## Continuous-flow cryocompression therapy after hip fracture surgery

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# Chapter 8

## Summary and general discussion

The present thesis addresses several aspects regarding continuous-flow cryocompression therapy (CFCT) after hip fracture surgery in order to treat pain and mitigate postoperative haemorrhage. By exploring its efficacy and by determining the thermodynamic aspects of CFCT an attempt is made to elucidate the treatment mechanism and define deep tissue temperature reduction. Furthermore, by use of a mesenchymal stem cell (MSC) model, we aimed to provide insight in the mechanism of effect of cryotherapy on MSC's. Thorough knowledge of these aspects will help clinicians to decide whether to instigate this therapy for patients after hip fracture surgery.

## Cryotherapy techniques, indications and outcomes

The traditional application of cryotherapy concerns applying a frozen substance or ice water to the target area, but nowadays a wide array of commercially available machines applies the cooling principles of cryotherapy. Although each apparatus' design is unique, a certain distinction can be made. While the first machines applied cryotherapy intermittently (manual 're-chilling' of the wrap was necessarily), the current machines are equipped with an internal pump facilitating an adjustable continuous-flow of ice-cold water, and most are also embedded with a dynamic pneumatic pressure adjunct. The pneumatic pressure adjunct increases the density of the target area, thereby further augmenting the cooling efficacy[1]. In **chapter 2** we provided an overview of fluid-based continuous-flow cryotherapy with and without a compression adjunct that is applied in the acute recovery phase of surgical repair for musculoskeletal injury of the lower extremity.

Cryotherapy is applied after total knee arthroplasty (TKA)[2,3], unicondylar knee arthroplasty[4], anterior cruciate ligament reconstruction[5–10], footfractures[11], arthroscopy[12] and after total hip arthroplasty (THA)[13–15]. In our overview half of the caseload in which cryotherapy is applied is after knee surgery. Not surprisingly in TKA and unicondylar knee arthroplasty high perceived postoperative pain scores that may limit postoperative mobilisation are not uncommon[16,17]. Cryotherapy is frequently instigated as part of a multimodal analgesic regimen, but only one study in our overview reported a profound analgesic effect after TKA[13], and the remainder of the studies found no convincing clinical effect on pain or postoperative haemorrhage. The moderate effect of cryotherapy is confirmed in meta-analyses[2,3], and the compression adjunct does seem to increase treatment efficacy after TKA. In contrast to knee surgery, few reports exist that assess the efficacy of cryotherapy after total hip arthroplasty. We only found three studies that reported on the analgesic efficacy of cryotherapy after elective total hip arthroplasty for end-stage

osteoarthritis (THA-OA). Herein two studies report an interesting decline in early pain scores as well as a moderate decline in analgesic use, but no clinical relevant results implicate that postoperative haemorrhage is mitigated. Strikingly, only one study assessed cryotherapy after acute bony trauma[11]. Stöckle et al. found no analgesic efficacy of cryotherapy, but did demonstrate a reduction of swelling after foot fracture surgery. It is remarkable that CFCT is not instigated more often for analgesic purposes after a sustained or fixated fracture, since fractures are generally accompanied by soft tissue trauma and oedema that are aggravated by subsequent surgical fixation. Due to this duplicate trauma these patients, and especially patients with extensive soft tissue trauma such as in hip surgery, should benefit most from CFCT.

Cryotherapy can be judged as safe, only 1.51% (9 of 596 patients) that received cryotherapy reported mild adverse events, which resolved after cessation. In addition incidence of serious cryotherapy-related complications is reported to be 0.0023%[18].

This study provides a clear overview that reveals significant treatment heterogeneity, and remarkably found only one study that assessed cryotherapy in fractures. All studies applied cryotherapy in a different way: duration, frequency, type of machine, use of a compression adjunct (static or dynamic), and temperature setting. These inconsistencies illustrate the lack of an evidence-based derivative that guides optimal treatment. Current recommendations are mostly based on old data and expert opinions that are based on clinical outcomes[13]. Since each treatment locus on the body has unique characteristics this derivative may vary. Future research should focus on a better understanding of the physiological effects of cooling; consequently a clear derivative should be developed that advocates how cryotherapy treatment can be optimized.



## Cryotherapy after hip surgery

In **chapter 3**, we aimed to determine the efficacy of CFCT after elective THA-OA. We demonstrated CFCT to reduce postoperative haemorrhage at day one, and subjects were positive about CFCT, but no effects were observed on postoperative pain or analgesic use. Shortly after this study had finished fast track protocols for THA-OA were implemented in our hospital that employ aggressive analgesic strategies together with immediate and stringent postoperative mobilisation. Applying cryotherapy parallel to these fast track protocols does not seem feasible *in a clinical setting*. However due to the positive findings in our THA-OA study, the relative similarity between THA-OA and hip fracture patients and that hip fracture

patients experience severe postoperative pain with duplicate trauma[16,19], we conducted a more extensive variant of this study in a multicentre setting in a hip fracture population.

