# Postoperative CRPS generation: a signalling pre-report as a hypothesis

Based on a longitudinally followed post-operative hematoma, treated with pentoxifylline, measured with infrared thermography.

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**Disclosure**
**There is no conflict of interest whatsoever.**
Untested ideas before review.

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**Foreword**

This article describes a relatively rare complication that occurred after a total hip arthroplasty.
A substantial postoperative haematoma with an estimated volume of two litres was further complicated by unbearable pain ten days after the surgery. No effective treatment was available.
The traditional pain management was successfully replaced (postoperatively because of its ineffectiveness) by an off-label treatment that had never been administered as part of mainstream medicinal therapy for this condition. In the Netherlands, careful documentation of facts and events are required for a medication to be categorised as off-label. Infrared thermography is one of the methods used to meet that requirement.
This article addresses counteracting postoperative pain with the administration of a non-traditional medicinal treatment which was decided upon because of the severity of the symptoms, the fact that postoperative CRPS is not rare, the frequent occurrence of chronic pain after this type of surgery, and the completely unexpected outcomes from the thermographic results. It also addresses a possible aetiology of CRPS, and the sensitivity to having a potential lateral CRPS on the opposite side of the body from where the surgery took place. The aspects of CRPS and sensitisation is the hypothesis.
The article contains four different aspects which assume a degree of cohesion, partially substantiated statistically, but have not been proven. They are:

* a description of another treatment for postoperative pain management than the traditional form of treatment.
* a description of an untraditional process monitoring using infrared thermography
* an analogy of the reported situation with the onset of postoperative CRPS: An hypothesis
* a correlation between the thermographic findings on sensitisation processes in the central nervous system and the possible consequences thereof for the onset of CRPS on the heterolateral side is: An hypothesis

The report is, and at the same time, is not a case report. That is confusing

There is too much uncertainty and it is too broad a field to be able to accept scientifically.
It requires too much reading and too much concentration, and ultimately the result is like a cake with four ingredients. It is no longer so easy to publish in these times when specialisation has taken place worldwide and because scientific journals have also followed that trend. The miller only has knowledge of and is only interested in the ground grain, and the seasoner is only concerned with the flavourful ingredients used. The baker wants the cake and is not interested in the composition of the cake flour.
The reader has been warned.

This is the reason why this is being published on the author's Chronic Pain Science Foundation site with the objective of spreading evidence-based ideas and discussion. This is a goal with which the scientific development had started. The article will be worked out in four specialised studies for the specialists, and will be published as such, which is currently the common scientific practice. Another common practice is that it is accompanied by a fee.

# Postoperative CRPS generation: a signalling pre-report as a hypothesis

**Abstract**

A single-case experimental approach was implemented to treat postoperative pain complicated by bleeding after a total hip replacement. Pentoxifylline replaced the initial medication and infrared thermography data were gathered to monitor changes of the autonomous regulation function using the healthy leg as reference. With very high VAS score after surgery, the standard medication was discontinued and replaced with 400 mg of pentoxifylline (PTX) three times daily. The VAS score dropped to 1 within one day, and remained under 4.

Infrared thermography measured both legs for 47 days. The maximum, minimum, and mean temperatures were recorded. Infrared images might clarify the pain and its disappearance. Noticeable similarities were found between all subsequent measurement values during rest, evening, and post-activity daytime. The similarity in values cannot be attributed to identical images of the legs noting that the locations of maximum and minimum temperatures differed daily.

It can be concluded that PTX eliminated an encapsulation of an inflammation process, and as a result, possibly prevented the potential of CRPS developing. In addition, pentoxifylline can possibly cause a change of sensitivity in a segment of the spinal cord, whereby the left and right sides synchronously mirror each other and the higher centres may also be involved. Such a process of synchronisation can play a role in the transition of an active Complex Regional Pain Syndrome process to the heterolateral side, even though literature does not confirm this.

Keywords
Anti-inflammatory, CRPS, NSAIDs, Postoperative pain, Prostaglandins, Infra-red thermography

## Introduction

A 71-year-old male doctor in good general health with bilateral hip osteoarthritis underwent a total left hip replacement on 9 June 2015. He had migraine headaches for which he took sumatriptan.

The operation was performed while the patient was under spinal anaesthesia. The approach was anterolateral. The procedure was successful. A few hours later a seriously acute bleeding occurred and the blood pressure lowered. The wound remained dry. The upper leg became red, very painful, and tense. Hb decreased to 5.6. An estimated 1.5 litres of blood were lost. The pain medication was standard: 1000 mg of paracetamol 4 times daily and 25 mg indomethacin 3 times daily. The VAS scores remained high. Within a week after discharged from the hospital, a VAS score greater than 10 was reached twice. Pain therapy proved to be ineffective. The pain was cramping and stabbing, as if the muscles were twitching around an immobile, inflamed mass. Localization of the pain: above and round knee.

