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**Author:** Thomassen, Bregje J.W.
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Chapter 1

Introduction and research questions
The number of hip (THA) and knee (TKA) arthroplasties performed in the Netherlands is still rising. During the first five years of the Dutch LROI database (2007-2011) 105,455 primary hip arthroplasties and 79,272 primary knee arthroplasties were registered.\(^1\) As of June 2014 about 150,000 TKA and 200,000 THA are registered. The projected increase until 2020 in prevalence of hip and knee arthroplasties will have important ramifications with regard to the number of joint arthroplasties expected and the subsequent increase in health care costs.\(^2\)

Health care costs are expanding and in all areas solutions are being sought to decrease the national burden of health care. The changes of the last decennia in daily orthopaedic practice, especially the increase in not only the number of total joint arthroplasties, but also in faster postoperative rehabilitation is considerable. The introduction of fast-track surgery by means of clinical pathways for elective joint arthroplasties has reduced some part the in-hospital inefficiency. Furthermore, techniques for reducing ‘surgical stress’ made a large change in the postoperative rehabilitation program.\(^3\) After surgical injury the body responds with profound changes in neural, endocrine and metabolic systems in addition to alterations in organ functions.\(^4-6\) These changes represent an universally conserved cellular defence mechanism of the body, but the stress-induced changes in postoperative organ function may also be implicated in the development of postoperative complications.\(^5,7\) Both pain and blood management are important issues, in order to reduce this surgical stress response, which could counteract fast postoperative rehabilitation.

**PAIN MANAGEMENT**

In the last decades the focus in pain management was on the prevention of side effects, such as drowsiness or nausea. The implemented analgesia regime to enhance faster postoperative recovery and reduce morbidity to the patient was achieved with a multimodal approach.\(^8,9\) This approach should minimize stimuli at each nervous level (central and peripheral) and limit activation of the central nervous system. The use of a variety of medications at relatively low doses takes advantage of multiple pain modulators. Thus, the medication addresses several different steps along the pain pathway, which results in lower narcotic use and therefore fewer side effects that interfere with mobilisation.

Pre-emptive analgesia is a pillar in this concept, the medication is given before the surgical injury takes place, in order to block the transmission to the nervous system as early as possible.\(^10-12\) Better pain control and fewer side effects are present than when a single modality (i.e. opioids) is used.\(^10-12\) Although there is still debate on the concept of
pre-emptive analgesia, more local analgesia techniques in THA and TKA were introduced in addition to the current gold standards of locoregional anaesthesia such as spinal or epidural.\textsuperscript{13} The beneficial effects of a femoral nerve block or local infiltration analgesia (LIA) in TKA have been widely studied in recent years.\textsuperscript{14-17} Different mixtures (content of the technique, composition of the LIA solution) and types of local infiltration (with or without catheter and its placement) are used around the world.\textsuperscript{15,18} Since LIA in THA and TKA has great effects on postoperative rehabilitation, it will also have implications on perioperative patient blood management. The impact of high-volume local infiltrations on the collection of shed blood for autologous blood transfusion is unknown.

**BLOOD MANAGEMENT**

Total hip and knee arthroplasty surgery have significant perioperative blood loss; the combined visible and invisible blood loss is reported to be 1500 mL on average.\textsuperscript{19,20} This blood loss eventually causes a decrease in the postoperative haemoglobin (Hb) level of approximately 3 g/dL.\textsuperscript{19} Therefore blood transfusions are frequently reported after this type of surgery. Nevertheless, a large variation in perioperative transfusion rates have been reported, with up to 69\% of patients being transfused, depending mainly on the used transfusion policy.\textsuperscript{21}

During the last two decades great efforts have been made to change the practice of a liberal blood transfusion policy to a more restrictive policy.\textsuperscript{22-24} The awareness that the HIV and hepatitis virus could be transmitted through allogeneic blood transfusions in the early 1980’s changed the attitude of both physicians as well as the public to the inherent risks of allogeneic blood. This also stimulated the emerging of a new discipline: ‘Transfusion Medicine’.\textsuperscript{25}

The restrictive blood transfusion policy, i.e. awareness and a strict transfusion trigger (the so-called 4-5-6 (mmol/L) rule that is currently advised in the Netherlands) has led to a decrease in allogeneic blood transfusions by 30-40\% in THA and TKA.\textsuperscript{26,27} Next to a restrictive blood transfusion policy several techniques for reducing the need for allogeneic blood transfusions became available. Alternatives for an allogeneic blood transfusion can be subdivided in two main groups: non-pharmaceutical interventions and pharmaceutical interventions.\textsuperscript{28,29}

The **non-pharmaceutical interventions** consist of preoperative autologous donation, perioperative normovolaemic haemodilution, the use of a perioperative cell saver or postoperative autologous blood retransfusion devices.
The pharmaceutical interventions comprise the pre-operative use of erythropoietin with (or without) iron supplementation, the perioperative use of anti-fibrinolytics such as tranexamic acid or fibrin glue.

Although we see a clear downward trend in transfusion needs, still many controversies are present about both the clinical effectiveness and the cost effectiveness of these alternatives. Although there is an awareness of transfusion medicine nowadays, the optimal algorithm for using these transfusion alternatives remains unclear. In addition, reported effects of many transfusion alternatives differ extensively leading to questions on methodology quality of PBM trials. Guyatt and co-workers developed several guidelines on this topic of quality assessment.\textsuperscript{30-32} Especially in surgical randomised clinical trials, bias is to a great extent determined by absence of concealment of allocation, blinding of patients (where possible) and outcome assessors and lost to follow-up.\textsuperscript{33-35} Evaluation of the quality of blood management trials comprises the second part of this thesis.

**SCOPE OF THE THESIS**

Evaluation of postoperative patient pain management (PPM) and patient blood management (PBM) in elective total knee and total hip arthroplasty:

- **Patient Pain Management (PPM)**
  - Postoperative analgesia in TKA patients with a more local technique, a femoralis block. What is an optimal dose in patients for an equipoise between pain and sufficient strength for postoperative rehabilitation (chapter 2)
  - Patient safety in presence of local infiltration analgesia (LIA) and autologous blood reinfusion devices in total knee arthroplasty (chapter 3, 4)

- **Patient Blood Management (PBM)**
  - An evaluation of two different transfusion alternatives was carried out in patients with specific haemoglobin values (chapter 5)
  - A cost calculation for erythropoietin alpha in daily practice was made based on the cost saving data in literature and transfusion figures from two large teaching hospitals (chapter 6)
  - Transfusion of shed blood collected with an autologous blood transfusion device is possible within 6 hours postoperative. Is there a difference in efficacy and an additional value of an autologous transfusion device (chapter 7)
• A new intra- and postoperative cell saving device was tested in revision and primary THA with the hypothesis that it would reduce allogeneic blood transfusions in the postoperative phase (chapter 8)

  Two methodological aspects in PBM trials were investigated. Firstly, the aspect of blinding is important in the conduct of a clinical trial but is it also important to be blind for study results when evaluating risk of bias (chapter 9). Secondly, the heterogeneity in drainage trials is investigated because transfusion figures divers significantly. Which variables are of additional value when transfusion trials are being compared (chapter 10).
REFERENCES

1. Nederlandse Orthopaedische Vereniging, Dutch Arthroplasty Registry (LROI), 2013


