Diplomarbeit

Computer-assisted cryotherapy after TKA

Computerkontrollierte Kryotherapie nach Knietotalendoprothesenimplantation

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Zusammenfassung

Hintergrund und Ziele: Obwohl bei lokaler Kälteapplikation klare Vorteile angenommen werden, ist ein allgemein gültiger Konsens hinsichtlich des Einsatzes nach Knietotalendoprothesenimplantation noch ausständig. In diesem Zusammenhang war das Ziel dieser prospektiven, randomisierten und einfach verblindeten Studie, primär die Sicherheit und sekundär die Effizienz eines neuen Kryotherapiegeräts, des cTreatment® Systems, bei PatientInnen nach primärer und unilateraler K-TEP Operation zu evaluieren und mit dem Standardkühltherapieregime zu vergleichen.

Methoden: 97 PatientInnen wurden in zwei Gruppen randomisiert, die das cTreatment® oder das Standardkühltherapieprotokoll mit Kühlelementen für sechs postoperative Tage erhielten. In dieser Zeit wurde auf das Auftreten von Nebenwirkungen geachtet. Neben Opiatverbrauch und Liegedauer wurden die weiteren sekundären Studienziele bestehend aus dem Kniegelenksumfang, der Gelenksmobilität und der Schmerzintensität am Aufnahmetag, dem zweiten, vierten und sechsten postoperativen Tag (POD) gemessen.

Ergebnisse: In beiden Studiengruppen fanden sich keine Nebenwirkungen. Es gab keine statistisch signifikanten Gruppenunterschiede hinsichtlich der Umfangmessungen, des PCA Verbrauchs, des NRS in Ruhe und der Länge des Krankenhausaufenthalts. Der NRS Score in Bewegung war signifikant niedriger in der cTreatment® Gruppe am zweiten POD ($P = 0,034$). Des Weiteren wurden statistisch signifikante Abweichungen zugunsten des cTreatment® bezüglich der Kniegelenksmobilität am sechsten POD sowohl bei der Flexion, wo rund 6,6 Grad mehr erreicht wurden ($86,2 \pm 7$; $P = 0,021$), als auch der Extension, mit Reduktion des Defizits auf -1,05 Grad ± 2,33 ($P = 0,022$), entdeckt.

Schlussfolgerung: Das cTreatment® System scheint ein sicheres Verfahren zu sein. Es war möglich, signifikante Vorteile bezogen auf den postoperativen Schmerz und die Remobilisation zu zeigen, welche auf eine Reduktion der inflammatorischen Reaktion, Sekretion und Blutung zurückzuführen sein könnten. Weitere Forschung könnte die ökonomischen Auswirkungen untersuchen.

Abstract

Background and Objectives: Although local cold application is supposed to have reasonable advantages, the universally valid consensus regarding its use after total knee arthroplasty (TKA) is still missing. In this context the aim of this prospective, randomized and single blinded study was to evaluate the safety, set primary objective, and efficiency, set secondary objective, of a new cryotherapeutical device, the cTreatment® System, in patients undergoing primary and unilateral TKA surgery compared to the standard cold therapy regimen.

Methods: 97 patients were randomized into two groups receiving the cTreatment® or the standard cold therapy protocol with cold pack application until six days after the surgical intervention. Throughout the hospital stay the potential occurrence of adverse effects was observed. The secondary objectives consisting of knee girth, joint mobility and pain intensity were measured on admission day, second postoperative day (POD), and the fourth and sixth day after surgery. Additionally the length of hospitalisation and total opiate consumption were recorded.

Results: No adverse effects were found in both study groups. There were no statistically significant differences between groups regarding the girth measurements, patient controlled analgesia (PCA) consumption, numeric rating scale (NRS) in rest and length of hospital stay. The NRS score in motion was significantly lower in the cTreatment® group on POD two (P = 0,034). Also statistically significant divergences to the benefit of the cTreatment® were detected regarding the knee mobility on POD six concerning both flexion, reaching averaged 6,6 degrees more (86,2 ± 7; P = 0,021), and extension, reducing the deficiency to -1,05 degrees ± 2,33 (P = 0,022).

Conclusion: The cTreatment® System appears to be a safe procedure. It was possible to prove significant benefits in terms of the postoperative pain and remobilisation, which might be attributed to a reduced inflammatory response, secretion and bleeding. Further research could investigate the economical impact.

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Glossary and abbreviations

TKA:	total knee arthroplasty
Et al.:	et alii
TNF – alpha:	tumor necrosis factor alpha
IL – 6:	interleukin - 6
VAS:	Visual Analogue Scale
PreOD:	preoperative day
POD:	postoperative day
PCA:	patient controlled analgesia
THA:	total hip arthroplasty
CTS:	Cryoceutical Treatment Server
cPad®:	Cryoceutical Treatment Pad
MEDOCS:	medical and nursing documentation and communication system; hospital information system used in the Public Hospitals of Styria (KAGes)
BMI:	body mass index
KAGes:	Steirische Krankenanstalten GmbH
p.m.:	post meridiem
h:	hour(s)
NRS:	Numeric Rating Scale
HG:	haemogram
CRP:	C-reactive protein
Coag:	coagulation of the blood
CK:	creatine kinase
HADS:	Hospital Anxiety and Depression Scale
KSS:	Knee Society Score
WOMAC:	Western Ontario and McMaster Universities Arthritis Index
AAS:	Adult Attachment Scale
CT:	cryotherapy group
Stand:	standard treatment group

SD:	standard deviation
Prox.:	proximal
Dist.:	distal

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1 Introduction

1.1 General approach

After introducing the total knee arthroplasty (TKA) surgery in the twentieth century it has become a common invasive procedure in orthopaedic surgery and in consequence one of the most central elements in therapy of end-stage gonarthritis, when conservative procedures are throughout exhausted (1). Closely adhering to indications for TKA, for instance pain at rest, need of analgesics in high doses, maximum distance travelled on foot of less than one kilometre per day and maximum time travelled on foot of less than one hour per day, the total knee replacement is able to make up for capital postoperative enhancements referring to the patient's pain and analgesics use, joint function and mobility and therefore resulting in a better quality of life (2-4).

Although, the TKA surgery itself achieved to maintain its ground, there are broad fluctuations in terms of its conduct per inhabitant and per year, which vary from 30 up to 199 per 100.000, most likely depending on the prevalence of osteoarthritis and national differences in health care systems (5).

In addition, endoprostheses make up for outstanding outcomes covering the loss of function of both the knee joint itself and its muscular-skeletal surroundings (6, 7). Despite all that, shortly after the surgical intervention patients commonly have to face pain, oedema and local inflammation as the direct consequences. This becomes all the more substantial considering, on the one hand, its intense manifestation after TKA surgery due to the numerous nerve endings periarticular, the massive resection of bone and near-to-bone soft tissue and finally the blood loss in an enclosed space, and on the other, its hindering impact on the postoperative physical therapy regimen and mobilisation. Consecutively the eventually massive manifestation of the postoperative pain and oedema eventuate in the inhibition of the knee joint's range of motion, especially the flexion of the knee. Consequently a prolonged duration of the patient's hospitalisation is mandatory taking into consideration that at the Department of Orthopaedic Surgery of the LKH-Univ. Klinikum Graz the average patient should not be discharged until reaching a flexion to the extent of 90 degrees.

Based on the large benefits of total knee replacement surgery in the therapy of progressed gonarthritis and adapting to the commonly known demographic landslide in age distribution not only surgical techniques in total arthroplasties, but also the implanted joint endoprostheses have consecutively been improved in the course of time in order to simultaneously achieve the best outcomes both in the patients' relief of burden and their gain of life-quality.

Nevertheless it would be entirely incomplete to simply set one's focus on the intraoperative progression in treatment, when on the one hand the further optimization regarding the design of the implanted endoprostheses will only be limited in the future and on the other hand its success is largely dependent on the perioperative and most notably on the postoperative proceedings as well, particularly when it comes down to the soft tissue management.

1.2 Theoretical basis of locally applied cryotherapy

Nowadays regionally performed cryotherapy belongs to the clinical routine primarily within the surgical wards, when it is often applied in acute injuries and trauma and in postoperative care amongst others. Above all, local cooling is involved in the perioperative treatment of patients undergoing limb-surgery, when it is commonly self-evidently applied. Of course this occurs to be important regarding certain sequelae associated with TKA, such as intense pain, localised oedema and haematoma, restricted mobility, and postoperative blood loss.

When in the second half of the last century the local cold application no longer was empirically used (8), this was because of the begin of research in this respect. Despite all that, on closer consideration the universally valid consensus of the optimal methods regarding locally applied cryotherapy is still clearly missing (9-11).

Generally speaking, the external application of cold therapy in the proximity of joints can be performed with various mediums such as ice (12-14), cooled fluids (12, 14-19), cooled air or cooled gas (12). The range of clinically utilized techniques includes various methods from common ice packs and gel filled cooling bags up to more sophisticated devices such as the Cryocuff, which simultaneously cools and compresses the joint, and even automated devices, which of course are much more costly and add a certain quantity of money per patient and hospitalisation (10, 18), even though not the device itself but the amount of time, which is required in order to be able to properly prepare and uphold the cryotherapy device, preponderates (18).

Nevertheless, local cooling usually still is a both relatively advantageously priced and universally accessible clinical procedure. Following a surgical intervention of the knee it aims for the minimization of the intraoperatively inducted tissue damage of all affected anatomical structures, from the skin to the articular capsule. Even if externally and superficially applied the cold actually outreaches transdermal structures, which consecutively implies, that not only the skin temperature is strikingly decreased but also the intraarticularly measured temperature (20). Further the cold's periarticular and deep expansion amounts to the fact, that all assumed effects triggered by local cooling, such as

moderating symptoms related to inflammation, pain and swelling (8), are superficial as well as profound equally active.

Around the middle of the last century, respectively towards the end of it, the influencing effect of cold on the one hand on the nerval transmission in the sense of deceleration of the conduction of action potentials in nerve fibres towards the central nervous system, and on the other hand right on the nociceptive gate in the periphery, was attested (21, 22). This is supposed to largely account for an additional analgesic effect besides the actual pain medication when locally applying cryotherapy after trauma such as TKA surgery.

Recently it has been shown that there exists a correlation between the intraarticular temperature in patients following a surgical intervention of the knee and the local prostaglandin E_2 levels measured in the surrounding tissue (23). Subsequently, apart from pain, local cold therapy may also diminish local inflammation, as prostaglandin E_2 is a mediator influencing pain, inflammation and fever. Also they stated a reduction in blood flow periarticular, which was sensed by using an ethanol exchange ratio and obviously is attributable to the vasoconstriction in cold tissue (22). An at least theoretical benefit in blood loss after TKA goes back to back with a cold-induced peripheral vasoconstriction and a, thereby, reduced periarticular blood flow (8).
Within the explorations of a recently published study in 2013, Jastrzabek et al. found that aside from prostaglandin E_2 also cytokine levels, which are known for triggering inflammation, may be sensitive to externally applied local cryotherapy (24). On one side, TNF-alpha levels decreased significantly after ten days of cold therapy even though it only was applied for three minutes a day in terms of gaseous, respectively air blowing methods. On the other side, no significantly relevant reduction in interleukin-6 (IL-6) levels could be found when local cryotherapy was applied in the same setting (24). Nevertheless it already could have been shown that IL-6 levels correlate with the extent of tissue damage related to the directly foregone surgical intervention when examining different approaches in total hip arthroplasty (25). Staying closely beneath the level of significance the IL-6 elevation of the minimal invasive approach was half the size of the comparative group's increase.

Local oedema and haematoma, which are due to vascular leakage and / or vascular trauma of all kinds of cause and extent, clinically appear as swelling and increase of girth, if they are located on the limbs. Likewise, as locally applied cooling therapy can reduce the surrounding blood flow (23) in order to create a potential benefit in blood loss, the treatment may reduce the posttraumatic, respectively postoperative oedema periarticular as an improvement in postoperative care in TKA patients when inducing vasoconstriction of blood vessels (22).
Additionally to the local cooling, externally applied physical compression surrounding a trauma site may reduce the extent of intravascular fluids flowing into the interstitium on the basis of an increase of the interstitial pressure compared to the hydrostatic. Peculiarly following TKA surgery the added compression in the proximity of the operative area of the knee may also prevent, respectively decrease the development of haemarthrosis.

On balance, cryotherapy in particular used in patients undergoing total knee replacement surgery could account for substantial enhancements in perioperative care taking into consideration that the treatment covers main sequelae closely related to the surgical procedure. As the cold penetrates all anatomical layers it could all over lead to a vasoconstriction-based reduction of blood loss and arising thereby to the prevention or decrease of local oedema and haematoma, reduction of local prostaglandins and inflammation, and inhibition of transmitted pain. These three cold-induced main factors, which are analgesia, reduction of swelling by way of oedema and bleeding, and decrease of inflammation (8), become all the more fundamental taking into account the difficulties in early postoperative rehabilitation and physiotherapy regimen consisting of restricted mobility mostly attributable to pain and swelling. An averaged faster recovery and mobility in terms of sooner independent ambulation could result in an earlier discharge from hospital.

1.3 Topic-related research and recent findings

Conducting a more specific evaluation of literature concerning local cryotherapy used in patients undergoing TKA, there are several more studies to be listed, even though the range regarding the issue is restricted at some point when searching in PubMed, and, referring to the statements based on the study results, absolutely controversial at the same time. This apparent controversy emanating from the questionable efficacy of local joint cooling in patients following total knee replacement surgery was found the most common cause for not using the very same in postoperative care, even though, within the borders of the United Kingdom 99 per cent of all patients following the surgical intervention are initially debated on possible use (11).

Despite many studies being completely diversely structured regarding, on the one side, the forms of intervention in the cryotherapy group as well as in the control group due to several differences in the method of application, times of application, duration of application and finally cooling temperatures used, and, on the other side, the forms of controlling and measuring, they often aim for similar set main parameters, for example the patient's pain and related extent of analgesic medication required, local swelling and knee girth, intra- and postoperative blood loss and related transfusion requirements, range of motion of the operative knee, and also adverse effects.

1.3.1 Forms of application

Multiple studies compared a combinational form of cooling and compression to compression of a joint only (15, 26). Kullenberg et al., respectively Morsi compared a combinational form of cooling and compression to a control group, which did not receive any intervention at all (19) or any besides epidural anaesthesia until postoperative day three (16). Other studies compared an isolated form of cooling therapy to a control group, which did not receive any therapy (17, 18). One recently published trial was reviewed, which randomized and compared patients in three different treatment groups receiving gaseous cryotherapy or traditional cold pack or cryocuff, though, they were not

able to observe a statistically significant clinical difference between the treatment groups (12).

Others analysed specific modifications of the cryotherapy treatment setting itself, such as two different temperatures in the same patients (15).