Chronic pain after hip surgery occurs frequently. Complex Regional Pain Syndrome is a complication that occurs seldom. The pain that occurs the most is that which lies closest to the joint involved, but heterolateral localisations also appear. The cause of the chronic pain is not completely clear, but the role of the autonomic nervous system in its development is a topic largely discussed. Vasoconstriction and hypertonia would then play a major role. There are several reports in the literature on pentoxifylline being a rheological pharmaceutical that influences pain.

The author of this article, who is a doctor and also the patient in this study has experience with chronic pain and CRPS within the framework of his postgraduate work. After consultation with the treating specialist, it turned out there was no satisfying alternative treatment for the complaints. So the author decided to carry out a n=1 longitudinal study.

The hypothesis was: Pentoxifylline is the first choice drug for the treatment of complicated postoperative pain and for preventing potential CRPS.

## Methods and materials

In addition to checking the usual vitals of blood pressure and body temperature, and collecting VAS scores, infrared thermography was used to measure the skin temperature of the affected leg while using the healthy leg as a reference. Infrared thermography has a very high sensitivity and specificity for CRPS.
Subsequently, the recovery process was monitored for 47 days using infrared thermography.

### Haematoma resolution

A dose of 400 mg of Pentoxifylline (PTX) taken orally three times a day was used for haematoma resolution.

PTX has been a registered medication for Claudicatio Intermittens with a rheological mechanism of action in the Netherlands since December 1986. It is, therefore, an off-label prescription. Its use is permitted under strict conditions explained in extensive documentation. It is a phosphodiesterase inhibitor which effects IL-6 and TNFα. It improves blood circulation and has a specific inflammation-inhibiting effect. It increases the temperature of a cold spot and decreases the temperature of a warm spot. The motivation behind the change of treatment and the hypothesis of this study is that the inflammation process was limited by vasoconstriction and could therefore not be reduced. A rheological treatment may make the difference here.

Because the doctor-investigator was also the volunteer in this study, there were no ethical obstacles.

**Infrared thermography**

A Flir Camera Type E60bx with Software Flir Tools version 5.2.15161.1001 was used for the measurement. Thermal sensitivity (NETD): 0.05 °C; Field of View: 25° x 19°; Infrared Focus Distance Min: 40 cm; Infrared resolution: 320 x 240; Image Capture Frequency: 60 Hz. Emissivity: 0.98, room temperature: 23 degrees Celsius. Controlled with a thermocouple Ysi-telethermometer and Kipp Plotter. Acclimatising equipment and patient: 15 minutes before first imaging. Position: standing. Distance 1.50 m

**Results**

**Pain scores**

The pain on the operated leg successfully reduced after changing the medication. The VAS score that was greater than 10 fell to 4 after six hours. It fell further to 1 by the end of the day. A relapse of pain three days later when migraine attack occurred. A 25 mg dose of sumatriptan was added to the medication, which is usual for a migraine attack. The leg was extremely painful, very tense, and felt cold four hours later. The situation was comparable to the two previous days. After that the scores that are shown in Figure 1 on 10 June no longer reached that level.

**Fig.1.**

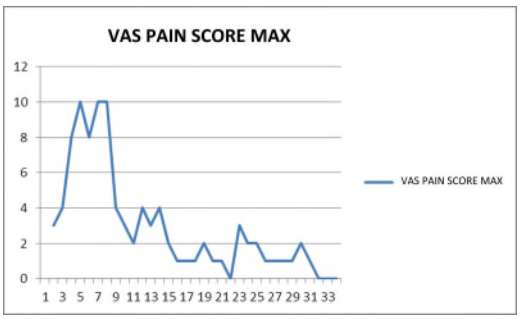



**Figure 1 Maximum Pain score**
**The maximum night time VAS scores. The measurements are on the X-axis. The VAS scores are on the Y-axis. Point 2 is 13 June Point 8: 19 June. After the analgesics were switched to PTX, the night-time pain returned to 1.**

**Table 1 Vas-scores in the first two weeks**

| | 13.6 | 14.6 | 15.6 | 16.6 | 17.6 | 18.6 | **19.6** | 20.6 | **21.6** | 22.6 | 23.6 | 24.6 | 25.6 | 26.6 | 27.6 | 28.6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 07.00 | 3 | 4 | 8 | 10 | 8 | 10 | **>10** | 4 | 3 | 2 | 4 | 3 | 4 | 2 | 1 | 1 |
| 24.00 | 1 | 1 | 3 | 2 | 2 | | 2 | 2 | >10 | 2 | 2 | 1 | 1 | 1 | 1 | 1 |

**Table 1: First row is the calendar date: dd.m. Second row: VAS scores from the night, registered at 7:00 am. Third row: VAS scores from 12:00 pm.**

**Infrared thermography**

The first thermography image showed a hot spot, possibly as a result of inflammatory reaction, encapsulated by a vasoconstrictive area, which disappeared in the second thermography image (see Table 2, Figure 3, Figure 4 and Figure 5).

**Table 2. Skin temperatures in three layers**
**First measurement: discontinued gradient from inner side to outside . Second measurement: continuous gradient**
The first thermography recording was carried out at 10:00 am on that day, six hours after taking the PTX (see Figure 3).

| Infrared measurements | Central temperature $^{o}C$ | Temp first layer $^{o}C$ | Temp second layer $^{o}C$ |
|---|---|---|---|
| Measurement at 10:00 am | 32.7 | 33.6 | 32.4 |
| Measurement at 11:00 pm | 30.4 | 30.5 | 30.8 |

Table 2 in graphics.