Hip fracture patients are a heterogeneous group treated surgically with cannulated hip screws, (hemi) arthroplasty, dynamic hip screw or with a intramedullary hip nail according to fracture type and the clinical patient profile[20,21]. In hip fracture patients altered pharmacodynamics and kinetics narrow the therapeutic window and consequently limit the use op opioid-based analgesics, combined with the painful nature of a hip fracture this leads to increased difficulty in providing adequate analgesia to hip fracture patients[16,19]. In **chapter 4 and 5**, we respectively report the design and the results of our multicentre trial that aimed to determine the efficacy of CFCT in the postoperative recovery phase of hip fracture patients. We found a mild reduction in numeric rating scale pain after 3 days of complete (per protocol) treatment, but no differences were found in analgesic use or on the other outcome parameters. The reduction in pain was not demonstrated in the regular intention to treat analysis, where 28% reported discomfort (usually cold intolerance) and 15.6% dropped out prematurely (usually at the first treatment). The remainder of the subjects were generally positive about their experiences with CFCT. The complication rates between groups were not significantly different.

The study in **chapter** 5 is the first to provide the results of CFCT, a non-pharmacological analgesic intervention, in a frail elderly hip fracture population. Conducting research with elderly remains challenging as declined perception and comprehension to understand study specific actions may cause additional anxiety and stressors, both of which have been related to an increase pain perception, which consequently may obfuscate a treatment effect[22]. It may also explain the high drop out rates that was observed in our study, as failure to comprehend the intention of study interventions will inevitably lead to uncooperative or unwilling subjects. Still, we were unable to demonstrate neither a significant decline in analgesic use nor a decline in postoperative haemorrhage. The staggering 50% decline in analgesic use that was previously reported seems unrealistic[13], as the other sparse studies report diverging analgesic efficacy[14,15].

In sub analyses we did not find evidence that the type of surgery was related to CFCT efficacy. Postoperative pain originates from soft tissue trauma and from bone trauma, in case of minimally invasive intramedullary hip nail, dynamic hip screw or cannulated hip screws the fracture site allows for painful micro motion[19], while in (hemi) arthroplasty the fracture site is removed, but at the expense of increased soft tissue trauma. Therefore dynamic (on locomotion) pain scores are much lower after (hemi) arthroplasty and fixation of undisplaced

hip fractures[19]. We hypothesized that CFCT only reduces pain that originates from soft tissue trauma, and does not reduce the pain that originates from deeper fracture micro motion pain. Hence static pain was measured as opposed to dynamic pain that incorporates fracture micro motion to a degree. Bone injury and micro motion are more painful than soft tissue injury because the periosteum has the lowest pain threshold of the deep somatic tissue. Currently it is unknown if CFCT penetrates to the bone level where it might reduce bone-derived pain, therefore future trials should assess pain during specific functions e.g. walking to assess for a analgesic effect on bone-derived pain.

## Continuous-flow cryocompression therapy thermodynamics

The analgesic efficacy of cryotherapy differs in various treatment foci such as in THA, TKA and after fixation or (hemi) arthroplasty of hip fractures, and it is not clearly established how cryotherapy exerts its analgesic effect. Two theories can be proposed: either superficial via an interaction on nerve conduction, or deep via an interaction with tissue metabolism and immunomodulation, or a combination of these theories. The demonstrated moderate efficacy of cryotherapy in TKA and the diverging results in the sparse THA reports are puzzling, but might be explained by the varying extent of soft tissue trauma. A major difference between the knee and hip joint is the extent of the connective tissue layer. While the knee virtually lacks a fat layer, a layer of up to several centimetres thick surrounds most hip joints. This connective (and fat) tissue layer has significant implications when it comes to the cooling efficacy of cryotherapy because penetration depth of cryotherapy and thickness of this subcutaneous tissue layer are strongly inversely related[23]. This inverse relation may contribute to the observed lack of efficacy observed in THA patients.

