were similar in the carbohydrate treated group vs. placebo group. There were no differences in LOS, anxiety, headache or thirst between the groups. Patients who received the placebo were hungrier preoperatively compared with those who received carbohydrate ($P < 0.05$); at other time points there was no difference in the feeling of hunger between the two groups. Median pain scores was lower at 12, 16 and 20 hrs in the carbohydrate group vs. placebo group (figure 5).

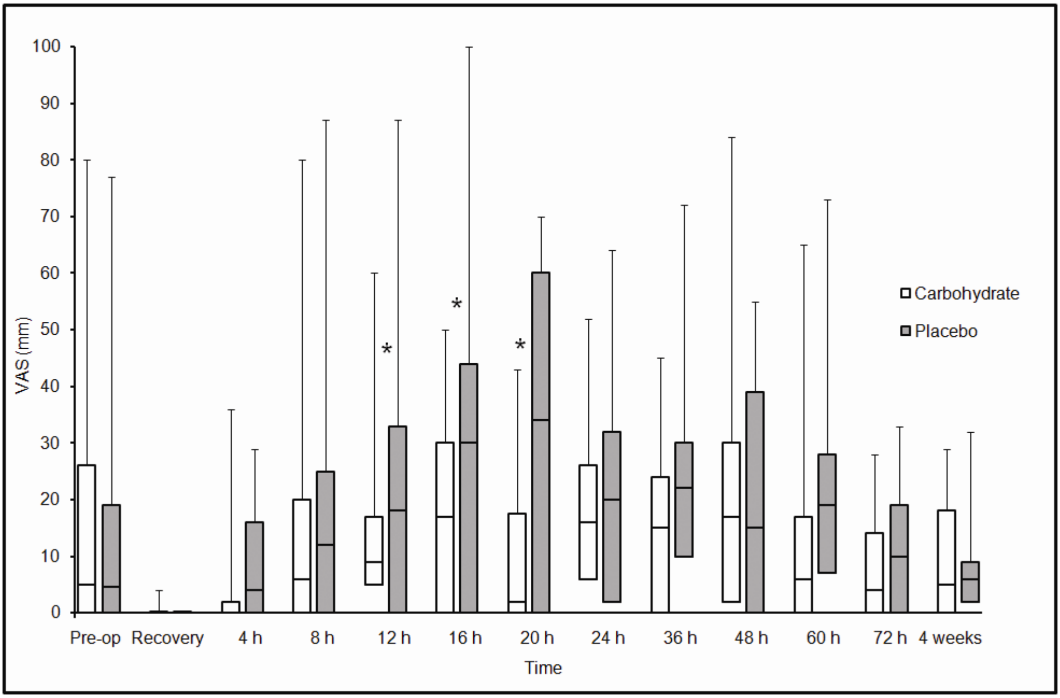

Figure 5. Pain scores from preoperative period until 4 weeks after surgery. Horizontal lines indicate medians, boxes indicate IQR and whiskers indicate upper range. * $P < 0.05$.

During the first 24 h of postoperative care median (IQR) administration of rescue morphine was 14 mg (5-20) in the placebo group and 12.5 mg (5-25) in the carbohydrate group (NS). Patients who received the carbohydrate solution were more tired from day 2 and onward ($P < 0.05$). The placebo group patients had more nausea immediately prior to surgery and at 36 and 48 hrs after surgery ($P < 0.05$). There were no differences in plasma glucose concentration except at 20 hrs after the end of surgery when the median values were 9.36 and 6.55 mmol l^{-1} for the placebo and carbohydrate groups, respectively ($P < 0.05$). There were no differences in haemoglobin, albumin, creatinine or SPMSQ scores between the groups.

Study II

"General anaesthesia with multimodal principles versus intrathecal analgesia with conventional principles in total knee arthroplasty: a consecutive, randomized study"

60 patients were allocated to one of the two treatment arms. Baseline patient characteristics were similar in both groups. The estimated median intraoperative blood loss was significantly higher in the GA group 100 ml (50-150) vs 0 ml (0-50) in the ITA group ($p < 0.05$). Pain scores were significantly higher in the GA group between 0-12 hrs and in the ITA group between 12-24 hrs (figure 6).

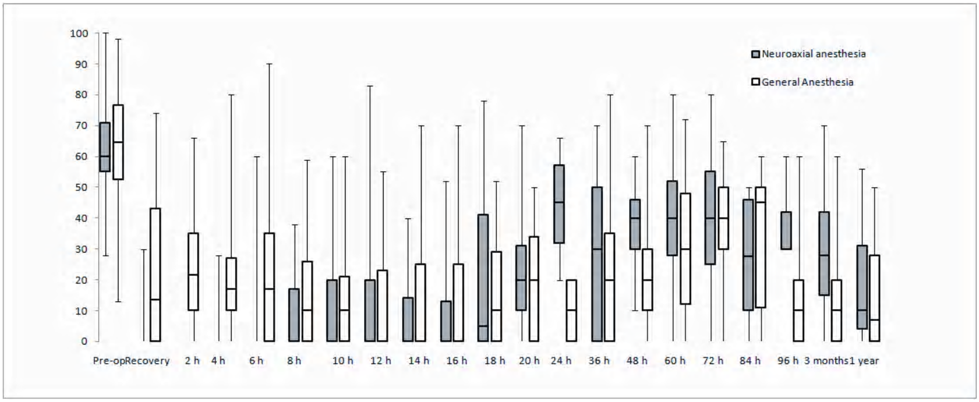

Figure 6: Pain scores for GA and ITA (neuraxial anaesthesia) groups. Line within the boxes indicate median and the boxes indicate IQR. Whiskers indicate range. Area under the curve analyzed for 0-12, 12-24 and 24-48 hrs using Mann-Whitney

U-test. Statistically significant differences (higher pain scores in GA group) between 0-12 hrs, $P < 0.05$, and (higher in ITA group) between 12-24 hrs, $P < 0.05$

50% of the patients that did not receive an indwelling urethral catheter had to have at least one intermittent catheterisation due to large bladder volume. Median LOS was 80 (68-93) hrs in the GA group and 99 (84-112) hrs in the ITA group ($p < 0.05$).