1.3.2 Pain

Concerning the pain, which is understandably involved in particularly the postoperative course of TKA and thereby often intervenes the standard operating regimen of mobilisation in an early phase, some studies' findings show significances in pain especially in short-term clinical rehabilitation regimen as listed below. Usually the data on the patients' pain intensity was gathered by use of a ten point visual analogue scale (VAS), about which each patient was told that very left was "no pain" at all and very right the "strongest pain" even imaginable. Pain scores were evaluated at different points in time following the surgical intervention, such as on preoperative day (PreOD) one (12), postoperative day (POD) one (15, 16, 26), POD two (19, 26), POD three (16, 26), POD seven (12), two weeks postoperatively and six weeks postoperatively (14). One reviewed study evaluated the pain by use of VAS at one and two hours postoperatively and afterwards every eight hours until POD six (19). Particularly around POD two, overall studies suggest slightly less pain in those groups, in which cryotherapy techniques were applied (9, 10). This statistically significant benefit favouring cryotherapy was not found on POD one and three in reviews (10), although one single study found a distinct and significant ($P < 0{,}001$) decrease in the mean VAS of the cryotherapy group, which was existent throughout the measurement ending on POD six (19). Again, the widest difference in VAS of the two study groups was measured around POD two in the very same results.

Some researchers compared TKA with postoperatively applied cryotherapy on one knee to TKA without using any cooling advices at all six weeks after having undergone the first one of the contralateral knee (19), respectively to a control group receiving the standard clinical routine including epidural anaesthesia (16) or compared cold therapy with compression therapy (26).

Possibly the majority of reviewed papers in literature claims explicitly, that there are no statistically significant differences in pain levels between the cryotherapy treatment group and the control group at any point of time (10, 16-18, 26).

1.3.3 Analgesia use

The amount of analgesia use in patients undergoing TKA is certainly and closely connected to the postoperatively subjectively experienced pain due to the clinically used techniques of treating the very same, which is analgesic medication. These are for instance, first, peripheral, respective regional nerve blocks concerning the N. femoralis, N. obturatorius and more seldomly N. ischiadicus and, second, opiate analgesia often in terms of patient controlled analgesia (PCA), which is already installed in the postanaesthesia care unit right after the actual surgical intervention in most cases.

In general sense, it has already been proved, that statistically significant reductions concerning the amount of postoperatively required analgesia are possible using cryotherapy after the reconstructive surgery of the anterior cruciate ligament of the knee joint (27).

More specifically, there is statistically significant data after TKA surgery regarding the reduction in the extent of analgesia consumption within the first two weeks postoperatively in the cryopneumatic therapy group (mean 509mg morphine equivalents) when compared to its control group (mean 680mg morphine equivalents) (14). Su et al. accordingly concluded that patients undergoing total knee replacement surgery on the one hand may feel less medicated and on the other hand are less likely to suffer from narcotic analgesia triggered adverse effects (14).

Aside from Su et al. another study was able to assess a significantly declined usage of postoperatively required analgesia in 30 patients undergoing bilateral TKA surgery when a cryotherapy device was applied (19). In this case, the extent of the seen difference was largest on POD one and steadily diminished towards POD six (19).

On the contrary, several studies, that investigated parameters based on analgesics, revealed no evidence of significant divergences in the sense of decreased narcotic requirements between the cold therapy and its comparative group (16-18, 26).

Also Radkowski et al. could not find any further effect, which would lead to a more powerful cold-induced analgesia due to a diminution of the applied cooling temperature from 75 degrees Fahrenheit (respectively 23,9 degrees Celsius) to 45 degrees Fahrenheit (respectively 7,2 degrees Celsius) (15).

1.3.4 Swelling / Knee girth

Unfortunately, in those little cases, where the data regarding the knee girth was considered and collected, it was rarely described how the measurements were performed. Demoulin et al. measured exactly at the height of three points; first, around the level of the knee joint line, second, five centimetres below and, third, ten centimetres above this level (12).

In two studies they understandably were able to prove a postoperatively strikingly augmented knee girth, which goes back to back with lowered knee ROM in the assessment after patients underwent TKA surgery compared to the patients' preoperative evaluation (12, 14).

The between-group comparison of the results of knee girth measurements regarding patients randomized to the cryotherapy group or to the control group did not show a statistically significant difference (14). In parallel, no significant differences between the study groups, which were all treated in diverse cold therapy settings, could be found (12).

Another study also tried to evaluate the postoperative knee girth, but the parameter was not properly surveyed and therefore could not be further analysed (18).

1.3.5 Knee ROM

The range of motion (ROM) of the knee joint was usually measured with the patient being laid in a supine position and the examiner using a hand-held goniometer. The goniometer's centre was approximately placed at the level of the lateral femoral epicondyle, when its proximal end was adjusted to the femoral trochanter major and its distal end was adjusted to the lateral malleolus of the fibula in order to be able to most precisely gauge the patient's ROM of the knee joint.

Kullenberg et al. performed measurements before TKA, on POD one, at the time of discharge and three weeks postoperatively. There was no disparity revealed on POD one, though, at the time of discharge the two study groups remarkably differed with the patients in the cold compression group having achieved 12,2 degrees of knee ROM more than the control group (75,1 degrees in cold compression group, 62,9 degrees in control group) (16). This aspect was still verifiable three weeks postoperatively when the cold compression patients had an averaged advance of knee ROM of an extent of 11,3 degrees (98,9 degrees in cold compression group, 87,6 degrees in control group) (16). Although the real clinical importance is questionable, study data displays that the averaged patient assigned to the cold therapy group obtains the level of independent ambulation even more than one day sooner. This may be, because they were able to better coordinate their femoral muscles. A possible connection to less postoperative knee swelling resulting from the locally applied combinational form of cooling and compression cannot be ruled out, because the knee girth progression was simply not measured (16).

Another study's evaluation until six weeks postoperatively, which was realised once per week, indicated a statistically significant ($P < 0,01$) enhancement in knee ROM within the cryotherapy group, though, the stated difference between the groups continuously declined towards postoperative week six (19).

No additional influence on the postoperative knee ROM after TKA based on a lowering of the applied cooling temperatures beneath 23,9 degrees Celsius was found so far (15).

There could not be revealed any significant improvements in knee ROM related to postoperative cryotherapy in several studies (14, 17, 18), though, it was not properly surveyed in one case (18).

1.3.6 Blood loss

The postoperative blood loss appears to be a clinical problem to be taken very seriously as there are confirmed losses which can reach up to 1500 ml (28). As a consequence, an impact on postoperative recovery after TKA surgery could be strong.

In one study's setting cold therapy was immediately applied after the surgical procedure and was continuously kept until the first change of dressing, which commonly took place

on POD three. They were able to prove a mean decrease of short-term blood loss within the first two days postoperatively which amounts to 200 cubic centimetres monitored by a hemovac drain, that was removed 48 hours after TKA (18). Though, there was no significant evidence for a decrease in transfusion requirements, which were administered beneath a symptomatic haemoglobin level of 8,0 mg/dL (18).

Within a different setting evaluating total body blood loss one was again able to show a relevantly lower blood loss within the cryotherapy group, which once more was recorded by the use of a hemovac drain until 48 hours postoperatively, and consequently, this was significantly reflected in the decline of transfusion requirements to the extent of 37 per cent (19).

Also Kullenberg et al. investigated the haemoglobin blood levels in patients before and after undergoing TKA. Starting from the averaged same haemoglobin levels preoperatively, the cryotherapy group revealed a statistically significant slighter drop on POD one (from 140 mmol/L to 120 mmol/L) than the control group did (from 140 mmol/L to 109 mmol/L) (16).

Resulting from large-scale systemic reviews performed by Adie et al. in 2010 and 2012 there are small reductions in postoperative blood loss after TKA based on cryotherapy after all (9, 10).

However, the postoperative drainage amount was not found influenced by a drop in used cooling temperatures in postoperative cryotherapy in the sense of a decline of 30 degrees Fahrenheit to 45 degrees Fahrenheit (15).

1.3.7 Adverse effects

As it is commonly assumed, possible adverse effects related to the local application of cold in course of cryotherapy surrounding the knee joint may be frostbite, nerve palsy, and inhibited wound healing.

One reviewed study reported altogether two cases of deep vein thrombosis below the popliteal fossa, which occurred once in the treatment and once in the control group (16). Further they faced one case of superficial soft tissue infection of unclear origin, which occurred in the treatment group (16). The cases of thrombosis might be related to a

delayed or hindered mobilisation due to a restricted knee ROM, considering that the patient's mobilisation as early as possible is one of the most elementary factors in the prophylaxis of deep vein thrombosis (29). Additionally, as the treatment group experienced the combination of cold and compression, it could be possible that the venous blood flow distal of the periarticularly applied cryotherapy was decelerated due to the compression. Accordingly, the stasis factor of the Virchow triad would be present.

In one study all four occurred adverse events were even found in the comparative group, which was neither treated with cold therapy nor compression (17).

Further no cryotherapy-based influence on the postoperative wound healing could be found (19).

In any other studies, which were worked through, there were no observed adverse events possibly related to the usage of cryotherapy of any form (15, 17-19, 26), aside from few patients asking for the termination of the cooling treatment because of subjectively experienced uncomfortableness (10), which is also defined as the most commonly cause for withdrawal from the trials in a current systemic review (9). The same systemic review, which searched a total of 707 patients for the eventual presence of adverse events, summarizingly claimed that cold therapy was a safe procedure (9).

1.3.8 Length of hospital stay

The length of hospital stay was defined by the studies, which investigated this parameter, as the number of days patients remained hospitalised after the TKA surgery.

A statistically significant shortened hospitalisation could be verified in one study ($P < 0{,}001$) (16). Here the averaged duration of hospital stay totals 4,8 days within the study group using cryotherapy in the postoperative phase, whereas the averaged length of hospitalisation within the control group was 6,2 days (16). This may possibly be a direct consequence of the fact that patients treated with postoperative cryotherapy started to ambulate independently even more than one day before patients in the reference group did (16).

Interestingly, Scarcella et al. were able to prove a statistically significant reduction of the length of hospitalisation to the exact same extent of 1,4 days on average in 50 patients

following total hip arthroplasty (THA) surgery when being randomized in the cryotherapy group (50 degrees Fahrenheit) compared to the control group (70 degrees Fahrenheit) (17). Likewise, within the results of the same study an obvious, if not necessarily statistically significant tendency towards a shortened hospitalisation was detected regarding patients following TKA (17). That these findings remained slightly beneath the level of significance may be due to the distinctly smaller study population undergoing TKA (24 subjects) than undergoing THA surgery (50 subjects). Further, TKA patients assigned to the cold therapy group started to ambulate independently on an average of one day sooner (mean 4,6 days) than patients in the reference group (mean 5,7 days), although this discovery again stayed very closely beneath the significance level ($P < 0,08$) (17).
Another study, which observed the parameter, did not find a significant sooner discharge stemming from cryotherapy (18).

1.3.9 Satisfaction

Despite the small number of publication dealing with the postoperative hospital stay from the patients' point of view, there are several publications leading to the assumption that the postoperatively applied cold therapy also has a beneficial effect on the patient's subjectively experienced hospital stay.
After performing a simple evaluation on subjective satisfaction, which could be answered by the patients using numbers from one (not satisfied) up to six (entirely satisfied), one study was able to verify a greater satisfaction within the study group treated with a cryopneumatic device after TKA surgery (14). This turned out to be supremely significant with $P < 0,0001$ (14). The patients were especially pleased in respect of pain and joint mobility.
Correspondingly, in another publication there were 26 patients reported having strong feelings about the cooling device, of whom 21 were randomised into the reference group and did not experience the cold therapy (17). Thereon one could conclude that actually being treated with cold postoperatively shows in a raised verge to complaint due to a thereby triggered satisfaction and effectively compensates for inconveniences and discomfort.

Although one publication did not record data on patients' satisfaction based on the cooling device, the involved nursing staff still was convinced of the treated population being pleased (18).

However, Adie et al. claimed in a recently published systemic review, that all published data on the topic considered the patient-oriented and subjectively experienced effects including personal satisfaction still need to be accurately enquired (10).

1.3.10 Limitations of reviewed studies

Possibly owing to the fact, that the reviewed publications partially were dated back before the year 2000, there unfortunately were some limitations to them.

The majority of reviewed studies enclosed patients with primary unilateral TKA (12, 13, 18), whereas one used one and the same patient in the treatment group and six weeks after in the control group as patients undergoing bilateral TKA were examined only (19). In this case, the study population could not be blinded either (19). Due to one study's retrospective design they had unequal numbers of patients in each study group, missing data and no blinded patients as well (18). Further, in the same study the allocation of patients to the test and reference group was performed by the surgeon's opinion and did not follow randomization (18).

Two studies had a very small study population consisting of 20, respectively 24 patients undergoing TKA surgery, which set a limit to their validity (13, 17).

Based on the common study results cooling intervention was once performed too late after TKA, on POD seven and POD ten, and thereby did not show an acute beneficial effect regarding cold therapy (13).

One other study was possibly performed at too many sites, which resulted in a great variability in proceedings and measurements postoperatively, especially because, additionally, there were various surgeons involved using endoprostheses based loosely on their preferences (14). There was rarely one surgeon in charge of every single intervention of the study subjects (19).

1.4 Study aim and objectives

Although there were various explorations performed on the very topic of locally and postoperatively applied cryotherapy in patients undergoing TKA surgery, there is currently no accordance regarding the ideal proceedings and therefore one is experiencing a lack of valid guidelines when treating the very same patients (9-11). In addition, the call for further and more accurate research on cryotherapy after TKA surgery, which was already made back in 2003 (11), was recently endorsed when two systemic reviews approaching the same difficulties performed by Adie et al. were published within the last three years (9, 10).

The purpose of the study, which underlies the present diploma thesis, was to evaluate a new cryotherapy device, the cTreatment® system (Waegener®, Belgium) consisting of the Cryoceutical Treatment Server 100 series (CTS) and the Cryoceutical Treatment Pad (cPad®), in comparison to the standard cooling protocol, which was the cold packs (cold/hot pack, Dahlhausen®) currently used at the Department of Orthopaedic Surgery of the LKH-Univ. Klinikum Graz, in patients undergoing primary and unilateral TKA surgery. In this connection it was particularly focused on the device's safety in respect of its direct use on the patient, which was set the primary objective and regarded as essential due to the cold therapy regime's actual intent. The device's safeness was basically defined by the potential occurrence of adverse effects related to the periarticularly applied cold therapy. The efficiency in terms of eventual improvements in the patient's postoperative rehabilitation and mobilisation, such as positive alterations of knee ROM, knee girth, pain and analgesics consumption and individual length of hospitalisation, were defined as secondary objectives.