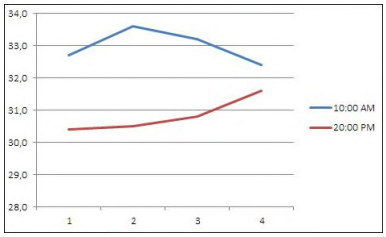



Fig.3.

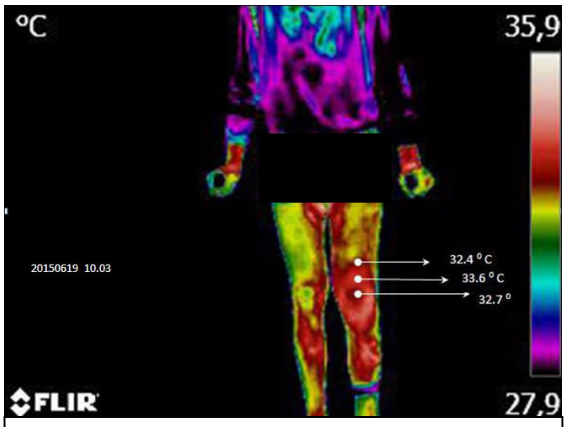



**Figure 3 First infra-red measuring Measurement after VAS >10 and 6 hours after changing the medication to PTX. The temperature is in $^{o}C$. The left leg is clearly swollen considerably. VAS score: 4**

Fig.4.

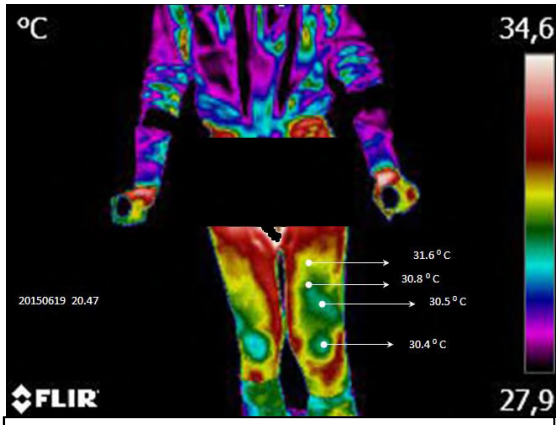



**Figure 4 Recording of the leg in the evening The three "layers" are still present, but the cold layer has now changed into a warm layer. Measurement values are 30.4 $^{o}C$, 30.5 $^{o}C$, 30.8 $^{o}C$, and 31.6 $^{o}C$. The vasoconstriction is now central surrounded by a warm vasodilatative layer. The core has clearly cooled down compared to the morning image. The VAS score during the recording of this image is 1.**

Fig 5. The thermography image of the left upper leg showed a warm area encircled by a colder zone around the knee (Figure 5).

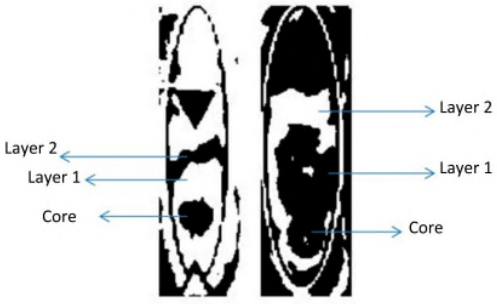



**Figure 5 Layers in binary filter**
**The upper area of the left leg in the morning and evening with a binary filter. The left image is six hours after taking 400 mg of PTX. The right image is 17 hours after taking 400 mg of PTX three times.**

**Left: A central black circle is under the triangle inside the oval measured cold area. A white (warm) ring is around the circle, which itself is encircled by a thinner darker ring (the arrow under the triangle). It represents the knee that is surrounded by a large warm area which itself is surrounded by a layer with vasoconstriction that is colder. The measurements are 32.7 $^{o}C$, 33.6 $^{o}C$, and 32.4 $^{o}C$, respectively.**

**Right: the same area. The core and layer 2 have cooled off, which is why they are represented in black. The encircling layer increased in temperature, which is why it is represented in white. The measurement values are 30.5 $^{O}$C, 30.8 $^{O}$C, and 31.6 $^{O}$C, respectively.**

Longitudinal skin temperature over 47 days
Fig.6.