Study III

"Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial".

124 patients were assessed for eligibility in the trial and 120 randomized patients all received their allocated intervention. Baseline patient characteristics were similar in the GA vs. the ITA group. Sixty-six % of the patients were ready to be discharged from PACU upon arrival without statistical difference between the groups. Median LOS was shorter in the GA group (46 h) compared with the ITA group (52 h, $P < 0.001$). In the early phase of the postoperative period, subjects in the GA group had higher pain scores, but from 6 h onwards the ITA patients had higher pain scores (figure 7).

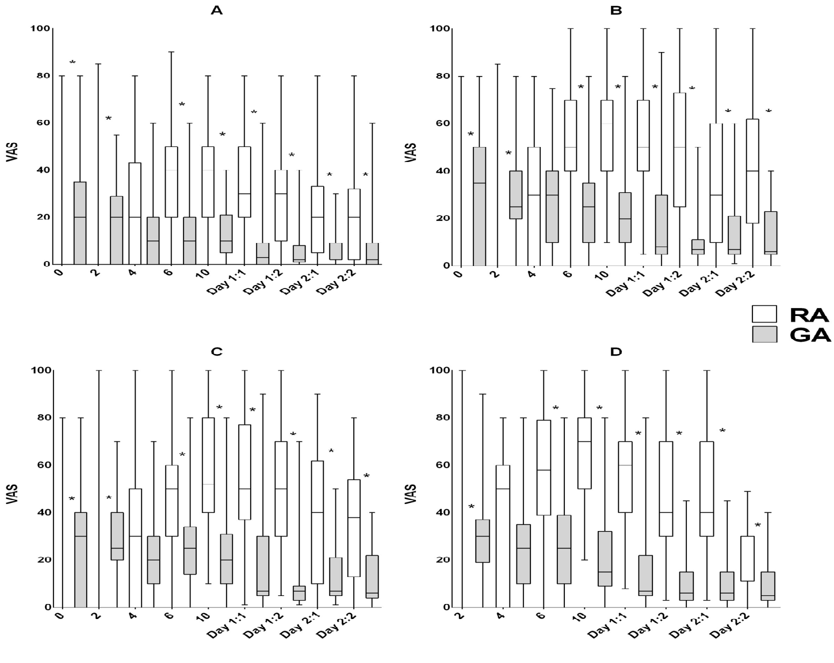

Fig 7. Pain at (A) rest, (B) during knee flexion, (C) with knee straight and hip flexion and (D) when walking. Gray bars = GA and white bars = ITA. A line within the boxes indicates median and the boxes indicate IQR. Whiskers indicate range. * $P < 0.001$. Numbers indicate time in hours after surgery. Day 1:1 and 1:2 is the day after the day of surgery at 08:00 and 14:00. Day 2:1 and 2:2 are the same time points but the second postoperative day.

The median (IQR) 24 h postoperative administration of morphine was 19 mg (11-28) in the GA group and 54 mg (37-78) in the ITA group ($P < 0.001$). The median (IQR) number of requested, but not administered PCA doses was 2 (0-7) in the GA group and 9 (1-26) in the ITA group ($P < 0.001$). Subjects in the ITA group had higher dizziness scores ($P < 0.05$). Orthostatic function was less affected in the GA group as 57 subjects in the GA group and 18 in the ITA group were able to walk 5 meters after 6 hrs ($p < 0.001$). Median PONV scores and number of patients that vomited were both higher in the ITA group. There was no difference between groups concerning total anaesthesia satisfaction score. However, significantly more subjects in the ITA group indicated that they would like to change the method of anaesthesia for a subsequent operation (14 vs. 2, $P < 0.05$).

Study IV

"Total intravenous general anaesthesia vs. spinal anaesthesia for total hip arthroplasty; a randomized trial"

124 patients were assessed and 120 were included and 118 received their allocated treatment. Baseline patient characteristics were similar in the GA vs. the ITA group. The median (IQR) time to fulfilling the discharge criteria from PACU was 0 (0) min in the ITA group and 90 (50-125) min in the GA group ($p < 0.01$). The median (IQR) LOS was shorter in the GA group 26 (23-30) hrs compared with the ITA group 30 (25-45) hrs. In the early phase of the postoperative period, patients in the GA group had higher median pain scores but from 6 h onwards the ITA patients had higher pain scores (figure 8). Subjects in the ITA group had higher median dizziness scores and their orthostatic function was more affected compared with the GA group. PONV was more frequent in the ITA group. There was no difference between groups in total anaesthesia satisfaction score. However, significantly more subjects in the ITA group indicated that they would like to change the method of anaesthesia for a subsequent operation (13 vs. 5, $P < 0.05$).