In **chapter 6**, we aimed to define deep tissue temperature during CFCT in postoperative hip fracture patients, by using measured skin temperature as input parameter for a simple numerical model. Second, the association between tissue temperature distribution and pain reduction was investigated to assess cryotherapy-induced analgesia of soft tissue derived pain. Thereby trying to substantiate our hypothesis stating that: CFCT does not reach the bone level, but that increased soft tissue penetration is associated with reduced numeric rating scale pain levels, consequently providing evidence that CFCT analgesia is mediated by attenuating soft tissue derived pain. We found CFCT to reduce temperature up to 3 cm in postoperative hip fracture patients. Forty-two per cent of our patients had a soft tissue layer of less than 3 cm in our study group, thus in these cachectic patients CFCT reduces temperature at the bone, where it might have implications for bone tissue healing when treated for a prolonged period

of time. However no association between tissue temperature distribution and pain reduction was demonstrated. Pain in hip fracture patients originates from traumatized skin, as well as trauma to muscle and bone tissue. The cryotherapy-induced skin analgesia apparently is insufficient for patients to perceive, because an equivalent or greater amount of pain originates from the deeper muscular and/or bone regions. The lack of an association between tissue temperature distribution and pain reduction illustrates this hypothesis, stating that CFCT only provides skin analgesia, and insufficiently or incompletely cools muscle and bone tissue in order to provide analgesia at these regions.

## Effects of cryotherapy in a mesenchymal stem cell model

Cryotherapy is used in an attempt to reduce pain in various musculoskeletal injuries, but its effect on the cells responsible for bone healing is unknown. It is well known that cryotherapy reduces tissue metabolism[24], but in the case of a recent fracture or fixation of a fracture, an elevated metabolic state, able to produce fracture callus and bone remodelling is warranted. Since we demonstrated that CFCT is able to reduce temperature at the bone level in cachectic patients in **chapter 6**, it should be explored if cryotherapy adversely affects osteoblast precursor proliferation and differentiation, cell functions that are responsible for bone tissue repair, in order to avert iatrogenic non or delayed unions of fractures.

**Chapter 7** presents the results of hypothermia in a MSC model under hypoxic conditions, thereby providing insight in the mechanism of the effect of cryotherapy on MSCs. In these experiments hypoxia was used as a surrogate for a sustained fracture. The combination of hypothermia and hypoxia decreased *VEGF*-165, which is a marker for vasculogenesis. Although differentiation and proliferation of MSC's were uninfluenced, the blunting of *VEGF*-165 could have implications for callus vascularisation, a later stage of bone healing. Our *in vitro* results implicate that hypothermia treatment *in vivo* that is applied to alleviate pain and inflammation, is not likely to harm early stages of callus formation but might have implications for later stages.

Our study is the first to describe the *in vitro* effects of hypothermia in a MSC model under hypoxia. Although more *in vivo* research is necessarily in order to draw firm conclusions about the effect of cryotherapy on bone repair. Our results from **chapter 6** demonstrated that in cachectic patients CFCT reduces temperature in a degree equivalent to our MSC experiments. Therefore application of CFCT might have adverse effects on the later stages of bone healing if it is applied for a prolonged period of time.

## Conclusions

The studies presented in this thesis have led to the following conclusions regarding the application of CFCT after hip fracture surgery and hypothermia:

- Cryotherapy is predominately applied after (semi) elective surgery, where its application for the various musculoskeletal injuries is heterogeneous and safe, it offers a mild reduction of opioid consumption and blood loss;
- Continuous-flow cryotherapy reduces postoperative blood loss after THA-OA one day after surgery and is valued by patients, it does not reduce pain;
- Continuous-flow cryotherapy has no analgesic benefits in the acute postoperative recovery phase of hip fracture surgery, nor does it reduce postoperative blood loss;
- In patients with soft tissue skin layer of less than 3 cm continuous-flow cryocompression therapy penetrates to the bone level in hip fracture patients;
- Tissue temperature reduction by continuous-flow cryocompression therapy and pain perception of hip fracture patients is not related. This might suggest that cryotherapy-induced analgesia originates from skin analgesia, rather than analgesia of muscle or bone derived pain;
- Hypothermia decreases *VEGF-165* gene and protein expression, but does not affect differentiation, or apoptosis of MSCs cultured under hypoxia. This implicates that hypothermia treatment *in vivo*, applied to alleviate pain and inflammation, is not likely to harm early stages of callus formation.