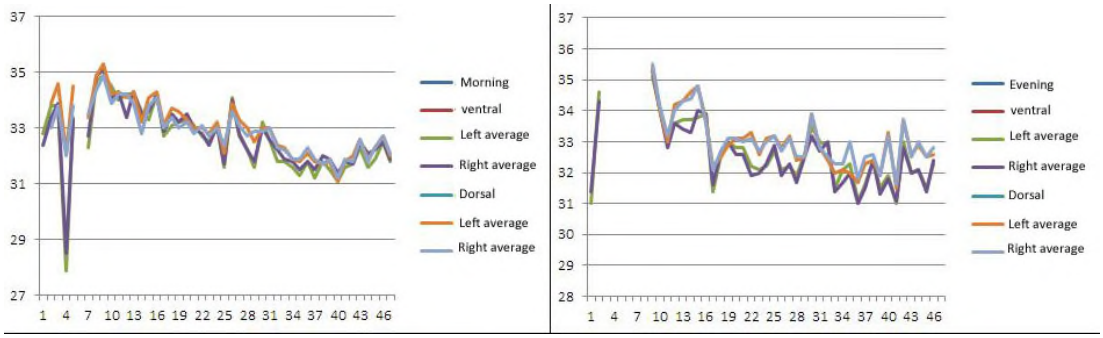



**Figure 6 Mean measurements infra-red**
**The temperature in Celsius is on the vertical axis. The measurement moments in the mornings over 47 days starting ten days after the surgery is on the horizontal axis. The average mornings after resting values of the ventral and dorsal side of both legs are on the left and the values for evenings after physical exertion are on the right.**

**Fig.7.**

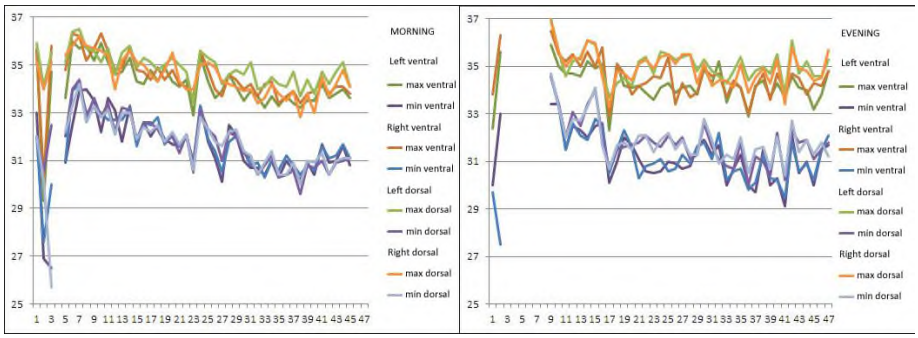



**Figure 7 Maximum and minimum measurements infra-red**
**The temperature in Celsius is on the vertical axis. The measurement moments in the mornings over 47 days starting ten days after the surgery is on the horizontal axis. The values of the maximum and minimum in the ventral and dorsal measurement areas of both legs are represented with the values of the mornings and after resting on the left, and the values of the evenings after physical exertion on the right.**

When in the rest position, there seems to be a high degree of similarity between the left and right with regard to the curves of the mean temperature, maximum temperature and minimum temperature in the diverse measurement areas. After physical activity, this correspondence occurs only after the 31$^{st}$ day of measurement. The temperature of all measurement points falls three to four degrees Celsius from the start of the measurements to the 31$^{st}$ day, whereas the body temperature varies by only 0.4 degrees Celsius.

**Statistics**

Even though the curves appear to be similar, that similarity is somewhat specious, it deceives. Similarities, in contrast with differences, are difficult to prove statistically, which is why the Δt of the left and right measured areas were chosen: maximum, minimum and mean, ventral and dorsal.

Because of extreme outliers before the ninth day, the tenth day was when the course of action started. Of all the Δt's, one T-test was performed that was tested against a tolerance of 0 with a reliability interval of 95%.

The manufacturer states that the accuracy of the device is ± 2 °C. The NETP (noise equivalent differential temperature) is 0.045 °C. However, the probable "absolute measurement error" lies between ± 0.045 °C and ± 1 °C (according to the manufacturer) when using a temperature-stable camera for recurring measurements at a

temperature from 23 °C. Therefore it is possible that two measurements taken under controlled conditions could differ by less than 1 °C, falling within the absolute measurement error. Measurement results can possibly have no clinical impact within a range of 0 to 1 °C.

An 1 or higher does not appear in the reliability interval of any of the Δt's. The average difference of all the measurements is therefore demonstrably smaller than that which would be found to be clinically relevant. The values of the Δt of the means of the total measured areas (dgem) fall within the accuracy of +- 1 ($^{O}$C). The optical finding that the curves are in agreement therefore seems to correspond with the statistical tests.

**Table 3. Statistical results of the infra-red measurements.**

| Statistical results | One-sample Test Test value=0 | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval of the difference | |
| | t | Df | Sig. (2 tailed) | Mean difference | Lower | Upper |
| Ochtvent_dmax | -4.939 | 39 | <0.001 | -0.25500 | -0.3594 | -0.1506 |
| Ochtdors_dmax | 6.112 | 39 | <0.001 | 0.35750 | 0.2392 | 0.4758 |
| Avvent_dmax | -3.916 | 38 | <0.001 | -0.24872 | -0.3773 | -0.1202 |
| Avdors_dmax | 2.415 | 38 | 0.21 | 0.10769 | 0.0174 | 0.1980 |
| Ochtvent_dmin | -1.537 | 39 | 0.132 | -0.10500 | -0.2432 | 0.0332 |
| Ochtdors_dmin | -0.253 | 39 | 0.802 | -0.01 | -0.0899 | 0.0699 |
| Avvent_dmin | -1.407 | 38 | 0.167 | -0.08205 | -0.2001 | 0.0360 |
| Avdors_dmin | -1.742 | 38 | 0.090 | -0.07692 | -0.1663 | 0.0125 |
| Ochtvent_dgem | -2.713 | 39 | 0.010 | -0.10000 | -0.1746 | -0.0254 |
| Ochtdors_dgem | 2.863 | 39 | 0.007 | 0.09750 | 0.0286 | 0.1664 |
| Avvent_dgem | 2.913 | 38 | 0.006 | 0.07949 | 0.0242 | 0.1347 |
| Avdors_dgem | -1.672 | 38 | 0.103 | -0.05385 | -0.1190 | 0.0113 |