The hypothesis at the bottom of the conducted trial was basically to prove the safety of a new medical therapeutical device used in postoperative cryotherapy, which is possibly able to substantially enhance the postoperative rehabilitation in patients undergoing primary unilateral TKA surgery.

2 Material and methods

2.1 Literature research

Before participating in the clinical trial, respectively composing the actual diploma thesis, an accurate literature research preceded in order to gain a systematic overview on the complex of themes itself on the one hand, and on the other hand to create a precise point of reference for the underlying study's results. In so doing, it was basically leant onto a web-based search via PubMed for gathering preferably recent study outcomes, which referred to the planned trial's key words. Those were most notably composed of "TKA" surgery and suchlike, "cryotherapy" and "cold therapy" and suchlike. In this connection it was attempted to collect information on both the usage and effects of cold and cryotherapy in general, but particularly when locally applied. In addition, it was focused on research combining cryotherapy with surgical procedures, most notably TKA surgery. Beginning with the primarily compiled results and papers the further literature research could be refined and more specified by implication.

2.2 Study design

Basing on the preliminary findings of the performed literature research and the exactly defined purpose of the trial it was decided, that the peri- and postoperatively locally applied cryotherapy related to TKA surgery in terms of the used cTreatment® system (Waegener®, Belgium) was examined best by means of conducting a prospective, randomized and single-blind, comparative and controlled clinical study within the wards of the Department of Orthopaedic Surgery of the LKH-Univ. Klinikum Graz in order to receive highly diagnostic and convincing results. Hereby it was also possible to fulfil the requirements for future studies in the field of cryotherapy after TKA set by the most recent systemic review in order to enhance the quality of evidence (9).

Therefore the required application form for the health care ethics committee was composed in December 2011 and subsequently answered in the positive. Right afterwards the assessment of the patients to be included could begin.

2.3 Study population

Due to the fact, that probably two reviewed studies had a limited validity stemming from the partially small number of included patients (13, 17), there was the initial attempt to make the population consisting of approximately one hundred patients. Therefore the ethics application form was modified from the first version, which only involved forty patients, to the second and final version, which involved more than one hundred patients. The number of patients included thereby also set the study's aim and marked its endpoint.

The process of acquiring subjects for the diploma thesis' underlying study could be finished in April 2013, when it was decided to terminate the study.

Within the list of planned hospitalisations in the Department of Orthopaedic Surgery it was continuously searched for potential patients undergoing TKA surgery, who could possibly be enrolled in the study. Every potentially eligible patient was talked to at his day of admission about the study's aim and the planned procedure. Accordingly, his clinical history in MEDOCS was searched in order to ascertain that both the patient's and the required study profile would match. Those criteria for a possible in- or exclusion are listed hereafter.

Inclusion criteria:
Between 18 and 90 years old; Severe degeneratively or traumatically caused gonarthritis or osteonecrosis of the knee joint; Planned endoprothetic treatment with TKA; Patient's informed consent regarding study design, therapy, procedure and the outpatient follow-up after discharge

Table 1: inclusion criteria

Exclusion criteria:
BMI above 40;
Sleep apnoea syndrome, opiate intolerance, noncompliance to PCA;
Acute fracture, severe infection and inflammation, rheumatoid arthritis or malignoma in the limb scheduled for intervention;
Every preceded surgical intervention of the knee joint except for arthroscopy;
Status post infection or current systemic infection (HI virus, hepatitis B or C);
Cold allergy or cold intolerance;
Raynaud's syndrome;
Cold urticaria, cryoglobulinaemia, paroxysmal cold haemoglobinuria;
Circulatory disorders of the affected knee joint;
Fibromyalgia or other chronic pain syndromes;
Taking of immunomodulatory drugs, such as cortisone, interferon or the like;
Depression, (generalized) anxiety disorder;
Substance dependence, alcoholism;
Gestation or possibility of gestation without adequate contraception of any kind;
Absence of patient's informed consent;
Mental incapacity

Table 2: exclusion criteria

Besides the patient's informed and written consent the criteria concerning a possible enrolment to the trial particularly include, on the one side, reasons, which might interfere with the patients' statistical comparability regarding the outcome, such as severe pre-existing locally and systemically conditions others than gonarthritis and foregone surgical interventions others than arthroscopy, and on the other side conditions, which would interfere with the planned study design including, for instance, the standardized medication and PCA and long cooling intervals during hospitalisation.

After it was assured that the patients fit the required criteria, they were fully informed about the study and its involved conditions. When they agreed with the discussed proceedings they were asked to sign the informed consent form before continuing.

At the end and after having to withdraw eight patients before they could properly set off within the study protocol, there were 97 patients included in the study, which is clearly above the initially set mark of 40 patients. This is largely because the noncompliance of several patients concerning the follow-up appointments after discharge, which were part of the diploma thesis' underlying study, could be anticipated at a very early point in the study's course and the statistical power should only be affected to a minor extent. Before extending the size of the study population a second application form for the health care ethics committee was composed and approved.

The subjects were able to leave the study at any point of time, without any need of further justification and any therapeutical consequences due to their withdrawal. Also it was possible to actively withdraw a subject from the trial at any time if there was urgent medical reason to do so.

2.4 Randomization

The process of randomization took place on the day of each patient's hospitalisation right after the patients giving their written informed consent to participate in the trial. For the randomization and therefore the uniform distribution of the 97 patients to the two study groups, which were the cTreatment® group on the one side and the comparative study group using cold packs on the other side, a web-based programme was used. This was the "Randomizer", which is accessible via http://www.randomizer.at and supervised by the Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz. Therefore the encrypted and secure randomization ran exclusively on the internet and was accessible 24 hours a day (30).

In order to achieve a proper stratification of the study population, which was assigned to the two study groups, the patient's individual treating number given by the KAGes, the patient's sex and the planned design type of the endoprosthesis to be implanted in the context of the TKA surgery, which was either the PFC® or the LCS® (DePuy®, Germany) endoprosthesis, had to be filled in the randomization form before starting the randomization itself. The result of all this was the proper consideration of individual factors for the randomization process.

2.5 Therapy group

After being randomized to the therapy group the patients were assigned to the locally applied cryotherapy treatment with the cTreatment® system until the end of the clinical study, which was set for POD six. That implied, that the first cooling session was already preoperatively on preoperative day one, which coincidently was the day of admission throughout all cases. The preoperative cooling with the cTreatment® was performed for at least one hour in total. The control group did not receive any preoperative cooling, as it is not part of the standard protocol at the Department of Orthopaedic Surgery in Graz. Furthermore patients assigned to the therapy group received the cryotherapy immediately postoperatively when they were transferred to the postanaesthesia care unit for six hours in total. Additionally there was the option for each patient to make use of the cTreatment® system for altogether four hours in the evening. This was thought as an optional pain therapy, which each patient was free to decide whether to utilize or not.
During the following postoperative days until the study's predetermined end on POD six, the local cryotherapy using the cTreatment® system was always applied abiding by the standardized protocol, which was mainly based on the company's product instruction. On each day cryotherapy should be used for four hours in total, which was divided into two hours in the morning and two hours in the afternoon, whereas the exact times of day considering the application slightly varied as the nursing staff had to cover the treatment additionally to their common daily routine. Generally, the cryotherapy in the morning started after the physiotherapy session and there was the attempt to start the treatment in the afternoon before two p.m. Also there was the option to use the cTreatment® in terms of additional analgesia in the evening for up to four hours on each POD. This was offered the patients over again on each day and they were free to decide whether to do so or not.
No additional cryotherapy treatment was used throughout the study apart from the listed protocol hereafter.

PreOD 1	TKA	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6
	6 h post-OP	2 h morning	2 h morning	2 h morning	2 h morning	2 h morning	2 h morning
≥1 h pre-OP		2 h afternoon	2 h afternoon	2 h afternoon	2 h afternoon	2 h afternoon	2 h afternoon
	4 h optional	4 h optional	4 h optional	4 h optional	4 h optional	4 h optional	4 h optional

Table 3: cTreatment® protocol in therapy group

According to information from the manufacturer, the Cryoceutical Treatment Server is a class IIa therapeutical medical device, which can be used to thermodynamically exchange heat controlled by the built in computer. The cTreatment® Server is connected to the cPad® with two tubes in order to provide the transfer of fluids at the right temperature. Therefore it is able to regulate both the flow and the fluid's temperature itself. Consecutively a locally cooling or heating effect on the patient's skin can be achieved. According to the instruction manual, the device is also secured by multiple built in safety precautions, which are supposed to prevent from any kind of adverse effects. In order to work it needs to be connected to an electrical socket as it lacks battery supplies. For an easy use the CTS is operated with a touch screen on the top of the device, which allows to start, pause, resume and stop the cooling therapy sessions and additionally offers an overview of the scheduled therapeutical units. Although the cooling automatically stopped after the set two, respectively four hours, it was always possible to pause the treatment and continue it at any time.

Figure 1: Cryoceutical Treatment Server at patient's bed

Figure 2: CTS touch display during session

The Cryoceutical Pad is connected to the cTreatment® Server with two flexible tubes and adjusted adapters as its direct extension and form of application. The specific adapters on the tube ends of both the cPad® and the CTS side use a certain anti-reflux design which prevents fluids from accidentally spilling when connecting or disconnecting the cTreatment® system before and after usage at the patient's bed. According to the instruction manual the pad is made of flexible Polyurethan, latex free and hypoallergenic to account for a high grade of dermatological tolerance. It transfers the heat energy of the fluid at the correct temperature and rate of flow to the patient's skin and therefore is the linking element of the applied cryotherapy. It is easy to use as it is simply wrapped around the body area to be treated, which was the knee joint in the present study, in order to ensure a maximum of contact surface and simultaneously efficiency regarding the heat exchange. The used cPad® was especially designed for the application on the knee joint. On that account it featured a central notch, which was supposed to be

centrally placed on the patella for an even better fit. The cPad® is fastened using its straps with hook and loop fasteners. Although it is generally possible to use the cPad® directly on the patient's skin it was always wrapped over the postoperatively applied dressings. For each patient in the therapy group a new and welded cPad® was used for the whole duration of the trial. Used cPads® were disinfected and accordingly used in terms of blinding within the reference group. After the trial had ended they were returned to the producing company, Waegener® in Belgium.

Figure 3: study setting at patient's bed including CTS and cPad®

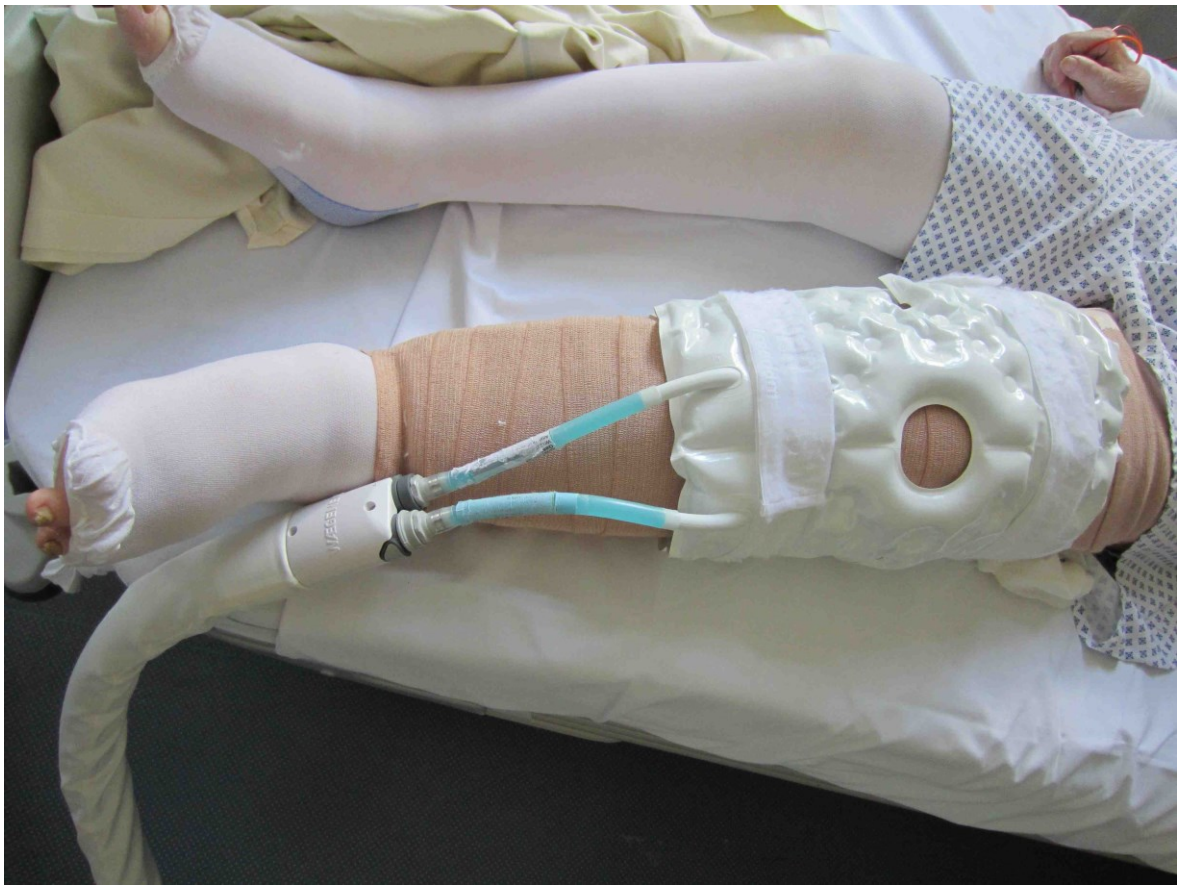


Figure 4: close-up of the cPad® and its connection system

2.6 Control group

Patients assigned to the control group were treated abiding by the standard cryotherapy regimen used at the Department of Orthopaedic Surgery in Graz. This standard procedure includes the usage of common cold packs (cold/hot pack, Dahlhausen®), which are wrapped over the body area to be treated, which was the knee following TKA surgery.

Patients randomized to the control group did not receive any locally applied cryotherapy before undergoing TKA surgery in contrast to the cTreatment® group. These proceedings correspond to the standard protocol of the treatment regimen within the wards of the Department of Orthopaedic Surgery. After TKA surgery patients received the cold packs therapy three times a day for twenty minutes each throughout the whole duration of the study, which ended on POD six. The exact times of day concerning the application slightly varied during the hospitalisation, which can be referred to the varying daily routine of the nursing staff, which again covered the therapy. On the day of the surgical intervention it

depended on the time of day the operation could be finished how often the cold packs were applied.

No additional cryotherapy treatment was used throughout the study apart from the listed protocol.

Day -1	TKA	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6
No cooling	1-3 times for 20 min post-OP	3 times for 20 min	3 times for 20 min	3 times for 20 min	3 times for 20 min	3 times for 20 min	3 times for 20 min

Table 4: cold pack treatment in control group

The cold packs used for the cryotherapy in the control group were hygienically disinfected and used again within the clinical routine afterwards.