## References


1. Holwerda SW, Trowbridge CA, Womochel KS and Keller DM. Effects of cold modality application with static and intermittent pneumatic compression on tissue temperature and systemic cardiovascular responses. *Sports Health* **5,** 27–33 (2013).
2. Adie S, Naylor JM and Harris I. Cryotherapy after total knee arthroplasty a systematic review and meta-analysis of randomized controlled trials. *J. Arthroplasty* **25,** 709–715 (2010).
3. Song, M. *et al.* Compressive cryotherapy versus cryotherapy alone in patients undergoing knee surgery: a meta-analysis. *Springerplus* **5,** 1–12 (2016).
4. Holmström A and Härdin BC. Cryo/Cuff compared to epidural anesthesia after knee unicompartmental arthroplasty. *J. Arthroplasty* **20,** 316–321 (2005).
5. Barber FA, McGuire DA and Click S. Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction. *Arthroscopy* **14,** 130–5 (1998).
6. Cohn BT, Draeger RI and Jackson DW. The effects of cold therapy in the postoperative management of pain in patients undergoing anterior cruciate ligament reconstruction. *Am. J. Sports Med.* **17,** 344–349 (1989).
7. Daniel DM, Stone ML and Arendt DL. The effect of cold therapy on pain, swelling, and range of motion after anterior cruciate ligament reconstructive surgery. *Arthroscopy* **10,** 530–533 (1994).
8. Dervin GF, Taylor DE and Keene GC. Effects of cold and compression dressings on early postoperative outcomes for the arthroscopic anterior cruciate ligament reconstruction patient. *J. Orthop. Sports Phys. Ther.* **27,** 403–406 (1998).
9. Konrath GA, Lock T, Goitz HT and Scheidler J. The use of cold therapy after anterior cruciate ligament reconstruction. A prospective, randomized study and literature review. *Am. J. Sports Med.* **24,** 629–633 (1996).
10. Ohkoshi Y. *et al.* The effect of cryotherapy on intraarticular temperature and postoperative care after anterior cruciate ligament reconstruction. *Am. J. Sports Med.* **27,** 357–362 (1999).
11. Stockle U, Hoffmann R, Sudkamp NP and Haas N. Continuous cryotherapy--progress in therapy of post-traumatic and postoperative edema. *Unfallchirurg* **98,** 154–159 (1995).
12. Woolf SK, Barfield WR, Merrill KD and McBryde AMJ. Comparison of a continuous temperature-controlled cryotherapy device to a simple icing regimen following outpatient knee arthroscopy. *J. Knee Surg.* **21,** 15–19 (2008).
13. Albrecht S. *et al.* Cryotherapy as analgesic technique in direct, postoperative treatment following elective joint replacement. *Z. Orthop. Ihre Grenzgeb.* **135,** 45–51 (1997).
14. Scarcella JB and Cohn BT. The effect of cold therapy on the postoperative course of total hip and knee arthroplasty patients. *Am. J. Orthop.* **24,** 847–52 (1995).
15. Saito N, Horiuchi H, Kobayashi S, Nawata M and Takaoka K. Continuous local cooling for pain relief following total hip arthroplasty. *J. Arthroplasty* **19,** 334–337 (2004).
16. Chung F, Ritchie E and Su J. Postoperative pain in ambulatory surgery. *Anesth. Analg.* **85,** 808–16 (1997).
17. Chan EY, Blyth FM, Nairn L and Fransen M. Acute postoperative pain following hospital discharge after total knee arthroplasty. *Osteoarthr. Cartil.* **21,** 1257–1263 (2013).
18. Wilke B and Weiner RD. Postoperative cryotherapy: risks versus benefits of continuous-flow cryotherapy units. *Clin. Podiatr. Med. Surg.* **20,** 307–22 (2003).
19. Foss NB, Kristensen MT, Palm H and Kehlet H. Postoperative pain after hip fracture is procedure specific. *Br. J. Anaesth.* **102,** 111–116 (2009).
20. Parker MJ and Handoll HHG. Gamma and other cephalocondylic intramedullary nails versus extramedullary implants for extracapsular hip fractures in adults. *Cochrane Database Syst. Rev.* (2008). doi:10.1002/14651858.
21. Parker MJ and Gurusamy KS. Internal fixation versus arthroplasty for intracapsular proximal femoral fractures in adults. *Cochrane Database Syst. Rev.* (2011). doi:10.1002/14651858.
22. Pinto PR, McIntyre T, Ferrero R, Almeida A and Araújo-Soares V. Risk factors for moderate and severe persistent pain in patients undergoing total knee and hip arthroplasty: a prospective predictive study. *PLoS One* **8,** (2013).
23. Otte JW, Merrick MA, Ingersoll CD and Cordova ML. Subcutaneous adipose tissue thickness alters cooling time during cryotherapy. *Arch. Phys. Med. Rehabil.* **83,** 1501–1505 (2002).
24. Erecinska M, Thoresen M and Silver IA. Effects of hypothermia on energy metabolism in Mammalian central nervous system. *J. Cereb. Blood Flow Metab.* **23,** 513–530 (2003).
25. Schaser K-D. *et al.* Prolonged superficial local cryotherapy attenuates microcirculatory impairment, regional inflammation, and muscle necrosis after closed soft tissue injury in rats. *Am. J. Sports Med.* **35,** 93–102 (2007).

26. Horst K *et al.* Long-term effects of induced hypothermia on local and systemic inflammation - results from a porcine long-term trauma model. *PLoS One* **11,** e0154788 (2016).

27. Kolar P, Gaber T, Perka C, Duda GN and Buttgereit F. Human early fracture hematoma is characterized by inflammation and hypoxia. *Clin. Orthop. Relat. Res.* **469,** 3118–3126 (2011).