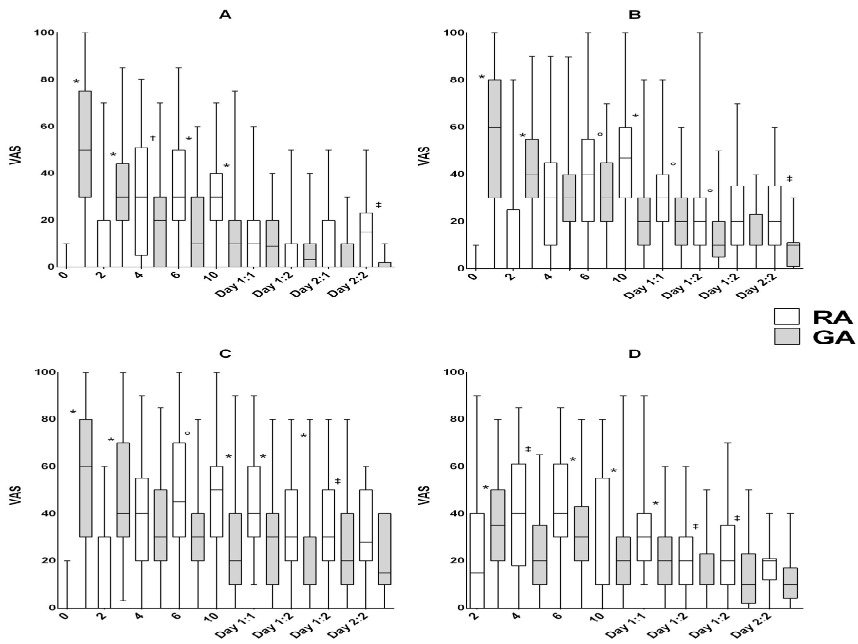

Figure 8: Pain (Visual Analogue Scale, VAS 0-100 mm) at (A) rest, (B) during knee flexion, (C) with the knee straight and hip flexion and (D) when walking. Filled bars = GA and open bars = ITA. Line within the boxes indicates median and the boxes indicate 25-75% interquartil range (IQR). Whiskers indicate range. * = $P < 0.001$, ° = $P < 0.01$ and ‡ = $P < 0.05$. Numbers indicate time in hrs after surgery. Day 1:1 and 1:2 is the day after the day of surgery at 08.00 and 14.00. Day 2:1 and 2:2 are the same time points but the second post operative day.

General discussion

Patients with OA suffer from pain, physical disability and a reduced quality of life leading to an increased risk due to the sedentary and inactive lifestyle the disease causes (127). OA generates a heavy burden equivalent to that of diabetes and ranks eighth among the leading causes of disability worldwide (128). An estimation of the economical impact of the disease puts the total annual cost in USA at $89.1 billions (129).

The results from this PhD project imply that perioperative oral carbohydrate nutrition has limited clinical effect on patients undergoing elective THA. Even though carbohydrate treated patients had lower pain scores and experienced less hunger and nausea the actual numerical differences were not impressive. Earlier studies have also failed to show any significant differences in pain among these patients (130). Furthermore, we found no difference in anxiety or thirst and there were no major differences in blood glucose concentrations between the groups. This is in line with previous studies (32). The carbohydrate-treated patients were more tired. This is more difficult to explain but could be caused by postprandial fatigue, which is seen more often after pure carbohydrate meals compared with fatty or mixed meals (131). The lack of any substantial clinical differences between the groups could be explained by the fact that the surgery performed was not of such a magnitude that it causes a significant reduction in insulin effect. Although we were unable to demonstrate any major clinical improvement with perioperative oral carbohydrates one should keep in mind that overnight fasting has several disadvantages. The European Society of Anaesthesiology guidelines for perioperative fasting strongly recommends feeding of patients with clear fluids up to 2 h before surgery (35). The intake of clear fluids before surgery has many advantages such as less thirst and hunger and reduced insulin resistance. However, we have raised the question as to whether carbohydrate fluids are the best perioperative liquid or whether water could be just as effective (132)?

When traditional perioperative regimens for managing TKA (including ITA with an opioid, tourniquet, indwelling urinary catheter and mobilisation the day after surgery) was compared with a more Fast Track like setup (GA, no tourniquet, no indwelling urinary catheter and early mobilization) the latter group had shorter LOS and no difference in pain scores. The absence of differences in pain scores could be explained by the use of glucocorticoids and accelerated recovery programme in the GA-based regimen (133). In addition, the GA patients did not have a tourniquet during surgery, which might have contributed to less pain. Thigh tourniquet is associated with intraoperative, ischemic nociception (134). The average GA patient stayed approximately 19 hrs less in hospital compared with the average ITA patient and this could be explained by the accelerated postoperative care regime (135). Furthermore, the GA group did not have a clinically significant increase in bleeding during surgery. Interestingly, the blood loss was less and the duration of surgery shorter when compared to other studies (136). This implies that older and more conventional principles of perioperative care can be replaced with a more Fast Track like setup, including GA, without adversely affecting LOS or comfort factors.

When all parameters except the method of anaesthesia (**study III**) were identical in a group of patients scheduled for TKA, GA seems to result in shorter LOS, less nausea and vomiting and dizziness. Also the GA group experienced less pain and was given fewer post operative doses of analgesia as compared to the ITA group. In a review by Macfarlane et al. reduced postoperative pain and morphine consumption among patients receiving RA compared with GA was reported (49). However, most of the studies included in their review were done before the introduction of LIA, which is simpler compared with many other regional anaesthetic techniques and has been widely used since 2008 in connection with TKA (57). In the ITA group, intrathecal morphine was not used despite being recommended and this may have influenced our results (56). However, the analgesic effects of intrathecal morphine are rather small, and in elderly patients the side effects can be undesirable for early recovery. Furthermore, the ITA patients were more prone to request a change in the method of anaesthesia in the event of a subsequent operation. This is interesting as anaesthetists themselves would prefer RA in a hypothetical situation of needing surgery for a lower extremity orthopaedic operation (137). Discharge from PACU can be achieved early and indwelling urinary catheters can be avoided. This study shows that modern GA such as TCI can provide excellent anaesthesia and transition to reasonable postoperative analgesia following TKA (138)

If THA patients are randomized to either GA or ITA the results are in line with those from the TKA study (126). However, there was no difference in morphine consumption between the groups as was the case in **study III**. We believe this could be explained but the fact that the THA patients in **study IV** did not receive any LIA, which the TKA patients in **study III** did (126). The day after the day of surgery 60% of the patients met or had met the discharge criteria from the ward. This is in line with previous reports (92). However, the average GA patient fulfilled discharge criteria earlier than the average ITA patient (26 vs 30 hrs), possibly due to reduced PONV and dizziness. Blood loss was quite limited (285 mL and 317 mL, respectively) and we believe this could be explained by the fact that our hospital is a referral unit, which results in extensive experience not only for the surgeons but also for anaesthesia personnel and other perioperative caregivers. Furthermore, subjects preferred GA over ITA in the event of another THA.