**Ocht= mornings; vent= ventral; d= Δt (left-right); max= maximum; dors=dorsal; Av= evenings; min=minimum; gem= average temperature of measured area.**

**This table gives the results of a t-test in which for four parameters the mean differences over time between left and right are being tested against 0. It also shows the 95% confidence intervals around the estimated mean differences. The three parameters tested are: the differences of the average, the maximum and the minimum values between right and left on the ventral and dorsal side in the morning and the differences on both sides in the evening.**

**The reason for this table was to show that the mean differences are of limited biological meaning. If we consider mean differences of 1,5 and less (say 1.0 or 0.5) as not biological relevant, it can be seen that all confidence limits are plus or minus 1,5 degrees. This implies that is has been proven statistically that the curves for right and left are biologically similar, assuming mean differences of less than 1,5 as irrelevant. In this table, all mean differences are even within the limits of +/- 0,5 degrees. So we might assume, that the measured curves are similar.**

## Discussion

### Treatment considerations

Orthopaedic surgeons are somewhat laconic regarding internal bleeding: "it disappears on its own", "do some proper exercise". On the other side, opening a surgical wound and irrigating the wound risks infection. That

makes a watchful waiting approach understandable and acceptable. A large haematoma, however, requires more care.

Haematoma resorption does not occur in the surrounding tissue. A total hip replacement has similarities to a fractured femur in that IL-6 and TNFa are released (2). Along with IL-1β, IL-6 and TNFa were also released in an experimental tibia fracture in rats (3). Within a short time after a trauma and in an oxygen-depleted environment, IL-1β, IL-6, and TNFa in low dosages have a positive effect, via a mild inflammatory reaction, on bone growth and angiogenesis, which are needed for recovery (2,4,5). It was found that the local IL-6 concentration reached a peak within 14 hours after the trauma and decreased within 48 hours. The anti-inflammatory cytokines then increased (6). The positive effect of the inflammatory reaction on bone growth is not present with a "hyper" inflammation, or with a long-lasting persistent inflammation reaction lasting longer than 14 days. Moreover, the important issue is not recovery and bone growth at a time when a serious haematoma is spread across a large surface between fasciae and is located close to myelinated nerve fibres. A perineural haematoma can cause nerve inflammation which results in damage to the myelin (7). The literature addresses a destructive inflammatory reaction but, with the exception of cases of Complex Regional Pain Syndrome (CRPS), there is no further evidence. IL-6 and TNFα are frequently called pro-inflammatory factors that are also associated with the aetiology of CRPS, which is an inflammation complication that can also occur by a postoperative total hip replacement.

In the case addressed in this article, there was an estimated blood volume of 1.5 litres which, because of gravity, gradually moved between the fasciae in the mesenchymal tissue caudally. Local blood accumulation and locally concentrated inflammatory processes can be expected. Such a blood mass does not get reabsorbed within two weeks. Along with nerve damage, the position in the vicinity of the thickly sealed nerve fibres can also change the sensitivity of the central nervous system, which is sensitisation.

"Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs" is the IASP's definition for sensitisation."

Increased sensitivity and a decreased sensitivity threshold of the peripheral nerves develop after tissue and/or nerve damage. Myelin sheathes become damaged and fibres can behave as unmyelinated C fibres, which stimulate the central neurons. Hyper excitable spinal neurons show reduced thresholds, greater evoked responses, increased receptive field sizes, and ongoing stimulus-independent activity (8)

Sensitisation as a result of a haematoma-related inflammation risks the aetiology of chronic pain and could possibly be a factor in the aetiology of CRPS. Chronic pain after THR is a frequently occurring condition, appearing in 10% of the cases (9).

Another possibility for the aetiology of sensitisation could be a link of post-ganglionic afferent neurons to sympathetic neurons, through which a direct influence of impulses from the damaged area could sensitise the sympathetic neurons (10). A third possibility is that the pro-inflammatory cytokines IL-6 and TNFα directly sensitise the primary afferent neurons, which could cause hyperalgesia (11). In addition, TNFα increases the frequency of spontaneously exciting post-synaptic impulse flows in the dorsal horn. IL-6 inhibits the frequency of inhibiting impulse flows in the dorsal horn (12,13) . In addition to the effect on the afferent neurons and the dorsal horn, TNFα is also a major factor in the development of neuropathic pain in the hippocampus, locus coeruleus, and the nucleus ruber (14). De definitie van neuropathic pain is volgens de IASP (2012) : "Pain caused by a lesion or disease of the somatosensory nervous system". According to IASP (2012) the definition of neuropathic pain is: "Pain caused by a lesion or disease of the somatosensory nervous system". That system contains the sensory receptors and covers the skin and epithelial tissues, skeletal muscles, bones, joints, internal organs, and the cardiovascular system. This definition seems to contradict the publication, mentioned under "14". However, that article mentions morphological change of the microglia affected by inflammation factors. In addition, the underlying cause of the lesion is known and there is disease. The contents coincide with the IASP definitions.