2.7 Methods of blinding

In order to be able to receive more exact results when comparatively investigating the cTreatment® system and the cold pack therapy, the study population was blinded. Consequently they did not know which study group they were randomized in. This also takes effect for the orthopaedic surgeon, who performed the TKA surgery. On the contrary the nursing staff covering the cryotherapy applications and the investigative personnel responsible for the measurements on the patients were not blinded.

In the context of the underlying study the actual effectiveness of the blinding methods concerning the operating surgeon and the treated patients themselves was evaluated in each patient's case on POD six by answering a questionnaire.

The blinding proceedings themselves were equally executed in each control patient's case and at every event of the cooling treatment. While the cryotherapy sessions in patients assigned to the cTreatment® group were in conformity with the common cooling therapy

approach listed above, there was always the cTreatment® Server in the room of patients assigned to the control group as well. The server was plugged into an electric socket too. It further was connected to a cPad®, which formerly had been used within the therapy group and also had been hygienically disinfected thereafter. The difference to the cryotherapy in the therapy group was the cold pack, which was placed beneath the cPad®. Because of the overwrapped cPad® the patient could not see the cold pack underneath, which actually accounted for the subjectively experienced cold, considering that the cTreatment® system was turned off in each case.

2.8 TKA surgery

The surgical intervention itself, in terms of the primary and unilateral TKA, was performed by only few orthopaedic surgeons from the Department of Orthopaedic Surgery at the LKH-Univ. Klinikum Graz. The endoprostheses, which were used for the replacement of the knee joint, were either the PFC® or LCS® designs and individually chosen by the executing surgeon in charge.

The surgical intervention was basically conducted without the preliminary use of an Esmarch exsanguination and subsequent tourniquet application. The closure of the blood arrest was directed when the level of the intraoperatively lost and at the dorsal circumference of the knee joint line collected blood exceeded two millimetres within two seconds. In spite of that the surgeon in charge could order the blood arrest's closure when subjectively perceiving severe blood loss at any time.

Each patient intraoperatively received drainages in order to discharge ichor and blood. All drainages were removed after 48 hours postoperatively.

After finishing TKA surgery there were always aseptic and elastic dressings applied in the operation room, which did not contain any cotton wool.

2.9 Medication and anaesthesia

For the purpose of a better comparability all patients did not receive regional or spinal anaesthesia but general anaesthesia, which does not account for a substantial deviation

from the standard anaesthetic protocol at the Department of Orthopaedic Surgery in Graz. Furthermore, this can be taken to mean a requirement for the placement in the study and therefore this single anaesthetic option already was communicated to eligible patients when informing them about the study on the day of admission to hospital.

The general anaesthesia itself was usually induced by injecting Propofol® and Ultiva® intravenously and maintained by using Sevofluran® as the volatile anaesthetic and continuing the administration of Ultiva®. No limiting standards were set for the exactly administered doses, since they depended on patient based individual factors and were not supposed to have any pervasively influencing effects on the trial's outcome. Approximately 30 minutes before finishing the TKA intervention patients intraoperatively received 0,015 – 0,03 mg/kg bodyweight hydromorphone as a long-acting analgesic. Additionally, patients were administered Novalgin® 4 x 1 g as a non-opiate analgesic with respect to potential contra-indications. In terms of a prophylaxis regarding postoperatively occurring nausea and emesis related to the inhalatively conducted general anaesthesia they were also administered Zofran® 8 mg.

The postoperative analgetic therapy was mainly based on the PCA system, which was applied immediately postoperative and filled with the diluted opiate hydromorphone. One vial at 20 mg / 1 ml was added 99 ml NaCl 0,9 %, which means that one millilitre by the PCA administered single dose contained 0,2 mg hydromorphone. Also the PCA was pre-set with the following preferences: One single dose amounted to 0,2 mg, the lock wait between two administered doses to 10 minutes at a maximum of 5 boluses per hour and the maximum dose within four hours was defined as 4 mg.

PCA	**Single dose**	**Lock wait**	**1 h maximum**	**4 h maximum**
hydromorphone	0,2 mg	10 minutes	5 boluses	4 mg

Table 5: standardized PCA protocol

In addition to that, Novalgin® 4 x 1 g was given as a non-opiate analgesic. Non-steroidal anti-inflammatory drugs and Perfalgan® were not allowed in the patients' medication throughout their placement in the trial's in-patient setting, which ended on POD six. The

patients were monitored by anaesthetists from the Department of Anaesthesiology at the LKH-Univ. Klinikum Graz by reference to the standardized PCA protocols, which are commonly used by the Department of Anaesthesiology. They include the surveillance of the pain score using VAS in rest and motion, depth of sedation, respiratory frequency, heart rate, blood pressure, adverse reactions as nausea and emesis and the total consumption of hydromorphone. The frequency of surveillance was hourly within the first four hours, two-hourly in the subsequent eight hours and afterwards every four hours until the removal of the PCA. The PCA was always removed after 72 hours postoperative and the total opiate consumption was recorded until this point in time.
In exceptional cases, when the PCA was not applied immediately after the surgical intervention but later on POD one, there was the possibility to administer Dipidolor® intravenously at individually adapted doses until the patient received the PCA system.

2.10 Measurements and collected data pre- and postoperatively

On the day of admission, which always was the day before the scheduled TKA surgery, and after the patient confirming his written informed consent concerning the placement in the preliminarily discussed trial several physical measurements were performed before, between and after sessions of the locally applied cryotherapy, which differed depending on the study group, which the subject had been assigned to. These physical evaluations primarily consisted of the quantification of the knee girth and the range of motion regarding the knee joint to be treated.

Similarly to a previously reviewed trial, the measurements concerning the patient's knee girth were performed at three different levels of the knee joint (12). In order to be able to consistently gather data from the preoperative knee girth's initial point, on which the swelling related to the surgical intervention was postoperatively added, it was decided to gauge the circumference at middle-patella, seven centimetres proximal of the proximal located patellar base and seven centimetres distal of the distal located apex patellae. First of all, the patella was manually defined through its soft tissue covering, longitudinally sellotaped, fixed with two fingers and its centre was first determined using a flexible ruler

and subsequently marked on the sellotape with a washable marker trying not to leave any residuals on the patient's skin. Thereafter, the levels below and above the patellar ends were first approximately sellotaped and again exactly marked using a flexible ruler. The measurement itself was performed three times in the sequence from proximal to distal with the result that every level was gauged independently three times. Consequently, the arithmetic mean was recorded for the statistical analyses. It was always tried to temporarily remove the postoperatively applied dressings in order to receive more accurate results regarding the actual girth of the affected knee joint. If this was not possible after consultation with the surgeon in charge, all the knee girth measurements in the very patient were performed with dressings kept on throughout the hospital stay. The sellotape was removed after finishing the examination.

The ROM of the knee joint was always measured with the patient being laid in a supine position and the examiner using a common, hand-held goniometer. The goniometer's centre was approximately placed at the level of the lateral femoral epicondyle, when its proximal end was adjusted to the femoral trochanter major and its distal end was adjusted to the lateral malleolus of the fibula in order to be able to most precisely gauge the patient's ROM of the knee joint. The patient was requested to first maximally extend and subsequently flex the limb until a further movement was limited by pain or other factors. The reached values of the greatest actively possible extent were recorded for the statistical evaluation.

In addition, there were non-physical evaluations performed. Among those, data concerning the subjectively experienced pain intensity was gathered. For this purpose the eleven-point numeric rating scale (NRS) pain score was used, because it was supposed to be more viable than the use of the VAS, which initially should have been used. Before verbally assessing the pain intensity by use of NRS, each patient was told that zero was equal to "no pain at all" and ten was equal to the "strongest pain even imaginable". The NRS score was always evaluated for the state of absolute rest and the state of motion, for instance during physiotherapeutic sessions, as study patients were requested to attribute a number to both states.

In relation with the subjectively indicated pain the more objectively evaluable analgesics consumption was recorded. As mentioned above, therefore the total hydromorphone usage administered by use of the PCA system at the point of time of 72 hours after the surgical intervention, when the system was removed, was noted and further analysed.

The physical examinations of the knee joint's ROM and girth and the NRS score evaluation were performed on admission day and POD two, four and six.

The length of the patients' individual hospitalisation was simply calculated by subtracting the date of discharge from hospital from the date of admission to hospital.

In the course of the regular change of dressings during the medical rounds the surgical area was exactly examined for potential cold-induced local alterations. In this context, it was particularly searched for signs of frostbite, nerve palsy, inhibited wound healing, deep vein thrombosis and infection. In case of occurrence, the patients had also been told to immediately call attention to eventual adverse effects related to the cold therapy, which they were preliminarily informed about.

Additionally to the relevant measured data for the diploma thesis, the following parameters were investigated within the context of the diploma thesis' underlying study and listed below for the sake of consistency and completeness.
In terms of the perioperative blood loss both the amount of intraoperatively lost and postoperatively via drainages discharged blood was separately recorded and finally aggregated. Also the amount of retransfused blood and the number of administered red cell concentrates, if those were clinically and based on the taken blood samples indicated and therefore given, was registered. The output from the drainages, which were removed after 48 hours, was daily measured, emptied and noted on the bottom end of the patient's temperature chart. Because of that, the noted outputs first needed to be summed up for further calculations. The intraoperative blood loss and retransfusion quantities were noted in the operating room documentations.
Furthermore, the common blood samples, which were taken according to the standard protocol at the Department of Orthopaedic Surgery in Graz and amongst other things

already included haemogram (HG) and C-reactive protein (CRP), were extended for coagulation of the blood (Coag), creatine kinase (CK) and IL-6. Blood samples were taken on admission day, POD one, three and five, which does not correspond to an essential deviation from the standard protocol and therefore was part of the standard routine and in-patient proceeding. On POD five it was renounced examining the IL-6 blood level.

PreOD 1	**TKA**	**POD 1**	**POD 2**	**POD 3**	**POD 4**	**POD 5**	**POD 6**
Knee girth			Knee girth		Knee girth		Knee girth
ROM			ROM		ROM		ROM
NRS			NRS		NRS		NRS
HG, CRP		*HG, CRP*		*HG, CRP*		*HG, CRP*	
Coag		*Coag*		*Coag*		*Coag*	
CK		*CK*		*CK*		*CK*	
IL-6		*IL-6*		*IL-6*			
KSS							*KSS*
McGill							*McGill*
WOMAC							*WOMAC*
HADS							*HADS*
SOZ17							*SOZ17*
AAS							*AAS*
SF-12®							*SF-12®*

Table 6: measurement protocol

On admission day and POD six, which was set the end of the trial in the sense of the in-patient setting, patients were additionally handed over questionnaires, which treated particularly social and pain scores. To these belonged, on the one side, the scores HADS, SOZ17, AAS and SF-12® and, on the other side, the scores KSS, WOMAC and McGill.

Although the evaluation of the questionnaires, the taken blood samples and the recordings of blood loss and retransfusion were part of the diploma thesis' underlying study they will no further be treated within the diploma thesis itself but eventually in publications elsewhere.

2.11 Statistical evaluation

All measurements and evaluations, which were acquired within the study course, were first collected and entered into a Microsoft® Excel sheet. Accordingly, the data set was pasted in IBM® SPSS® Statistics software version 20. SPSS® software was used in order to perform all statistical analyses.

In this regard descriptive statistics were conducted using basic calculations of means, standard deviations, ranges, minima and maxima. For the comparisons between the two study groups on admission day, POD two, POD four and POD six measured data was first checked for the existence of normal distribution by use of Shapiro-Wilk and Kolmogorov-Smirnov tests. If that was present, the independent-samples t-test as parametric test was performed in order to accentuate the differences between the therapy regimes at each point of time. If a normal distribution did not exist, the Wilcoxon-Mann-Whitney test as non-parametric test was performed in order to obtain values of significance regarding between-group distinctions.

The transformation of the test results into graphic representation was based on Microsoft® Excel and IBM® SPSS® Statistics software.

Throughout the statistical analyses, the level of significance, respectively the P-value was defined as $\leq 0{,}05$.

3 Results

3.1 Study population

As mentioned above, the study population, which could be statistically analysed, was consisting of 97 adult patients who gave their written informed consent on participating. 53 female and 44 male patients met the inclusion criteria and did not show any characteristics, which were preliminarily defined as exclusion criteria. 46 patients were randomized into the cryotherapy group (CT) receiving the cTreatment®, whereas the standard treatment group (Stand) receiving cold packs contained 51 subjects.

	Study Group	Frequency	Per cent
Group	CT	46	47,4
	Stand	51	52,6
Total		97	100,0

Table 7: study group distribution

The mean age in the cryotherapy group was 70,35 years ± 9,41 standard deviation (SD) and 71,67 years ± 8,69 SD in the control group. The youngest study patient was 50 years old and the oldest patient was 88 years old. A statistically significant difference between the study groups concerning the distribution of age and sex could not be detected (P > 0,05).