In summary, our results in fast-track THA and TKA do not support previous data on the benefits of ITA, compared with modern GA on early recovery, calling for large-scale prospective comparative studies.

Strengths and limitations

This thesis is based on four prospective consecutive randomized trials, which are considered to belong to level I of evidence. **Study I** was double blinded and **studies II-IV** were singled blinded. We utilised the fact that Hässleholm hospital is the largest centre for elective primary THA and TKA in Sweden, and that most patients pass through our hospital without participating in any studies. This makes Hässleholm hospital (the setting of the studies in this thesis) an ideal venue for clinical research.

Several limitations have to be acknowledged. In **studies II-IV** both patients and staff in the operating theatre were, for obvious reasons, aware of the method of anaesthesia being used. This potential bias is difficult to eliminate. However, once the patients left the operating theatre, staff responsible for monitoring and assessing home readiness was blinded as to treatment group. In **studies III-IV** we did not use intrathecal morphine in the ITA group despite recommendations (55,56) and this may have slightly influenced our results. Furthermore, oxycodone was administered to the patients in the GA group at the end of surgery. This was done due to the short-lived analgesic effects of remifentanil used in the TCI technique. At the same time, we found it less appropriate to administer intraoperative oxycodone in the ITA group, receiving intrathecal local anaesthetics.

Another limitation was that our studies mainly focused on comfort factors and not serious morbidity or mortality, which would require sufficiently powered prospective randomized trials. When interpreting the clinical significance of the results presented in this thesis one should keep in mind that many of the previous trials that reported an increase in serious complications following GA as compared to ITA were done prior to the introduction of the Fast Track technique.

Clinical implications

Perioperative nutrition for orthopaedic surgery (i.e. THA) has limited effect and should not be used in standard cases. Early mobilisation and GA has clinical benefits for patients undergoing TKA and could be used. In the same group of patients thigh tourniquet reduces blood loss but the clinical importance is limited. Indwelling urinary catheters can be avoided in both TKA and THA patients. GA also has favourable, but not so pronounced, recovery effects after THA and hence GA is an alternative equivalent to ITA.

Future perspective

The use of GA with TCI as opposed to ITA has shown to be beneficial in terms of short term recovery parameters in patients undergoing THA or TKA. As mentioned above the high initial pain scores for THA patients receiving GA could possibly be explained by the fact that they were not given LIA. LIA was not administered to this group due to the fact that earlier studies have failed to show any beneficial effect of this analgesic modality to the THA patient (77). Is it possible that LIA may have a significant pain reducing effect when used in conjunction with GA for the THA patient? Further research is needed.

We do not know, at this point, whether the beneficial effects of GA only refers to TCI. Could it be that GA using inhalation anaesthetics will produce the same effects? Furthermore, could TKA with the patient in supine position be performed with laryngeal mask instead of endotracheal intubation?

Future improvements could also include the use of preoperative high-dose glucocorticoids, gabapentinoids, duloxetine and ketamine (139,140). Thrombo-embolic prophylaxis is an area that probably deserves further studies. Since LOS has been substantially reduced in recent years together with early mobilisation old treatment principles in this field may need a revision. Dizziness, PONV and general weakness are other areas where improvements are needed.

There is a need for optimisation of the multimodal opioid sparing analgesia, especially after discharge since pain for the first weeks or months after TKA remains a problem (23). In the future it may be necessary to divide our focus between “medical” versus “surgical” morbidity since approaches for improvement will be different (23). Finally, as the number of arthroplasties increase we will probably also see an increase in revision surgery. In this area we have limited fast track data and both pain and morbidity may be more complex than in primary TKA and THA surgery.

Conclusions

I Perioperative carbohydrate nutrition to patients scheduled for THA has limited clinical benefits

II Comparing older, traditional regimens (including ITA with an opioid, tourniquet, indwelling urinary catheter and mobilisation the day after the surgery) for TKA with GA and a more Fast Track-like setup showed that the latter technique resulted in shorter LOS without adversely affecting pain scores and without a clinically significant increase in bleeding.

III. When using GA compared to ITA for TKA, patients in the latter group had a less favourable recovery profile in a Fast Track protocol.

IV When using GA compared to ITA for THA patients in the latter group showed the same results as TKA patients except for the fact that there was no difference in morphine consumption between the groups.

Populärvetenskaplig sammanfattning

Osteoartros (populärt kallat utsliten led) är ett vanligt tillstånd i höft- och knäled. Smärta, stelhet och minskade möjligheter att röra sig fritt är vanliga symtom. Att byta ut leden helt vid en operation är ett effektivt sätt att lindra patienternas besvär. Dessa operationer är vanliga i hela västvärlden och prognoser tyder på en tilltagande tendens i det årliga antalet operationer av detta slag. Traditionellt har dessa operationer genomförts med patienterna fastande, minst från och med midnatt före operationen. Likaledes har den dominerande tekniken för att erhålla en smärtfri operation varit att ge patienterna en ryggbedövning.

Vi har undersökt om det innebär några fördelar för patienterna som genomgår byte av höftleden att erhålla näringsdryck kort tid före operationsstart och igen direkt efter avslutad operation (studie I). Resultaten visade vissa förbättringar men dessa var av kliniskt tveksam betydelse.