**Medication**

Medication should focus on improving perfusion in the injured area, promoting resolution of the haematoma, and curbing inflammatory reaction. Paracetamol – the commonly used drug for pain treatment – is not classified as a NSAID. It has a neutral $H^+$ binding capacity, which prevents it from constricting or dilating vessels. Infrared thermography reveals that it does not improve circulation, perfusion is not promoted, neither is resolution, and one cannot expect to see an inflammatory effect.

Indomethazine is a NSAID that inhibits the production of prostaglandins, specifically prostaglandin E-type that has a vasodilatative and inflammation promoting effect. Paracetamol as well as indomethazine causes a colder image to appear with infrared thermography, which does not promote perfusion nor

resolution. It does have an antiphlogistic effect, but not specifically against inflammatory reactions caused by TNFα and IL-6. To the contrary, diverse publications report that indomethazine increases plasma concentration of TNFα.

Pentoxifylline, a methylxanthine, inhibited the release of TNFα and IL-1β through formalin-induced pain in an animal model, and the conclusion was that local administration of PTX is a valuable method for dealing with inflammatory pain (15). In an experiment involving a deliberate tibia fracture, PTX reduced the mRNA expression and the cytokine protein concentrations of TNFα, IL-1β and IL-6 (16). PTX reduced the level of pain in a neuropathic pain model (17). Xanthine derivatives, including PTX, are prostaglandin agonists-antagonists (18). Prostaglandins also play a role in pain, nerve stimulation and regulations systems (19) .
In a study on people in 1989, infrared thermographic images of chronic pain sites had already shown that PTX increased the temperature of cold spots and reduced temperature in hot spots. There was also a significant correlation between pain and thermographic change (20). Of the medicinal products mentioned, PTX best meets the theoretical requirements for the pharmaceutical used.

In retrospect, the decision to change medicine was probably the correct choice. The quick reaction after the first administration of PTX in this case study corresponds with the properties of PTX described in the literature. The decrease of the VAS scores from greater than 10 to 4 within six hours after changing the medication, and the further decrease to a score of 1 suggest a direct effect of PTX. It is less probable, albeit still possible, that the reduction of pain was caused by discontinuation of the high dosage of analgesics because on the one side, the VAS scores after continued administration of PTX fell even further and remained low, and on the other side the analgesics used would have to have an effect conversion from pain reduction to pain increase with a high dosage. There is, however, no evidence in the literature to support this.

That vasoconstriction, along with the inflammation, has played a role in this case is supported by the unintended test met sumatriptan, which also has a strong vasoconstrictive effect.

In closing, shortly after starting PTX, and for a long time after several administrations of PTX, the thermographic image shows an area with inflammatory reactions encapsulated by a vasoconstrictive area. It is possible that the inflammation factors — those present and those possibly actively formed at the site — were unable to shift location, which could only be possible after relieving the vasoconstriction. PTX reduces vasoconstriction and inhibits inflammation mediators such as IL-6 and TNFα.

**Infrared thermography**

Frequent non-invasive monitoring is necessary during aftercare. Pain, redness, and warmth are common with inflammatory processes, but are not externally visible to the naked eye when it is a deep inflammatory process. The effects resulting from viscerocutaneous processes are, however, visible an infrared thermograph is placed on the skin in the segmental area that accompanies the visceral processes.
Inflammation manifests itself as a warm area on the skin, although the source of the warmth may be in a relatively different area compared to the skin. The visceral segment is not always in the same area as the cutaneous segment (21). What one observes with an infrared camera is, therefore, also a combination of processes lying directly in or against the skin, and the vasoactive effect of the arteriovenous complexes in the lowest layer of skin. The latter takes place by most of the pathological processes. Figure 3 is an example of an infrared camera image. The haematoma is not located immediately beneath the skin. The leg was not blue, green, or yellow in the resolution phase. Nevertheless, a reactive process and its nature is visible as a result of viscerocutaneous reflex activity. The temperature expresses the result of the autonomic measurement and regulation system with vasoconstriction and/or vasodilatation in the accompanying skin area (1,20,21,22,23). Infrared thermography is an easy, benign, non-invasive method for following a process.