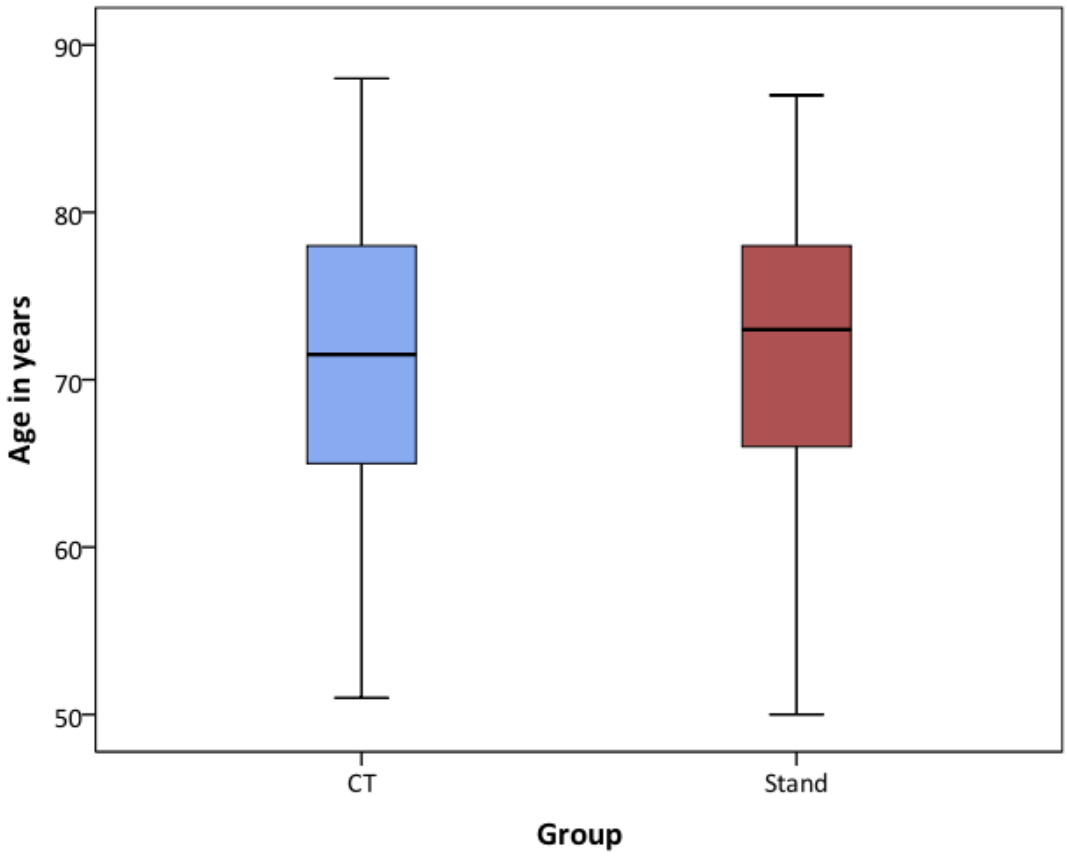


Figure 5: age distribution in study groups

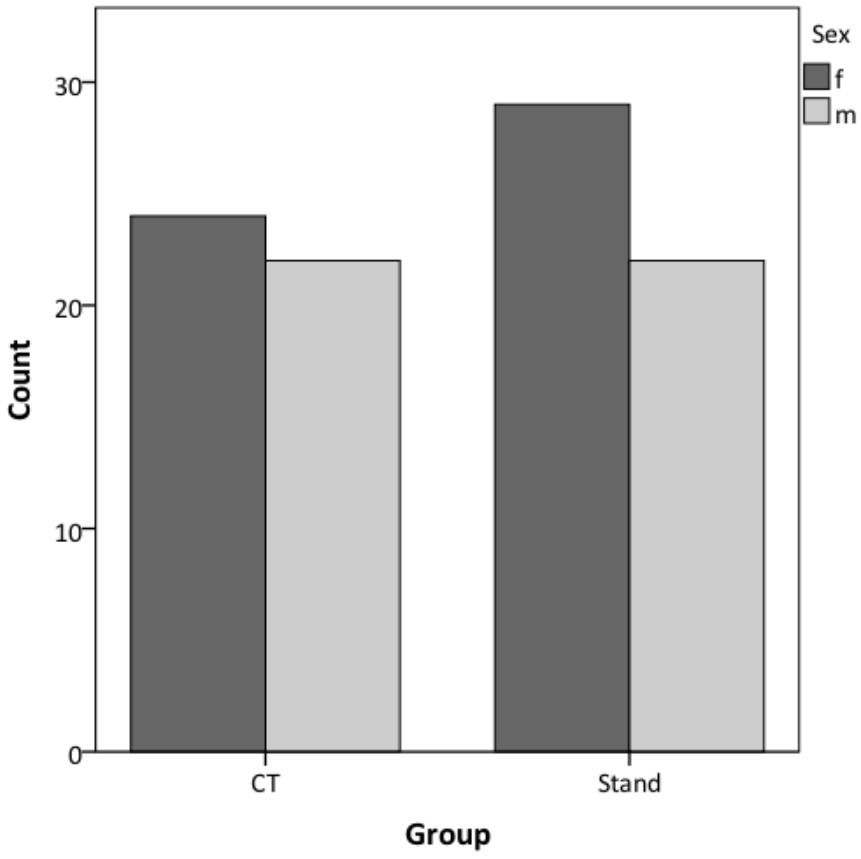


Figure 6: sex distribution in study groups

Among the initially participating 105 study patients, who had given their informed consent, eight had to be withdrawn from the study after being randomized but right at the outset of the trial and therefore were excluded regarding the statistical evaluation. Still, they are listed hereafter. Four of them were randomized into the cTreatment® group and the other four into the comparative group. The mean age of the withdrawn patients, of whom five were female and three were male, was 67,17 years ± 11,66 SD.

Sex	**Frequency**	**Per cent**
Female	5	62,5
Male	3	37,5
Total	8	100,0
Group	**Frequency**	**Per cent**
CT	4	50,0
Stand	4	50,0
Total	8	100,0

Table 8: sex and group distribution in withdrawn patients

The reasons for the withdrawal of the eight listed study patients above were varying. Two of the withdrawn subjects revoked their informed consent before the study proceedings even started, in two cases it was intraoperatively decided to implant other endoprostheses than defined as the study inclusion criteria, one patient received spinal anaesthesia although discussed otherwise when informing about the study's requirements and proceedings, one patient suffered from an allergic reaction on the scheduled day of TKA surgery and was not able to adhere to the study protocol, one patient was discharged, because the surgical intervention was cancelled due to non-medical issues and one patient did not observe the cryotherapeutical protocol and showed incompliance in the first place.

3.2 Endoprostheses distribution

The distribution of the used endoprostheses for the performed TKA surgeries approximately reflects the normal endoprostheses usage at the Department of Orthopaedic Surgery of the LKH-Univ. Klinikum Graz in patients undergoing TKA. In total, there were 66 PFC® endoprostheses implanted but only 31 LCS® endoprostheses.

	Study Group	Endoprosthesis		Total
		LCS	PFC	
Group	CT	13	33	46
	Stand	18	33	51
Total		31	66	97

Table 9: endoprostheses distribution in study groups

33 PFC® endoprostheses were implanted in the cryotherapy group, but only 13 LCS® endoprostheses. There was a similar distribution within the control group, in which 18 LCS® and also 33 PFC® endoprostheses were used during the TKA surgery. There was no statistically significant difference in the utilisation of the two different types of endoprostheses between the two study groups (P=0,463).

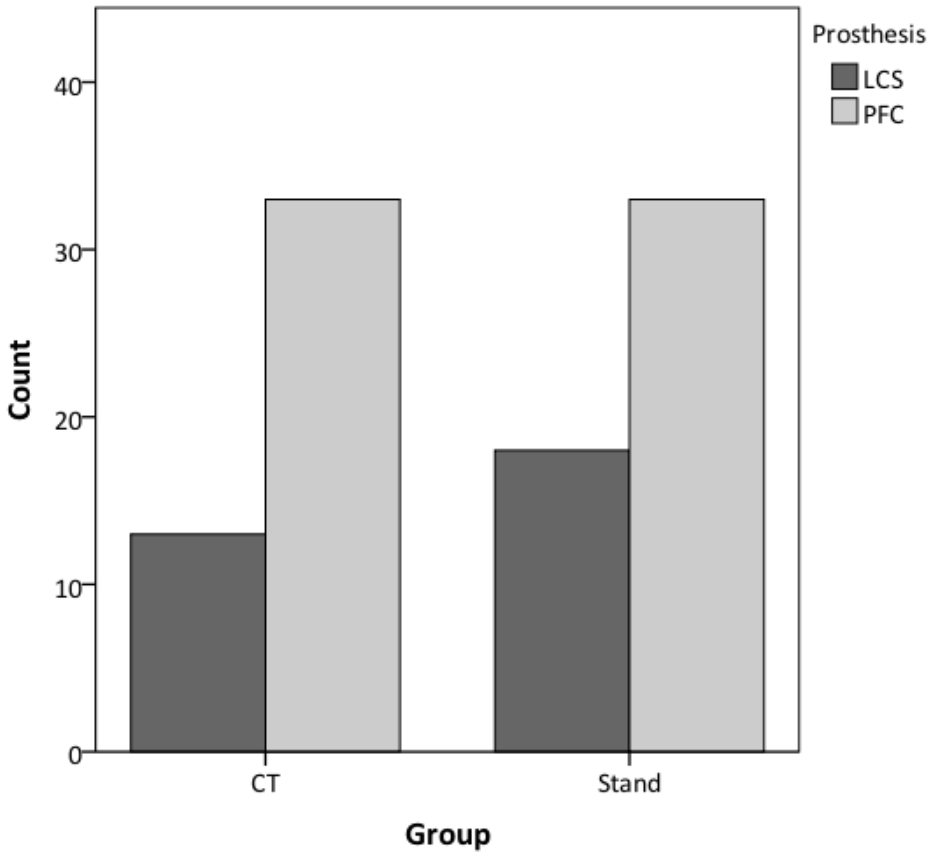


Figure 7: endoprostheses distribution in study groups

3.3 Adverse effects

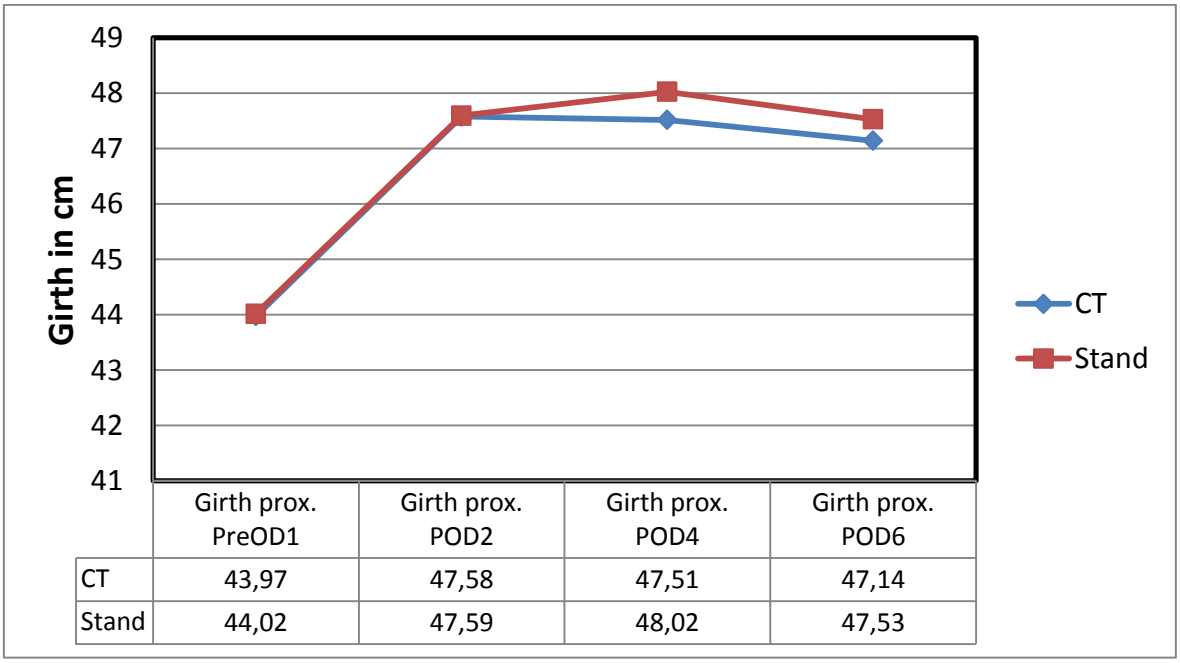
Throughout the proceedings of the whole study it was not possible to detect any sort of eventual adverse effect neither in the course of the regular ward rounds and dressing changes, nor did any patient mention side effects, which they were preliminarily informed about. This fact applies to both the cryotherapy group and the standard group.

During the process of physically measuring other parameters on POD two, four and six patients rarely claimed a certain discomfort due to the cryotherapeutical treatment regime regarding, on the one hand, the daily invested amount of time for the therapy, and on the other hand, the cold itself, which was perceived as unpleasant.

3.4 Swelling / Knee girth

The girth of the knee joint was measured at three different levels, which were mid-patellar, seven centimetres proximal of the patellar base and seven centimetres distal of the apex patellae.

Analysing the collected data regarding the swelling proximal of the joint, there is no statistically significant difference between the study groups before the surgical intervention (P = 0,966), when the mean girth in the cTreatment® group was 43,97 cm ± 4,29 SD and 44,02 cm ± 4,92 SD in the control group. After the TKA surgery the girth drastically increased in both study groups on POD two without any statistically significant difference between the groups. Whilst the cryotherapy group already showed a minimal girth decrease towards POD four, the standard group continued to slightly rise. However, these findings stayed beneath statistical significance (P = 0,563). On POD six the postoperative swelling decreases to 47,14 cm ± 3,47 SD in the therapy group and 47,53 cm ± 4,64 SD in the reference group. It was not possible to detect a significant between-group difference regarding the course of swelling proximal of the patella (P > 0,05).



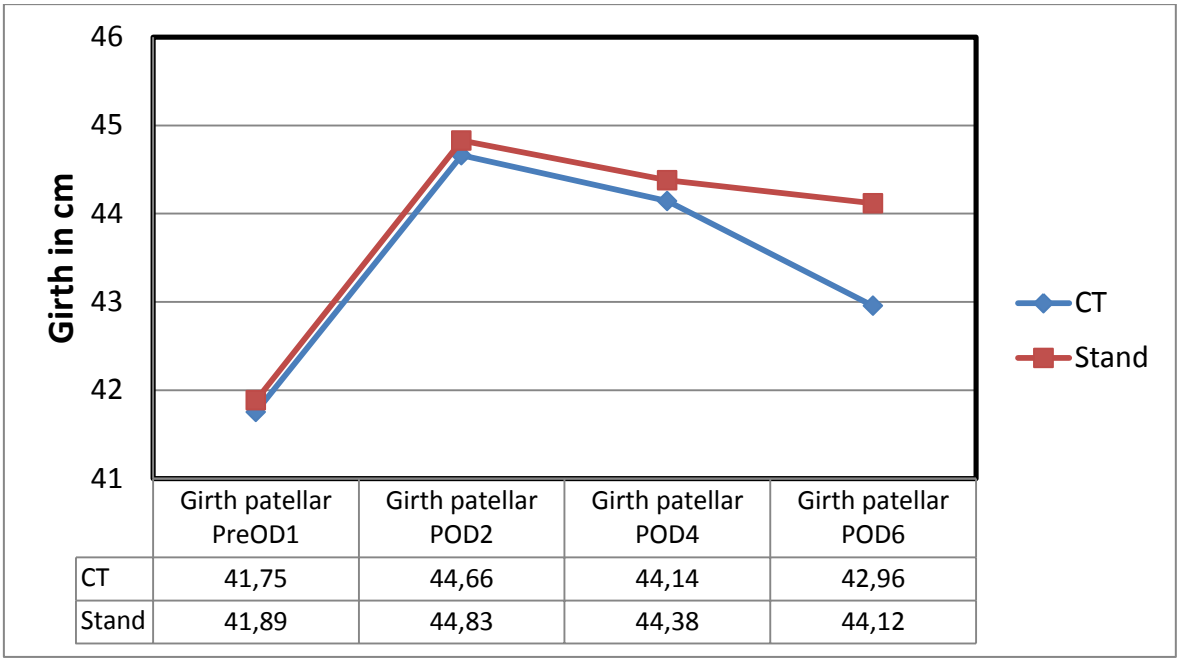
	Girth prox. PreOD1	Girth prox. POD2	Girth prox. POD4	Girth prox. POD6
CT	43,97	47,58	47,51	47,14
Stand	44,02	47,59	48,02	47,53

Figure 8 proximal girth alterations in the course of the study

Girth proximal	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	43,97	4,29	0,966
	Stand	44,02	4,92	
POD2	CT	47,58	3,71	0,985
	Stand	47,59	4,80	
POD4	CT	47,51	3,58	0,563
	Stand	48,02	4,65	
POD6	CT	47,14	3,47	0,659
	Stand	47,53	4,64	

Table 10: measurement results and between-group significances of proximal swelling

A similar course of events was shown in respect of the knee girth measured mid-patellar. In the preoperative starting situation on PreOD one the cTreatment® group had a mean of 41,75 cm ± 2,63 SD, whilst the comparative group featured a mean girth of 41,89 cm ± 3,69 SD. Both did not significantly differ (P = 0,840). Postoperatively an analogical increase was found on POD two in both groups with a mean circumference of 44,66 cm ± 2,51 SD in the cryotherapy and 44,83 cm ± 4,3 SD in the standard group. Towards POD four the swelling mid-patellar decreased approximately to the same extent. Towards POD six the mid-patellar swelling in the cryotherapy group dropped down to a mean girth of 42,96 cm ± 5,47 SD. The knee girth in the control group decreased more steadily to mean 44,12 cm ± 3,85 SD. Although a clear advance concerning the cTreatment® group, particularly approaching POD six, could be detected, it did not reach a statistically significant level (P = 0,645).