Vi har också jämfört ett äldre, traditionellt sätt att sköta patienterna med bl.a. ryggbedövning, kateter i urinblåsan, sen mobilisering och avsnörande förband kring låret på de patienter som fick sin knäled bytt med narkos, utan kateter i urinblåsan, avsnörande bandage eller tidig mobilisering. Fynden från denna studie (studie II) visade gynnsamma resultat med den nyare tekniken avseende bl.a. sjukhusvistelsens längd.

I studie III ingick patienter som fick sin knäled bytt. Alla patienter erhöll samma vård med undantag av att hälften av patienterna fick ryggbedövning och hälften fick narkos. Vi fann att smärta, sjukhusvistelsens längd, illamående och kräkningar, yrsel, förbrukning av smärtlindrande medel samtliga visade på bättre resultat hos dem som fick narkos. Dessutom visade det sig att om patienterna, i händelse av en ytterligare operation själva fick välja så önskade fler patienter att få narkos istället för ryggbedövning .

I den sista studien (studie IV), som utfördes på patienter som genomgick byte av höftleden, jämfördes ryggbedövning och narkos på ovanstående sätt (studie III). Resultaten var likartade med studie III med den skillnaden att förbrukningen av smärtlindrande medicin efter operationen var identisk oavsett om patienterna fick narkos eller ryggbedövning.

Sammanfattningsvis visar resultaten av studierna som ingår i denna avhandling att näringsdryck omedelbart före och efter höftledsbyte resulterar i måttliga förbättringar för patienten. Att snabbt komma på benen och att undvika kateter i urinblåsan samt avsnörande förband på låret är gynnsamt för patienter som ska byta sin knäled. Att byta höft eller knäled i narkos istället för med ryggbedövning medför bättre komfort och kortare vårdtid för patienter som ska byta sin höft- eller knäled.

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References

1. årsrapport 2013. Svenska knäprotesregistret 2013.
2. Healthcare Cost and Utilization Project. 2007 Outcomes by patient and hospital characteristics for ICD-9-CM principal procedure code 81.54 Total Knee Replacement. 2009.
3. Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. Lancet 2012;380:1768-77.
4. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ. Knee replacement. Lancet 2012;379:1331-40.
5. Lalmohamed A, Vestergaard P, Klop C, Grove EL, de Boer A, Leufkens HG, van Staa TP, de Vries F. Timing of acute myocardial infarction in patients undergoing total hip or knee replacement: a nationwide cohort study. Arch Intern Med 2012;172:1229-35.
6. Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 2009;91:935-42.
7. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
8. Kneale J, Davis PS. Orthopedic and trauma nursing. Churchill Livingstone 2005;2nd. ed.
9. Crawford RW, Murray DW. Total hip replacement: indications for surgery and risk factors for failure. Ann Rheum Dis 1997;56:455-7.
10. Rissanen P, Aro S, Sintonen H, Slatis P, Paavolainen P. Quality of life and functional ability in hip and knee replacements: a prospective study. Qual Life Res 1996;5:56-64.
11. The national board of health and welfare. Statistics: The National board of health and welfare, 2008. 2009.
12. Thorngren. Swedish National Hip register: Yearbook: Annual Report for 2010 Lund, 2011. 2012.
13. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 2008;248:189-98.
14. Birkmeyer JD, Dimick JB, Staiger DO. Operative mortality and procedure volume as predictors of subsequent hospital performance. Ann Surg 2006;243:411-7.
15. Polk HC, Jr., Birkmeyer J, Hunt DR, Jones RS, Whittemore AD, Barraclough B. Quality and safety in surgical care. Ann Surg 2006;243:439-48.
16. Khuri SF, Henderson WG, Daley J, Jonasson O, Jones RS, Campbell DA, Jr., Fink AS, Mentzer RM, Jr., Steeger JE. The patient safety in surgery study: background, study design, and patient populations. J Am Coll Surg 2007;204:1089-102.

17. Main DS, Cavender TA, Nowels CT, Henderson WG, Fink AS, Khuri SF. Relationship of processes and structures of care in general surgery to postoperative outcomes: a qualitative analysis. J Am Coll Surg 2007;204:1147-56.
18. Schifftner TL, Grunwald GK, Henderson WG, Main D, Khuri SF. Relationship of processes and structures of care in general surgery to postoperative outcomes: a hierarchical analysis. J Am Coll Surg 2007;204:1166-77.
19. Rowell KS, Turrentine FE, Hutter MM, Khuri SF, Henderson WG. Use of national surgical quality improvement program data as a catalyst for quality improvement. J Am Coll Surg 2007;204:1293-300.
20. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002;183:630-41.
21. Kehlet H, Wilmore DW. Fast-track surgery. Br J Surg 2005;92:3-4.
22. Moiniche S, Hansen BL, Christensen SE, Dahl JB, Kehlet H. [Patients' activity and length of stay after hip arthroplasty with balanced analgesia and early mobilization]. Ugeskr Laeger 1992;154:1495-9.
23. Kehlet H, Thienpont E. Fast-track knee arthroplasty -- status and future challenges. Knee 2013;20 Suppl 1:S29-33.
24. Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, Kehlet H. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth 2011;106:230-8.
25. Kehlet H. [Painless and risk-free surgery--a vision of the future?]. Ugeskr Laeger 1994;156:3468-9.
26. Husted H. Fast-track hip and knee arthroplasty: clinical and organizational aspects. Acta Orthop 2012 Suppl;83:1-39.
27. Maltby JR. Fasting from midnight--the history behind the dogma. Best Pract Res Clin Anaesthesiol 2006;20:363-78.
28. Esahili AH, Boija PO, Ljungqvist O, Rubio C, Ware J. Twenty-four hour fasting increases endotoxin lethality in the rat. Eur J Surg 1991;157:89-95.
29. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr 2005;24:32-7.
30. Awad S, Constantin-Teodosiu D, Macdonald IA, Lobo DN. Short-term starvation and mitochondrial dysfunction - a possible mechanism leading to postoperative insulin resistance. Clin Nutr 2009;28:497-509.
31. Ljungqvist O, Thorell A, Gutniak M, Haggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. J Am Coll Surg 1994;178:329-36.
32. Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammarqvist F, Almstrom C, Lindh A, Thorell A, Ljungqvist O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg 2001;93:1344-50.
33. Kaska M, Grosmanova T, Havel E, Hyspler R, Petrova Z, Brtko M, Bares P, Bares D, Schusterova B, Pyszkova L, Tosnerova V, Sluka M. The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery--a randomized controlled trial. Wien Klin Wochenschr 2010;122:23-30.