In the infrared thermographic series of measurements a few unexpected phenomena appeared. Firstly, one was a temperature decrease of three to four degrees during the first 31 measurement days (42 days calculated from the day of the operation). That means an increase of more than four degrees happened shortly after the operation compared to the rest position before the operation. The body temperature remained stable with a variation of a maximum of 0.4 $^{O}$C. A temperature increase of 0.2 $^{O}$C happened at the physiological level. A temperature increase of 1.5 is thermographically significant. A skin temperature increase of more than three degrees Celsius is very high, and in this case, cannot develop through a change of the total body temperature. That means that there was no postoperative systemic inflammatory reaction induced by the developed haematoma, such as what can happen with a tibia fracture. Locally there certainly was an inflammatory condition. The decrease can be attributed to a reduction of the inflammatory reaction resulting from recovery *and* the administration of PTX that not only improves conditions for perfusion, but also inhibits the pro-

inflammatory mechanism of action of TNFα and IL-6.
It is improbable that the temperature curves obtained from the left leg are only caused by the TNFα inhibition induced by PTX.
First of all, the skin area of the healthy right leg is three to four degrees higher after the surgery, identical to the leg that received surgery, while the body temperature was elevated 0.4 degrees Celsius.
If the reduction in the following six weeks were a result of the TNFα inhibition, the postoperative concentration in the right leg would have to be just as high as it was on the left side, but the right leg was not damaged, and there was no haematoma either. Therefore, a TNFα concentration increase in the healthy leg is very improbable.
Secondly, the PTX was only administered for ten days after the surgery. Therefore, it is impossible that the temperature increase was caused by PTX. A maximum dose of 100 mg of indomethazine was administered in the same ten days. Vasodilatory substances – released as prostaglandin E when tissue is damaged, if there is fever, and when there is vasodilation – is then maximally inhibited. A strong temperature decrease would have to have been present in the healthy leg.
Thirdly, PTX causes vasodilatation as a result of a phosphodiester inhibition, which means one would expect a substantial temperature increase after ten days of having discontinued indomethazine and replacing it with PTX. This increase was also found in an earlier study on chronic pain. In that case, the temperature decreased to the same degree on the left and the right side.
Another possibility of the temperature regulation response is an effect by the autonomic nervous system that should have all information regarding the condition of the operated leg.
The term of 31 measurement days (42 calculated from the day of the operation) is in agreement with the mean recovery time after orthopaedic surgery.

Secondly, it is remarkable that the curve of the non-operated side in rest position is practically identical to the side that received the operation while there was no local reactive event on the right side. The infrared thermography images in this situation comprise the viscerocutaneous reflex pathways through autonomic regulation from segmental sections of the spinal system (1,21,22,23).

The course of the mean temperature and the progress of the maximums and minimums within the measured area during rest position is the same on the right side as it is on the left side, whereas the thermographic detailed image in the measured areas are not identical *and* the maximums and the minimums on the left and right were also not perfect reflections of each other. That applies not only to the ventral side, but also to the dorsal side (Figures 6 and 7).

One would expect that the most damaged side would have other values than the less damaged side. Normally there are strong differences between the left side and the right side with lateral damage (20). That may be a sign of a spinal cord sensitisation condition which would develop within ten days after surgery. It would also be a sensitisation condition that is not limited to one segment: L1, extending to and including segments L2, L3 ventrally and L3, L4, S1, S2 and S3 dorsally (24), which is from L1 caudal to the end of the spinal cord. This would be a sensitisation condition that is not only in the ipsilateral part of the dorsal horn, but is also heterolateral. There would then be a reflected situation. The sclerotome of the knee and ankle is in the area. Sensitisation of these areas therefore may also mean facilitation of an already existing sensitisation in the knee and ankle with the risk of the development of chronic pain or possible CRPS. That can occur homolaterally or heterolaterally because of the mirrored sensitisation.
A useful function of aiming for a mirrored sensitisation condition is that it can serve as a potential guide for recovery of the diseased side by using the healthy side as an example. PTX could have played a role in this because it can act as a form stabilisation for the sensitisation of the neuronal activity in the dorsal cord. An earlier study with PTX also showed a left-right symmetry in the treatment of chronic lateral pain sites (20). In this case study, PTX could be the drug to treat postoperative pain with infrared thermographic left-right differences.

## Conclusions

### The outcomes do not conflict with the hypothesis.

In retrospect, the decision to change the medication to PTX was a successful choice. A recovery complicated by postoperative bleeding is a potential system-threatening situation, which should not be dismissed with "exercise properly" as a medical recommendation. An embolism during inflammation processes has to be

avoided through improvement of the blood circulation. Medicines with a vasoconstrictive mechanism of action should be avoided.

PTX turns out to be the best therapeutic option based on theoretical considerations in this n=1 tested situation. Obviously, more structured further research is needed to substantiate this. The high degree of similarity of the measurement curves of the left and right sides cannot be unambiguously explained, but left-right sensitisation can perhaps be involved. It is possible that the stabilising function of PTX affects the sensitisation condition at the spinal level, but further research is needed.