	Girth patellar PreOD1	Girth patellar POD2	Girth patellar POD4	Girth patellar POD6
CT	41,75	44,66	44,14	42,96
Stand	41,89	44,83	44,38	44,12

Figure 9: mid-patellar girth alterations in the course of the study

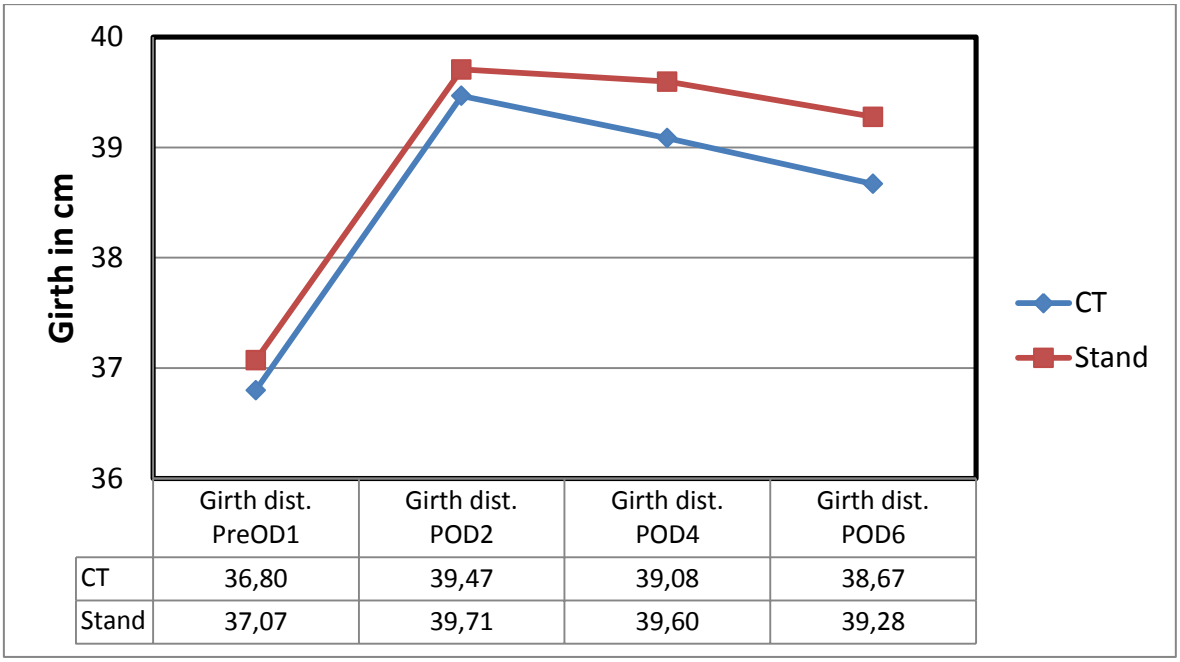
Girth patellar	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	41,75	2,63	0,840
	Stand	41,89	3,69	
POD2	CT	44,66	2,51	0,616
	Stand	44,83	4,30	
POD4	CT	44,14	2,70	0,739
	Stand	44,38	3,82	
POD6	CT	42,96	5,47	0,645
	Stand	44,12	3,85	

Table 11: measurement results and between-group significances of patellar swelling

In regard of the process of measuring the joint girth distal of the patella the statistical results again show a very similar course. Before the surgical intervention the mean knee girth in the cTreatment® group was 36,8 cm ± 2,95 SD and 37,07 cm ± 3,53 SD in the standard group. Once more the knee girth distinctly increased due to the surgical

intervention towards POD two, when the measured circumference was 39,47 cm ± 2,8 SD in the test population and 39,71 cm ± 3,81 SD in the reference population indicating a postoperative swelling to the approximately same extent. Towards POD four it was possible to detect a decrease in both groups, although it appeared to be more obvious in the cTreatment® group, which consistently declined girth in order to reach a mean of 38,67 cm ± 2,93 SD on POD six. On the contrary, the standard group seemed to display a slightly slower downsizing of the measured girth distal of the joint reaching a mean of 39,28 cm ± 4,09 SD on POD six.

However, it was not possible to prove more than a tendency in terms of a statistically significant between-group difference regarding the swelling distal of the patella (P = 0,482).



	Girth dist. PreOD1	Girth dist. POD2	Girth dist. POD4	Girth dist. POD6
CT	36,80	39,47	39,08	38,67
Stand	37,07	39,71	39,60	39,28

Figure 10: distal girth alterations in the course of the study

Girth distal	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	36,8	2,95	0,885
	Stand	37,07	3,53	
POD2	CT	39,47	2,80	0,840
	Stand	39,71	3,81	
POD4	CT	39,08	2,95	0,503
	Stand	39,6	3,77	
POD6	CT	38,67	2,93	0,482
	Stand	39,28	4,09	

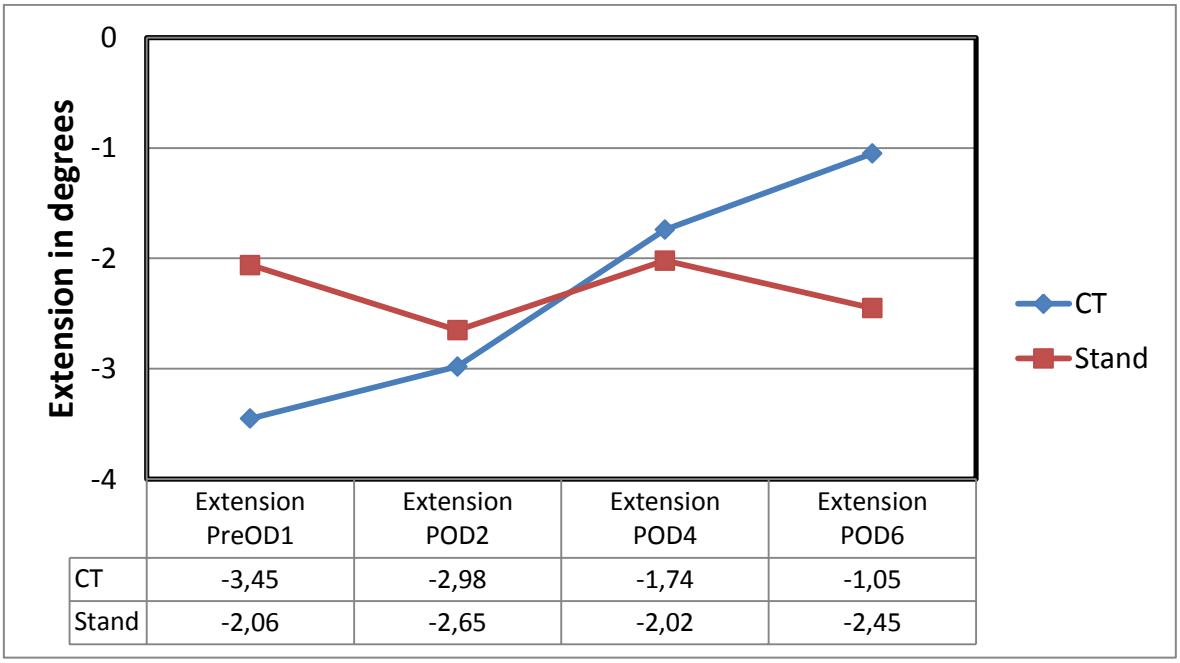
Table 12: measurement results and between-group significances of distal swelling

3.5 Knee ROM

Regarding one half which compiles the parameter knee ROM, the extension, both study groups had unlike initial values on PreOD one. Whilst the cTreatment® group featured a mean deficiency of extension to an extent of -3,45 degrees ± 5,6 SD, the mean extension deficiency within the standard group was measured at -2,06 degrees ±2,86 SD. This situation at the starting point still remained beneath the level of significance. The further analysis of the measurements on POD two and four indicated, on the one hand a decline in the extension deficiency within the cTreatment® group with a mean of -2,98 degrees ± 3,84 SD on POD two up to -1,74 degrees ± 3,25 SD on POD four, and on the other hand a postoperative gain of the extension shortcoming within the reference group towards POD two with a mean of 2,65 degrees ± 3,24 SD in the standard group, which enhanced on POD six in order to almost reach the preoperative starting point on POD four, before it again deteriorated on POD six with an extension deficiency of -2,45 degrees ± 3,28 SD. On the contrary, the improvement of the extension shortcoming steadily progressed towards POD six in the cryotherapy group, when it reached -1,05 degrees ± 2,33 SD.

Whereas the study groups did not statistically significantly differ on PreOD one, POD two and four, they definitely did on POD six, which equals the study's ending point. Displaying a reduced extension deficiency of -1,05 degrees ± 2,33 SD, the cTreatment® group is able

to extend the treated knee joint to a significantly greater extent than the control group (P = 0,022). This becomes all the more notable considering the study groups' starting points on admission day, which even conversely differed, when not necessarily reaching the statistically significant level.



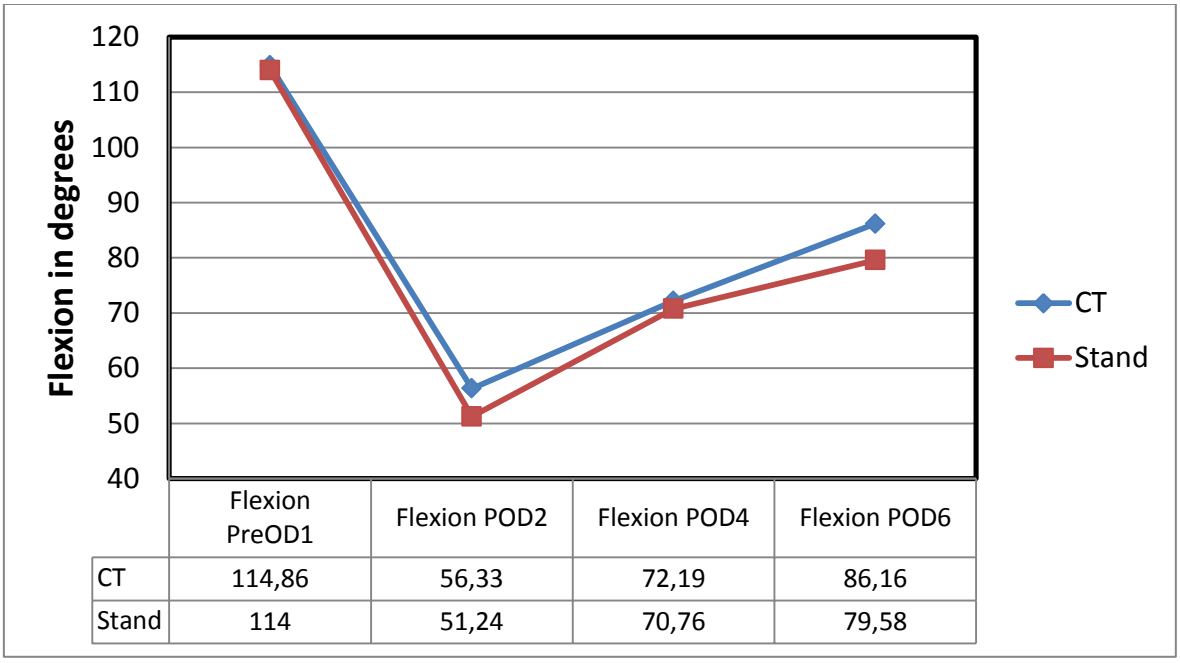
	Extension PreOD1	Extension POD2	Extension POD4	Extension POD6
CT	-3,45	-2,98	-1,74	-1,05
Stand	-2,06	-2,65	-2,02	-2,45

Figure 11: alterations of extension in the course of the study

Extension	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	-3,45	5,6	0,623
	Stand	-2,06	2,86	
POD2	CT	-2,98	3,84	0,858
	Stand	-2,65	3,24	
POD4	CT	-1,74	3,25	0,482
	Stand	-2,02	3,07	
POD6	CT	-1,05	2,33	0,022
	Stand	-2,45	3,28	

Table 13: measurement results and between-group significances of knee extension

Investigating the other half, which assembles the knee ROM, the flexion, no unlike starting points of the two study groups could be found. The cTreatment® group featured a mean flexion on admission day of 114,86 degrees ± 15,13 SD. The comparative group showed approximately the same mean with 114 degrees ± 13,59 SD. The flexion range greatly dropped down after the TKA surgery on POD two to a mean of 56,33 degrees ± 11,3 SD in the cTreatment® group and 51,24 degrees ± 16,1 SD in the comparative group. Although, in the cTreatment® group the postoperative flexion extent is on average 5,09 degrees higher, it closely stayed beneath significance (P = 0,089). Towards POD four the two groups nearly converged when regaining a larger ROM with the cryotherapy group reaching 72,19 degrees ± 9,34 SD and the standard group 70,76 degrees ± 16,75 SD in maximal flexion. On POD six the mean flexion in the cTreatment® group arrives at 86,16 degrees ± 6,97 SD. The regain of the flexion range in the standard group presents more slowly achieving 79,58 degrees ± 13,57 SD. At this time the between-group difference could be found statistically significant (P = 0,021).