34. Ljunggren S, Hahn RG, Nystrom T. Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: A double-blind, randomised controlled clinical trial. Clin Nutr, e-published ahead of print.
35. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Soreide E, Spies C, in't Veld B. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2011;28:556-69.
36. Ljunggren S, Hahn RG. Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. Trials 2012;13:97.
37. Yagci G, Can MF, Ozturk E, Dag B, Ozgurtas T, Cosar A, Tufan T. Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial. Nutrition 2008;24:212-6.
38. Yuan CS, Foss JF, O'Connor M, Roizen MF, Moss J. Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol 1998;38:1017-20.
39. Protic A, Turina D, Matanic D, Spanjol J, Zuvic-Butorac M, Sustic A. Effect of preoperative feeding on gastric emptying following spinal anesthesia: a randomized controlled trial. Wien Klin Wochenschr 2010;122:50-3.
40. Bouritius H, van Hoorn DC, Oosting A, van Middelaar-Voskuilen MC, van Limpt CJ, Lamb KJ, van Leeuwen PA, Vriesema AJ, van Norren K. Carbohydrate supplementation before operation retains intestinal barrier function and lowers bacterial translocation in a rat model of major abdominal surgery. JPEN J Parenter Enteral Nutr 2008;32:247-53.
41. Sutipornpalangkul W, Harnroongroj T. Protein depletion in Thai patients with hip fractures. J Med Assoc Thai 2007;90:2332-7.
42. Hahn RG, Ljunggren S. Preoperative insulin resistance reduces complications after hip replacement surgery in non-diabetic patients. BMC Anesthesiol 2013;13:39.
43. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr 2013;32:34-44.
44. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab 2001;280:E576-83.
45. Miller RD. Miller's anesthesia. 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier.
46. Schwilden H. A general method for calculating the dosage scheme in linear pharmacokinetics. Eur J Clin Pharmacol 1981;20:379-86.
47. Dorr LD. Regional anesthesia improves perioperative events in patients having total hip or knee replacement. J Bone Joint Surg Am 2010;92:1264.
48. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S, Callaghan JJ. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. J Bone Joint Surg Am 2013;95:193-9.
49. Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? Clin Orthop Relat Res 2009;467:2379-402.
50. Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anaesthesia improve outcome after total hip arthroplasty? A systematic review. Br J Anaesth 2009;103:335-45.

51. McCartney CJ, McLeod GA. Local infiltration analgesia for total knee arthroplasty. Br J Anaesth 2011;107:487-9.
52. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 2004;101:950-9.
53. Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth 2009;102:179-90.
54. Wattwil M. General or regional anaesthesia--pro general. Acta Anaesthesiol Scand Suppl 1997;110:54-5.
55. Fischer HB, Simanski CJ. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia 2005;60:1189-202.
56. Fischer HB, Simanski CJ, Sharp C, Bonnet F, Camu F, Neugebauer EA, Rawal N, Joshi GP, Schug SA, Kehlet H. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. Anaesthesia 2008;63:1105-23.
57. Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. Acta Orthop 2008;79:174-83.
58. Wall PD. The prevention of postoperative pain. Pain 1988;33:289-90.
59. Katz J, McCartney CJ. Current status of preemptive analgesia. Curr Opin Anaesthesiol 2002;15:435-41.
60. Anaesthesia 1998;53, Supplement S1.
61. Mirakhur RK, Morgan M. Intravenous anaesthesia: a step forward. Anaesthesia 1998;53 Suppl 1:1-3.
62. Doze VA, Shafer A, White PF. Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anesthesia. Anesthesiology 1988;69:63-71.
63. Millar JM, Jewkes CF. Recovery and morbidity after daycase anaesthesia. A comparison of propofol with thiopentone-enflurane with and without alfentanil. Anaesthesia 1988;43:738-43.
64. Juckenhofel S, Feisel C, Schmitt HJ, Biedler A. [TIVA with propofol-remifentanil or balanced anesthesia with sevoflurane-fentanyl in laparoscopic operations. Hemodynamics, awakening and adverse effects]. Anaesthesist 1999;48:807-12.
65. Wang Y, Yan M, He JG, Zhu YM, Hu XS, Li X, Wu WD. A randomized comparison of target-controlled infusion of remifentanil and propofol with desflurane and fentanyl for laryngeal surgery. ORL J Otorhinolaryngol Relat Spec 2011;73:47-52.
66. Marsh BJ, Morton NS, White M, Kenny GN. A computer controlled infusion of propofol for induction and maintenance of anaesthesia in children. Can J Anaesth 1990;37:S97.
67. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997;86:24-33.
68. Sites BD, Beach M, Biggs R, Rohan C, Wiley C, Rassias A, Gregory J, Fanciullo G. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty. Anesth Analg 2003;96:1083-8.