**Therapeutic consequences**

The sole advice by orthopaedic surgeons to "exercise properly" is not valid advice because the pressure on the inflammatory process that cannot be relieved could possibly worsen. Severe tissue loss with damage to neuronal systems could possibly arise. In CRPS, which is another form of inflammation that can appear after total hip replacement surgery or after damage to neuronal systems, mediators such as IL-6 and TNFα also play a part. These substances, even in the thermographic cold resting position at recovery, appear in significant quantities in the damaged area (25). PTX with its rheological mechanism of action and effect on IL-6 and TNFα probably has a therapeutic basis by THR operations with complicated bleedings in the context of postoperative pain management and the prevention of CRPS. The use of Indomethazine as a painkiller in this type of situation can even be dangerous because of the reported serum concentration increase of TNFα.

**Postscript**

**Vasoconstrictive zone**

There is nothing in the literature addressing why an encapsulated vasoconstrictive zone can develop around an hot spot area. Increased sympathetic activity (an already existing old scar) could possibly cause it, or possibly an increased production of E-type prostaglandins. Further research is needed to determine this. It probably also plays a part in the development of CRPS.

Fig.8.

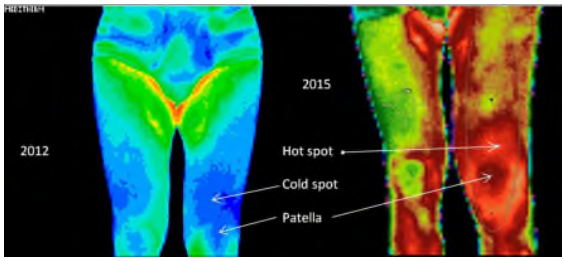



**Figure 8. Infrared thermography 2012-2015. The same area.**

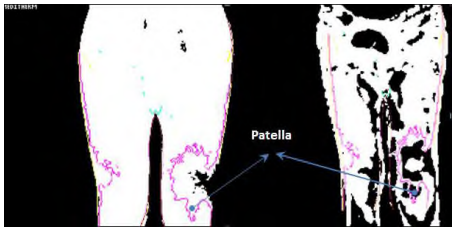
**An encapsulated vasoconstrictive zone can develop around an inflammation (rubor, calor, dolor) area (hot spot 2015). Increased sympathetic activity (an already existing old scar: cold spot in 2012)**
**Left a ventral image of the upper leg in 2012. A cold spot above the patella, which was changed into a hot spot encircled by a vasoconstrictive edge via the haematoma dated 19 June 2015 as if the centre underwent an "upgrade" to a hot spot**

Using binary filtering (20), a cold spot found in 2012 was investigated to confirm it was indeed a cold spot, and the hot spot found in 2015 and the cold spot from 2012 were localised on the same sites. Binary filtering gives the possibility to control and to judge about temperatures, without possessing the exact values because each pixel possesses its own value, a value between 0 and 255. 0 is black and 255 is white. If a binary filter is used, the colour information is removed, but the clarity information is held. The lower the value of the pixel is, the colder the image is around this pixel. The warmer the area is, the higher the pixel value is.

With a binary filter the pixels with a value above the threshold are white. Under the threshold black. With a threshold value of 85 for both images you see:

All the pixels with a value beneath 85 are black. The blue area in the 2012 image is a cold spot indeed. In the same area in the 2015 image is a cold spot too. The same? In the next image is the contour of the 2012 image projected on the 2015 image:

Figure 9.




The pain site on the left leg has indeed been localised in the same area as the cold spot found in 2012. A cold spot was also seen in 2015 with a central apple-shaped hot spot, surrounded by a cold vasoconstrictive zone.

**Reliability and reproducibility of the measurement results**

Figure 10.

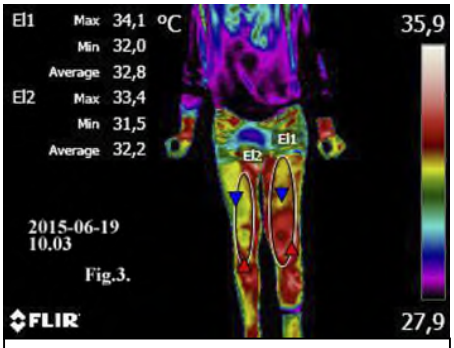



**Figure 10. Calculation of the mean surface temperature using the oval samples. The surfaces are not identical.**

Flir software calculated the values of the mean, maximum and minimum temperature using image samples. Square, rectangular, round or oval samples can be made. An oval shape is most fitting for a maximum surface of the thigh, including the knee. The ovals of the left side and the healthy right side do not have equal surfaces. The position of the leg is not identical, and the operated side has a minimum volume of 1.5 litres of blood more than the right side. The size of the right leg, measured from the middle of the knee to the middle of the hip, was 10 centimetres larger than the right side. The question is if the results and conclusions are reproducible when new series of ovals with the accompanying values are taken into consideration.

For that purpose, after the measurements were taken the images made were set in grayscale and processed using Adobe Photoshop Elements 10 version: 10.0.0 (10.0.20110914.m.17521). Sample images were made from the thigh to the knee in the exact same format of 2000 pixels. The values were set using a histogram. Because the pixels have intrinsically kept the same value as when the images were made, they each represent the same value as they had before Adobe Photoshop Elements was used, however, now the calculations are made with precisely the same sizes on the left and the right sides.

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www.infrarood-camera.eu

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