	Flexion PreOD1	Flexion POD2	Flexion POD4	Flexion POD6
CT	114,86	56,33	72,19	86,16
Stand	114	51,24	70,76	79,58

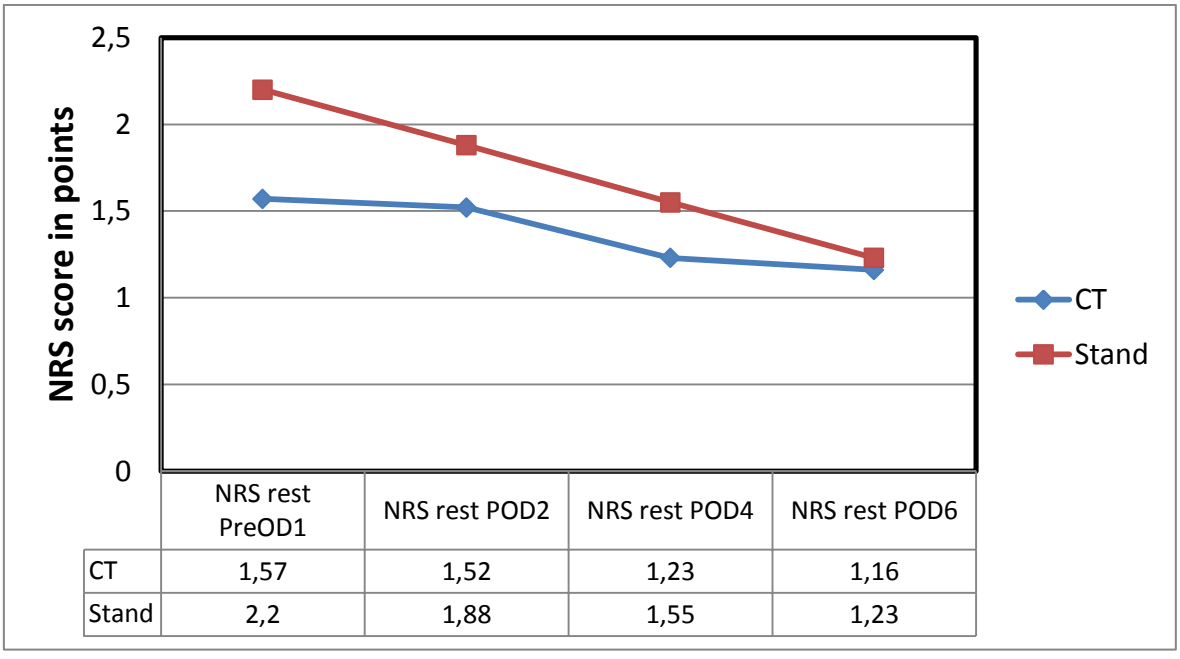
Figure 12: alterations of flexion in the course of the study

Flexion	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	114,86	15,13	0,772
	Stand	114	13,59	
POD2	CT	56,33	11,3	0,089
	Stand	51,24	16,1	
POD4	CT	72,19	9,34	0,867
	Stand	70,76	16,75	
POD6	CT	86,16	6,97	0,021
	Stand	79,58	13,57	

Table 14: measurement results and between-group significances of knee flexion

3.6 Pain (NRS)

The sheerly subjectively measured pain in terms of the NRS score was collected both in rest and in motion, for instance during a physiotherapeutic session.



	NRS rest PreOD1	NRS rest POD2	NRS rest POD4	NRS rest POD6
CT	1,57	1,52	1,23	1,16
Stand	2,2	1,88	1,55	1,23

Figure 13: alterations of NRS in rest in the course of the stud

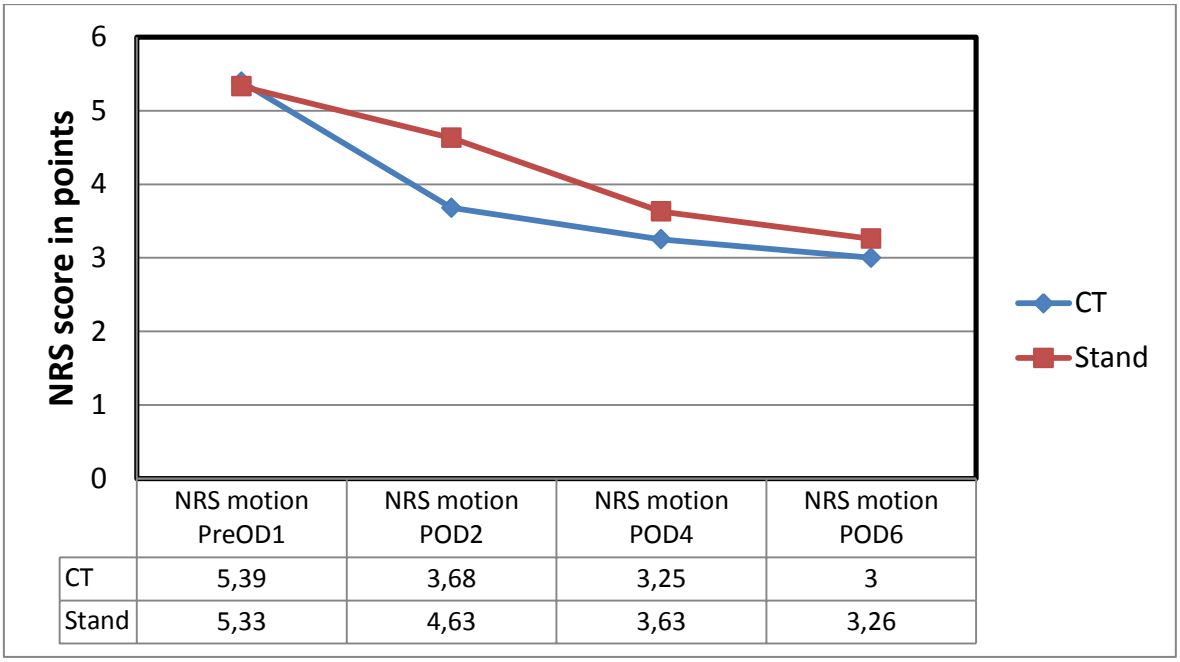
NRS in rest	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	1,57	1,19	0,082
	Stand	2,2	1,65	
POD2	CT	1,52	1,27	0,102
	Stand	1,88	1,22	
POD4	CT	1,23	0,91	0,143
	Stand	1,55	1,1	
POD6	CT	1,16	0,84	0,748
	Stand	1,23	0,96	

Table 15: measurement results and between-group differences of NRS in rest

First, the alteration related to the NRS in rest will be discussed. On admission day the groups did just not significantly differ (P = 0,082), the standard group with a mean NRS of 2,2 ± 1,65 SD still suffering from slightly more pain than patients in the cTreatment® group having a mean NRS of 1,57 ± 1,19 SD. Despite this unlike starting points the study groups managed to postoperatively converge as the control group showed a non-significant but greater reduction in NRS. From POD two, when standard group hit 1,88 ± 1,22 SD and the cryotherapy group reached 1,52 ± 1,27 SD, they almost parallel declined towards POD four, when the control group displayed a mean NRS of 1,55 ± 1,1 SD and the cTreatment® group dropped to 1,23 ± 0,91 SD. From POD four to POD six the groups once again converge in order to only minimally differ at the study's end point, when the cryotherapy group featured a mean NRS of 1,16 ± 0,84 SD and the reference group a mean of 1,23 ± 0,96 SD.

In general, regarding the curve shapes the standard group shows a more steady and sharper decline, whereas the cryotherapy group's curve only indicates a slight decrease in NRS over the course of the study.

Aside from the difference on admission day, which stayed beneath the level of significance, no further between-group divergences could be detected concerning the NRS score in rest.



	NRS motion PreOD1	NRS motion POD2	NRS motion POD4	NRS motion POD6
CT	5,39	3,68	3,25	3
Stand	5,33	4,63	3,63	3,26

Figure 14: alterations of NRS in motion in the course of the study

In regards to the alterations in NRS in motion there was no significant between-group difference detectable before the surgical intervention in terms of the TKA surgery. The cTreatment® group started at a mean NRS of 5,39 ± 2,37 SD and the standard group at 5,33 ± 2,05 SD. When the cryotherapy group postoperatively reached 3,68 ± 2,12 SD on POD two, it dropped statistically significantly lower than the comparative group (P = 0,034), which did not exceed 4,63 ± 2,11 SD. This divergence could not be found with growing postoperative distance to the surgical intervention. On POD four the study groups already approached again concerning their NRS in motion scores. At the study's end point, respectively on POD six, the cTreatment® group showed a mean NRS of 3 ± 2,05 SD. The control group finished with a similar score of 3,26 ± 2,05 SD.

NRS in motion	Study Group	Mean	Standard Deviation	P Value
PreOD1	CT	5,39	2,37	0,824
	Stand	5,33	2,05	
POD2	CT	3,68	2,12	0,034
	Stand	4,63	2,11	
POD4	CT	3,25	2,06	0,246
	Stand	3,63	1,89	
POD6	CT	3	2,05	0,423
	Stand	3,26	2,05	

Table 16: measurement results and between-group differences of NRS in motion

3.7 Analgesia use

Unlike the sheerly subjectively evaluated NRS score, the parameter pain was also measured as the opiate consumption of each patient was summed up after 72 hours, when the PCA systems were removed.

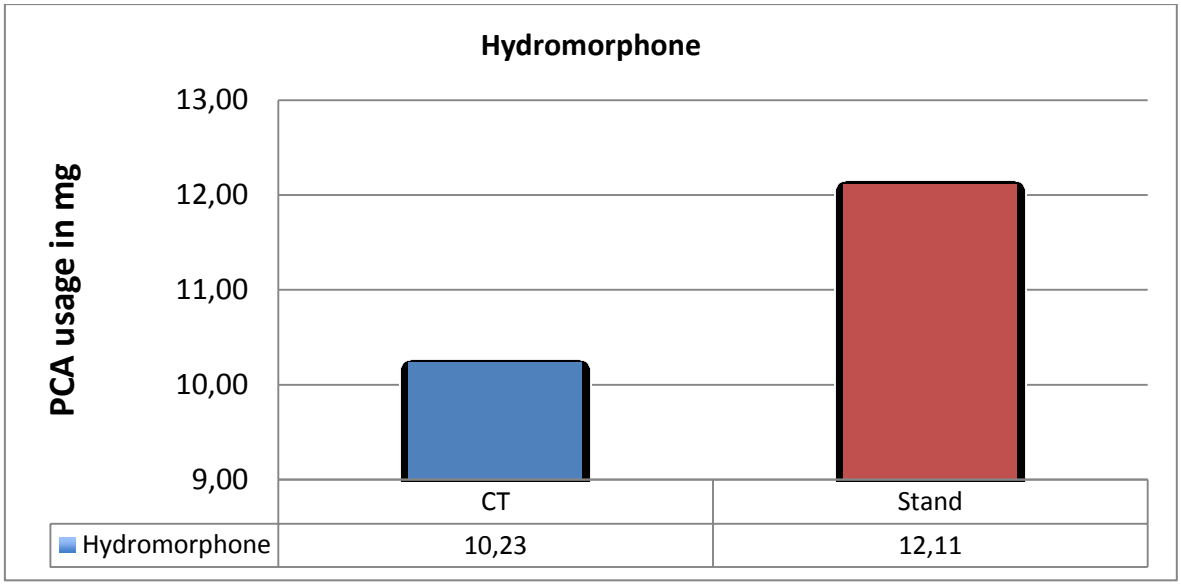


Figure 15: hydromorphone consumption in study groups

In total, the mean consumption of hydromorphone after 72 hours, in other words until the PCA system was removed, was 10,23 mg ± 5,05 SD in the cTreatment® group. The standard group featured a mean opiate consumption of 12,11 mg ± 7,97 SD. Although, a clear tendency indicating a lower administration of hydromorphone by use of the PCA system within the cTreatment® group was observed, the difference to the comparative group did not undercut the level of statistical significance (P = 0,409).

Hydromorphone	Mean	Standard Deviation	P Value
CT	10,23	5,05	0,409
Stand	12,11	7,97	

Table 17: PCA consumption and between-group significance

3.8 Length of hospital stay

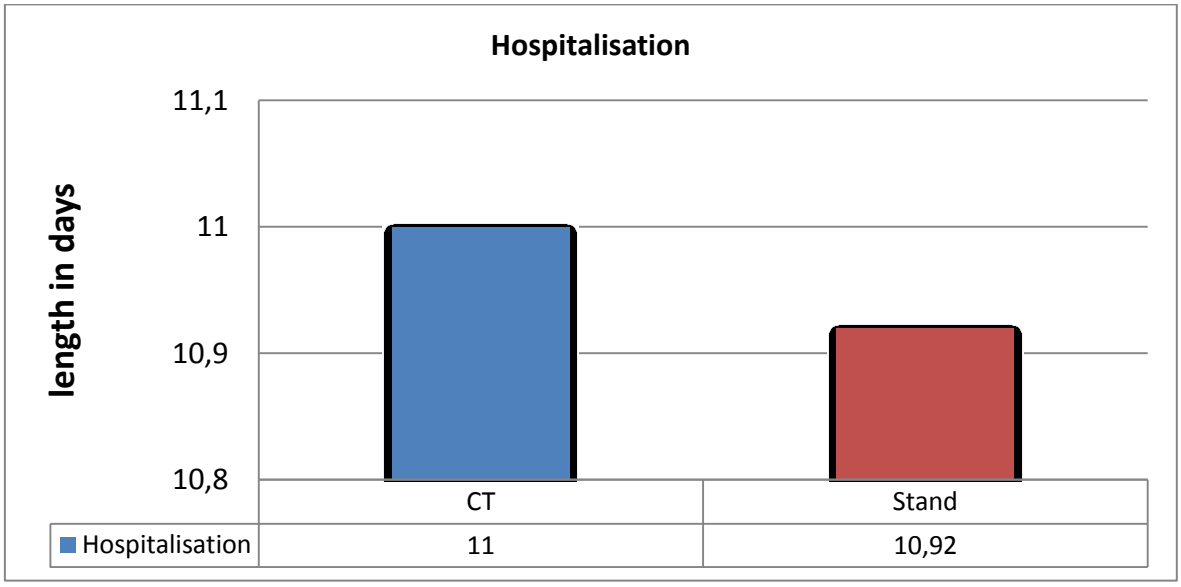


Figure 16: length of hospital stay in study groups

There was no statistically significant divergence between the two study groups observed in terms of the length of their hospitalisation (P = 0,556). The cTreatment® group showed a mean stay of 11 days ± 2,64 SD. Likewise did the standard group indicate a similar length of stay of mean 10,92 days ± 3,57 SD.