69. Eisenach JC, De Kock M, Klimscha W. alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996;85:655-74.
70. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. Br J Anaesth 2013;110:21-7.
71. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology 1994;81:591-601; discussion 27A-28A.
72. Bailey PL, Rhondeau S, Schafer PG, Lu JK, Timmins BS, Foster W, Pace NL, Stanley TH. Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993;79:49-59; discussion 25A.
73. Bianconi M, Ferraro L, Traina GC, Zanoli G, Antonelli T, Guberti A, Ricci R, Massari L. Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. Br J Anaesth 2003;91:830-5.
74. Kehlet H, Andersen LO. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. Acta Anaesthesiol Scand 2011;55:778-84.
75. Andersen KV, Nikolajsen L, Haraldsted V, Odgaard A, Soballe K. Local infiltration analgesia for total knee arthroplasty: should ketorolac be added? Br J Anaesth 2013;111:242-8.
76. Kollinius-Bringland M, Affas F, Wretenberg P. [Acute renal failure after local infiltration anesthesia. Two cases related to orthopedic surgery described]. Lakartidningen 2013;110:284-5.
77. Lunn TH, Husted H, Solgaard S, Kristensen BB, Otte KS, Kjersgaard AG, Gaarn-Larsen L, Kehlet H. Intraoperative local infiltration analgesia for early analgesia after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Reg Anesth Pain Med 2011;36:424-9.
78. Solovyova O, Lewis CG, Abrams JH, Grady-Benson J, Joyce ME, Schutzer SF, Arumugam S, Caminiti S, Sinha SK. Local infiltration analgesia followed by continuous infusion of local anesthetic solution for total hip arthroplasty: a prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am 2013;95:1935-41.
79. Kuchalik J, Granath B, Ljunggren A, Magnuson A, Lundin A, Gupta A. Postoperative pain relief after total hip arthroplasty: a randomized, double-blind comparison between intrathecal morphine and local infiltration analgesia. Br J Anaesth 2013;111:793-9
80. Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: anesthetic and perioperative considerations. Anesthesiology 2009;110:1139-57.
81. Balderi T, Carli F. Urinary retention after total hip and knee arthroplasty. Minerva Anestesiol 2010;76:120-30.
82. Viscusi ER, Martin G, Hartrick CT, Singla N, Manvelian G. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. Anesthesiology 2005;102:1014-22.
83. Oishi CS, Williams VJ, Hanson PB, Schneider JE, Colwell CW, Jr., Walker RH. Perioperative bladder management after primary total hip arthroplasty. J Arthroplasty 1995;10:732-6.
84. Sokol AI, Jelovsek JE, Walters MD, Paraiso MF, Barber MD. Incidence and predictors of prolonged urinary retention after TVT with and without concurrent prolapse surgery. Am J Obstet Gynecol 2005;192:1537-43.

85. Souter KJ PD. Bladder function after ambulatory surgery. Journal of Ambulatory Surgery 2005;12:89-97.
86. Waterhouse N, Beaumont AR, Murray K, Staniforth P, Stone MH. Urinary retention after total hip replacement. A prospective study. J Bone Joint Surg Br 1987;69:64-6.
87. Tenke P, Kovacs B, Bjerklund Johansen TE, Matsumoto T, Tambyah PA, Naber KG. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008;31 Suppl 1:S68-78.
88. Iorio R, Whang W, Healy WL, Patch DA, Najibi S, Appleby D. The utility of bladder catheterization in total hip arthroplasty. Clin Orthop Relat Res 2005:148-52.
89. Hakvoort RA, Thijs SD, Bouwmeester FW, Broekman AM, Ruhe IM, Vernooij MM, Burger MP, Emanuel MH, Roovers JP. Comparing clean intermittent catheterisation and transurethral indwelling catheterisation for incomplete voiding after vaginal prolapse surgery: a multicentre randomised trial. BJOG 2011;118:1055-60.
90. Miller AG, McKenzie J, Greenky M, Shaw E, Gandhi K, Hozack WJ, Parvizi J. Spinal anesthesia: should everyone receive a urinary catheter?: a randomized, prospective study of patients undergoing total hip arthroplasty. J Bone Joint Surg Am 2013;95:1498-503.
91. Jans O, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H. Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. Br J Anaesth 2011;108:436-43.
92. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop 2011;82:679-84.
93. Bundgaard-Nielsen M, Jans O, Muller RG, Korshin A, Ruhnau B, Bie P, Secher NH, Kehlet H. Does Goal-directed Fluid Therapy Affect Postoperative Orthostatic Intolerance?: A Randomized Trial. Anesthesiology 2013;119:813-23.
94. Husted H, Holm G, Rud K, Bach-Dal C, Hansen HC, Andersen KL, Kehlet H. [Length of stay after primary total hip and knee arthroplasty in Denmark, 2001-2003]. Ugeskr Laeger 2006;168:276-9.
95. Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. Acta Orthop 2008;79:168-73.
96. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark. Arch Orthop Trauma Surg 2010;130:263-8.
97. Lunn TH, Andersen LO, Kristensen BB, Husted H, Gaarn-Larsen L, Bandholm T, Ladelund S, Kehlet H. Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Br J Anaesth 2013;110:66-73.
98. Jorgensen CC, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. Br J Anaesth 2013;110:972-80.
99. Jorgensen CC, Kehlet H. Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. Acta Anaesthesiol Scand 2013;57:631-8.

100. Wu CL, Rowlingson AJ, Partin AW, Kalish MA, Courpas GE, Walsh PC, Fleisher LA. Correlation of postoperative pain to quality of recovery in the immediate postoperative period. Reg Anesth Pain Med 2005;30:516-22.
101. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 2003;362:1921-8.
102. Kehlet H. Postoperative opioid sparing to hasten recovery: what are the issues? Anesthesiology 2005;102:1083-5.
103. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F. The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. Anesth Analg 2007;104:1380-96, table of contents.
104. Paul JE, Nantha-Aree M, Buckley N, Cheng J, Thabane L, Tidy A, DeBeer J, Winemaker M, Wismer D, Punthakee D, Avram V. Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial. Can J Anaesth 2013;60:423-31.
105. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain Intensity on the First Day after Surgery: A Prospective Cohort Study Comparing 179 Surgical Procedures. Anesthesiology 2013;118:934-44.
106. Andersen LO, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia 2009;64:508-13.
107. Puolakka PA, Rorarius MG, Roviola M, Puolakka TJ, Nordhausen K, Lindgren L. Persistent pain following knee arthroplasty. Eur J Anaesthesiol 2010;27:455-60.
108. Rakel BA, Blodgett NP, Bridget Zimmerman M, Logsden-Sackett N, Clark C, Noiseux N, Callaghan J, Herr K, Geasland K, Yang X, Sluka KA. Predictors of postoperative movement and resting pain following total knee replacement. Pain 2012;153:2192-203.
109. Gan TJ, Alexander R, Fennelly M, Rubin AP. Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. Anesth Analg 1995;80:81-5.
110. Kauste A, Tuominen M, Heikkinen H, Gordin A, Korttila K. Droperidol, alizapride and metoclopramide in the prevention and treatment of post-operative emetic sequelae. Eur J Anaesthesiol 1986;3:1-9.
111. DiIorio TM, Sharkey PF, Hewitt AM, Parvizi J. Antiemesis after total joint arthroplasty: does a single preoperative dose of aprepitant reduce nausea and vomiting? Clin Orthop Relat Res 2010;468:2405-9.
112. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999;91:8-15.
113. Cole PJ, Craske DA, Wheatley RG. Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. Br J Anaesth 2000;85:233-7.
114. Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg 2003;97:1452-7.
115. Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 1998;87:88-92.

116. Oddby-Muhrbeck E, Eksborg S, Helander A, Bjellerup P, Lindahl S, Lonnqvist P. Blood-borne factors possibly associated with post-operative nausea and vomiting: an explorative study in women after breast cancer surgery. Acta Anaesthesiol Scand 2005;49:1346-54.
117. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005;100:475-80.
118. Dorr LD, Chao L. The emotional state of the patient after total hip and knee arthroplasty. Clin Orthop Relat Res 2007;463:7-12.
119. Mallory TH, Lombardi AV, Jr., Fada RA, Dodds KL, Adams JB. Pain management for joint arthroplasty: preemptive analgesia. J Arthroplasty 2002;17:129-33.
120. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, Collins KS. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002;359:1276-82.
121. Memtsoudis SG, Sun X, Chiu YL, Stundner O, Liu SS, Banerjee S, Mazumdar M, Sharrock NE. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology 2013;118:1046-58.
122. Leslie K, Myles P, Devereaux P, Williamson E, Rao-Melancini P, Forbes A, Xu S, Foex P, Pogue J, Arrieta M, Bryson G, Paul J, Paech M, Merchant R, Choi P, Badner N, Peyton P, Sear J, Yang H. Neuraxial block, death and serious cardiovascular morbidity in the POISE trial. Br J Anaesth 2013;111:382-90.
123. Katz JN, Barrett J, Mahomed NN, Baron JA, Wright RJ, Losina E. Association between hospital and surgeon procedure volume and the outcomes of total knee replacement. J Bone Joint Surg Am 2004;86-A:1909-16.
124. Katz JN, Losina E, Barrett J, Phillips CB, Mahomed NN, Lew RA, Guadagnoli E, Harris WH, Poss R, Baron JA. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States medicare population. J Bone Joint Surg Am 2001;83-A:1622-9.
125. Andersen LO, Kristensen BB, Husted H, Otte KS, Kehlet H. Local anesthetics after total knee arthroplasty: intraarticular or extraarticular administration? A randomized, double-blind, placebo-controlled study. Acta Orthop 2008;79:800-5.
126. Harsten A, Kehlet H, Toksvig-Larsen S. Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial. Br J Anaesth 2013;111:391-9.
127. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ 2011;342:d1165.
128. Brooks PM. The burden of musculoskeletal disease--a global perspective. Clin Rheumatol 2006;25:778-81.
129. Leigh JP, Seavey W, Leistikow B. Estimating the costs of job related arthritis. J Rheumatol 2001;28:1647-54.
130. Lauwick SM, Kaba A, Maweja S, Hamoir EE, Joris JL. Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy. Acta Anaesthesiol Belg 2009;60:67-73.
131. Cunliffe A, Obeid OA, Powell-Tuck J. Post-prandial changes in measures of fatigue: effect of a mixed or a pure carbohydrate or pure fat meal. Eur J Clin Nutr 1997;51:831-8.

132. Protic A, Tokmadzic VS, Sustic A. Oral carbohydrate treatment before surgery. Eur J Anaesthesiol 2012;29:259-60.
133. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011;115:575-88.
134. Estebe JP, Davies JM, Richebe P. The pneumatic tourniquet: mechanical, ischaemia-reperfusion and systemic effects. Eur J Anaesthesiol 2011;28:404-11.
135. Holm B, Kristensen MT, Myhrmann L, Husted H, Andersen LO, Kristensen B, Kehlet H. The role of pain for early rehabilitation in fast track total knee arthroplasty. Disabil Rehabil 2010;32:300-6.
136. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesth Analg 2010;110:199-207.
137. Katz J. A survey of anesthetic choice among anesthesiologists. Anesth Analg 1973;52:373-5.
138. McCartney CJ, Choi S. Does anaesthetic technique really matter for total knee arthroplasty? Br J Anaesth 2013;111:331-3.
139. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet 2011;377:2215-25.
140. Lunn TH, Kehlet H. Perioperative glucocorticoids in hip and knee surgery - benefit vs. harm? A review of randomized clinical trials. Acta Anaesthesiol Scand 2013;57:823-34.