Hospitalisation	**Mean**	**Standard Deviation**	**P Value**
CT	11	2,64	0,556
Stand	10,92	3,57	

Table 18: length of hospital stay and between-group significance

4 Discussion

The aim of the study was to assess a new medical device, the cTreatment® system, in peri- and postoperative care in terms of cryotherapeutical intervention in patients undergoing primary and unilateral TKA surgery. A priori, the study protocol contained the peri- and postoperative cold treatment of the knee joint, as cold induced benefits are particularly notable with regard to the extensive soft tissue trauma including oedema, haematoma, both in the sense of swelling, and pain due to the performed surgical intervention.

In the study setup it was consciously passed on a control group not receiving any locally applied cold therapy at all in favour of comparing the cTreatment® system to the traditional standard cooling protocol of the study site, because, on the one hand, positive effects concerning cryotherapy in patients undergoing TKA surgery have already been shown in recent systemic reviews (9, 10) and participating patients were not supposed to be cut off from those benefits when giving their informed consent and, on the other hand, on grounds of its advantages it is often self-evidently applied belonging to the clinical routine referring to surgical interventions of the knee joint (27). Also, it was assumed, that eventual significant between-group divergences had a greater impact on the future cold therapy protocol when a new system was compared to the actual and currently applied standards.

In the course of the statistical analysis of the study results it was clearly possible to positively cover the main objective, which was preliminarily defined as the safety of the cTreatment® system. There was no occurrence of any adverse event recorded throughout the clinical trial, which could possibly be related to the usage of the cTreatment® system. Additionally, patients within the comparative group, which were treated with the standard cold pack regimen, did not show adverse reactions either. These facts lead to the collective claim, that the two different types of locally applied cold therapy did not trigger an adverse effect in the investigated 97 patients, although, one reviewed study in the literature research stated by-effects in the sense of deep vein thrombosis appearing

both in the treatment and control group (16). In this context and as previously assumed, the thrombosis might potentially have depended on an insufficient remobilisation regimen in participating patients of both the cold therapy and comparative group, given the fact, that the incidents occurred in both study groups and the early remobilisation is one of the most important factors in prophylaxis of deep vein thrombosis (29). Scarcella et al. observed a total of four adverse events, which only affected the control group (17), which could not be found reproducible in the current study either. Apart from this, the findings in the present study are in conformity with the majority of reviewed papers of the literature research, which did not detect any sort of adverse events related to the locally applied cryotherapy (15, 17-19, 26). Something, which was not recorded as adverse effect in the underlying study, but could be termed slight side effect, was the subjectively experienced discomfort, that some patients in the cTreatment® group mentioned during the treatment sessions. In a recent systemic review it was found the most common reason for withdrawal from the trials (9), though, such strong sorts of uncomfortableness leading to withdrawal were not observed in the conducted study. The subjectively experienced sort of discomfort might also be closely related to the high frequency of the application sessions, which was at least twice a day, and their single durations of at least two hours each. This treatment protocol contained more frequent and / or longer sessions for a longer time after the surgery than many of the reviewed studies (12, 13, 18), which accounted for a distinctly longer total treatment time per day and consecutively for the understanding of the patients. Radkowski et al., Scarcella et al. and Morsi represent an exception using the cryotherapy continuously throughout the hospital stay until discharge, respectively until POD six (15, 17, 19). So does Su et al. continuing the cold therapy even for two weeks after the surgical intervention (14). Unfortunately, those studies did not cover results on subjectively experienced discomfort. Some patients of the present study did even claim that the cryotherapy regimen nearly occupied their whole daily routine. This subjective perception could additionally contribute to the experienced uncomfortableness, although it would rather belong to the individual satisfaction than adverse effects strictly speaking.

Summarizingly, the cTreatment® used within the context of the applied treatment protocol appears to be a safe cryotherapeutical device used in patients undergoing TKA surgery.

In fact, given its safety it is interesting to consider the potential benefits found over the course of the study, which are related to the usage of the cTreatment® system especially when thinking of an eventual future field of application and the chance, if a possible undertaking of the standard regimen's role was possible.

In this context, the tested cryotherapeutical device could not achieve a statistically significant reduction in the postoperative swelling of the knee joint compared to the comparative group, given the fact that both groups did not significantly differ at the starting point on admission day. This applies for all measurements performed, meaning for seven centimetres proximal of the patellar, mid-patellar and seven centimetres distal of the patellar. Over the course of the assessments the mean girth of the knee joint strikingly increased after the TKA surgery in both groups, as it was already described in the findings of the literature research (12, 14). This is probably attributable to the variable intraoperative soft tissue trauma with consecutive secretion, bleeding and oedema as well as to individual postoperative reaction. Yet, no significant between-group differences ($P > 0,05$) were observed in the postoperative course of therapy. Even the biggest divergence between the mid-patellar girth measurements on POD six of the cTreatment® group (mean 42,96 cm ± 5,47 SD) and the control group (mean 44,12 cm ± 3,85 SD) did not undercut the level of significance with $P = 0,645$. Generally, there were slight tendencies noticeable favouring the cTreatment® system, particularly postoperatively towards POD four and six, but all of the results did not reach significance. The same was already stated by Demoulin et al., who also performed girth evaluations at three different levels at the knee joint, and Su et al. comparing different application forms of cryotherapy, respectively comparing cold therapy to a control group without any cooling regimen (12, 14).

Furthermore, it must be stated that in some patients participating in the underlying study it was not possible to acquire the data on the knee circumference with dressings removed. In those cases it was tried to measure with dressings kept on throughout the trial until POD six. In fact, it cannot be ruled out that there were minor alterations to the actual knee girth gauged due to the inconsistent character of the dressings, which were regularly changed. Still, that the dressings account for the not achieved undercutting the significance level must be seen as rather unlikely.

In respect of the monitored parameter of pain evaluated by use of NRS score, a distinctly significant difference between the study groups had not been expected, at least not within the first 72 hours after the surgical intervention. This was to a great extent because of the possibility of individual pain modulation using the PCA system, which was removed after 72 hours postoperatively. Based on the controllable administration of hydromorphone, each patient was able to directly influence the subjectively perceived pain, which again was quantified with the NRS score.

On the contrary, the statistical analysis displayed a significant between-group divergence in NRS in motion on POD two (P = 0,034), when the cTreatment® group featured a mean NRS in motion of 3,68 points ± 2,12 SD and the control group 4,63 ± 2,11 SD. A similar benefit, also described exclusively on POD two, favouring cryotherapy concerning pain scores was stated in recent systemic reviews (9, 10), whereas one study found significant benefits in VAS throughout POD six yet comparing cryotherapy to no cold therapy at all and still detecting the widest between-group divergence on POD two (19).

However, this causal chain of thought mentioned above was mirrored by the study's results referring to the NRS score in rest. No significant divergence between the study groups was found on admission day (P = 0,082) and in the postoperative phase on POD two (P = 0,102), four (P = 0,143) and six (P = 0,748).

The reason, why the difference in the present study was only noticeable in motion, could possibly be based on the fact, that pain is less adjustable with drugs when in motion than in rest due to a greater fluctuation range and unpredictable peaks, for instance during physiotherapy, when the cTreatment® was parallel applied with the patients' limb being in the continuous passive motion machine. An immediate adjustment by use of the PCA system appears almost impossible in that case, so that actual differences between the study groups could be revealed even with the aid of a subjectively graded scale, the NRS in motion.

The objectively measured pain by use of the statistical analysis of the total PCA consumption after 72 hours, when the PCA system was removed, did not considerably differ from the pain measured by use of NRS. The cTreatment® group featured a total consumption of 10,23 mg ± 5,05 SD hydromorphone, whereas the standard group

consumed a total of 12,11 mg ± 7,97 SD. Although, the mean difference between the study groups appears to be notable in terms of a distinct statistical tendency, a statistical significance could not be detected (P = 0,409), which is in conformity with multiple reviewed studies (16-18, 26). Only Su et al. and Morsi were able to assess significant reductions in narcotic requirements related to TKA surgery comparing a cryopneumatic device to standard icing regimen (14), respectively cryotherapy to no cold therapy at all (19).

The absent possibility to prove statistical significance might result from intensely varying data regarding the individual hydromorphone consumption by use of the PCA in patients assigned to both the cTreatment® group and the standard group.

The statistical analysis of the underlying study's data on knee ROM showed clear between-group significances around POD six, which were reached in both the extension (P = 0,022) and flexion (P = 0,021) of the knee joint, both times favouring the study group assigned to the cTreatment® system. Although, conforming with reviewed literature the mobility of the knee joint still remained depressed on POD six compared to the starting point on admission day, which is probably due to trauma sequelae from the TKA such as pain, periarticular swelling and spasm (16).

Separately regarding the extension of the knee joint in the present study the cTreatment® group featured a mean extension deficiency of -1,05 degrees ± 2,33 SD, whereas the standard group showed -2,45 degrees ± 3,28 SD on POD six, which was found significant with P = 0,022, as mentioned above. It becomes all the more relevant considering the development over the course of the trial, because the two study groups differed conversely on admission day. Still, no statistical significance could be verified for the preoperative phase.

The statistical analysis of the flexion in the underlying study displays a similar course. On POD six the cryotherapy group presented with a mean flexion of 86,16 degrees ± 6,97 SD and the standard group exhibited 79,58 ± 13,57 SD. This was found significant with P = 0,021.

The between-group divergences on POD six militate against several papers from the literature review (14, 17, 18), but are in line with results from two reviewed trials (16, 19). Kullenberg et al. were able to verify, that the cold compression group reached a mean of

12,2 degrees higher knee ROM than the comparative group at the time of discharge (16). Even three weeks after TKA surgery they were 11,3 degrees better in knee ROM than the control group, when they achieved 98,9 degrees. Morsi observed a significant enhancement in knee ROM even for six weeks after the surgical intervention (19).

Given the fact, that Kullenberg et al. could not find a between group disparity until POD six, but was still able to prove the significant difference three weeks after TKA (16), and that the present study also started observing significant between-group differences on POD six, it was interesting if one would have continued monitoring the alterations to the knee ROM after POD six in the underlying study in order to be able to compare results to those of Kullenberg et al. Perhaps a similar development could have been observed in a phase after POD six.

Basically, the knee ROM might possibly be improved under the usage of the cTreatment® system because it had an increased impact on the postoperative inflammatory response, secretion, consecutively oedema, peri- and intraarticular bleeding, which was tendentially displayed in the results of the knee girth, not necessarily reaching significance, and consequentially pain, which could significantly be shown in terms of the NRS in motion on POD two (P = 0,034).

Currently, there is still a rather standardized length of hospital stay applicable within the wards of the Department of Orthopaedic surgery at the LKH-Univ. Klinikum Graz in patients having undergone TKA surgery. Nevertheless, these patients could generally be discharged, if the subject is in adequate general state of health especially containing well modulated pain and if the patient is able to reach a flexion level of the knee joint of 90 degrees. The listed criteria above will strictly be taken into consideration in the foreseeable future.

Based on the present study's statistical results of the knee ROM, which exhibited significant benefits for the cTreatment® system on POD six, and the not significantly diverging results concerning the pain evaluated in NRS and hydromorphone, it was preliminarily assumed, that patients assigned to the cryotherapy group could be discharged sooner than patients in the standard group. In actual fact, the length of hospital stay within the cTreatment® group was mean 11 days ± 2,64 SD compared to 10,92 days ± 3,57 SD in the standard group not showing any sign of significant difference

between the groups (P = 0,556). Actually, the reason accounting for this fact might be, that possibly the potential criteria of discharge were not consistently and uniformly observed, as the process of discharge in patients after TKA surgery is still mainly based upon the standardized protocol in this respect. This could perhaps be attributable to clinical habits formed over the years and related to the postoperative practice with patients undergoing TKA surgery, which lead to inattentiveness in this very respect. As a consequence, a possible shortening of hospitalisation in patients treated with the cTreatment® could be shown in the future, even though it was not possible to detect yet.
Nevertheless, two studies were actually able to find a cryotherapy-related reduction of the length of hospitalisation to an extent of 1,4 days on average in patients undergoing TKA (16) and THA surgery (17), which was possibly due to a sooner begin of independent ambulation within the cryotherapy group of both studies (16, 17). The point of time starting independent ambulation is a parameter, which unfortunately was not covered in the present study, but could possibly have given a better insight in the disparity between the flexion development and the equal hospitalisation lengths.

In the direct comparison of the two used methods of cold therapy, the standard cold pack and the cTreatment® system, each procedure possesses its own specific advantages and downsides apart from the stated study results, which should be additionally taken into consideration when balancing their use.
The traditional cold pack is easy to use and self-explanatory in its application even for patients to be treated. Also, it is relatively advantageously priced. Its stiffness particularly when taken right out of the freezer and in early utilization stands out disadvantageously, because it limits the contact area between skin and pack surface and also makes it more difficult to be fastened to the area to be treated. As the cold pack is initially frozen and then progressively warms up, it is often too cold at first, stays within the borders of the approximately optimal cooling temperature for rather a short period of time and accordingly gets too warm afterwards.
The cTreatment® system contains the cPad®, which is specifically designed for the usage on the knee joint featuring a central patellar notch and straps for quick and secure fastening. The cTreatment® Server provides the cPad® with cooled gel exactly at the right temperature in order to constantly maintain the optimal epidermal cooling temperature.

As the fluids never freeze, the cPad® can be easily wrapped around the knee joint ensuring a maximum of contact surface. Nevertheless, the technology is rather pricy and one needs a short introduction on its correct usage.

Generally, when investigating a new medical device, the results showing benefits matter the most. Still, in this connection we supposed, that possibly the more relevant question in an ever increasing economically orientated health care system is, if the usage of the cTreatment® system in patients undergoing TKA surgery only adds expense to the common costs involved in hospitalisation or is there a striking benefit to it, which compensates for the additional expenses.
Nevertheless, the future actual costs of the Waegener® cTreatment® system, which accounted for an additional expense of 250 to 300 euros per treated patient in the context of the underlying study at the Department of Orthopaedic surgery at the LKH-Univ. Klinikum Graz, are rather unknown at the moment, which helps to complicate the answering of the question above. Nevertheless, it features a clearly statistical significance regarding the knee ROM on POD six, almost reaching 90 degrees in flexion (mean 86,16 degrees ± 6,97 SD; P = 0,021), which theoretically would make it possible to discharge the average patient after TKA on the sixth postoperative day or at least short after, as long as the general medical condition was adequate. On that regard, also an economical advantage seems clearly possible.

A final answer will probably be apparent, when further clinical research on the development of the knee ROM after POD six will be performed. In this context, it should be again focused on the knee girth and pain as well in order to be able to better explain the benefits in the mobility. Additionally, the re-evaluation of the length of hospitalisation is recommended, because from where we stand a distinct reduction is expected when closely abiding by the discharge criteria. The cTreatment®‘s economical impact could be clarified in this context.

5 References

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