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Newsletter

ALKANTIS Proof of Concept
Medical Evidence

This Newsletter N°13 reports the outcomes of the clinical study made to demonstrate the proof of the ALKANTIS Concept .
This study has been presented by Pr Champault in the USA/ Orlando on March 7, 2013 during the American Hernia Society (A.H.S.) congress, later in Poland during the European Hernia society (E.H.S.)congress on May 14, 2013 and during the MESH congress held in France, Paris last June.
This article has already been selected by the Hernia world congress committee and will be presented in Milan in June 2015.

Does perioperative local cooling improve immediate outcomes after ambulatory open inguinal hernia repair?

A prospective randomized study.

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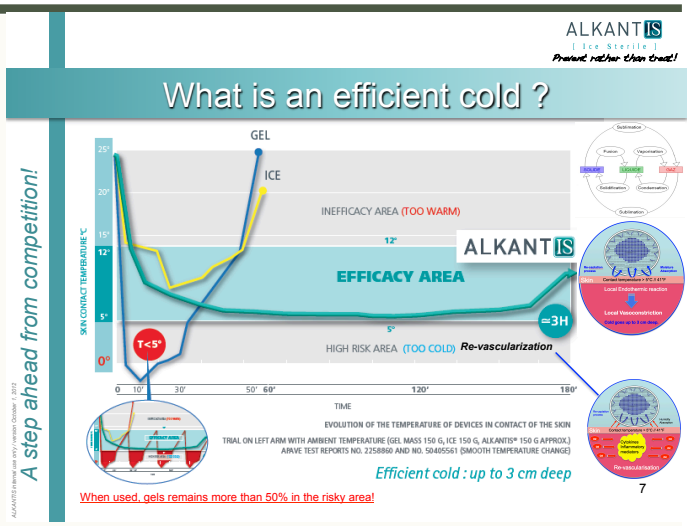
Abstract

Background:

Local external cooling has been mainly used in sport injuries, where its benefit for pain relief is well recognized.

Objective:

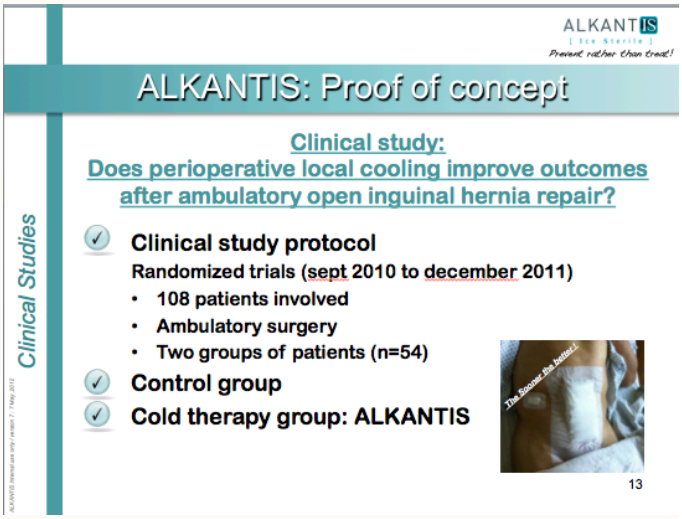
Pain and local complications are the major determinants of outcome after inguinal hernia repair., To evaluate the respective impact of peri-operative cooling of the surgical site and usual care after open inguinal hernia repair, we performed a prospective randomized single institution study



Methods:

One hundred and eight consecutive patients with primary unilateral inguinal hernia were included the study. For each patient, repair was performed by local direct access during ambulatory surgery. The first study group underwent standard pre- and postoperative local care (control group). In the second group (cold compress group), a single-use disposable sterile cold compress was applied on the surgical site for at least 30 minutes before and 2 hours after surgery. The primary endpoints were immediate postoperative pain using a visual analogue scale (VAS), and local complications . Secondary endpoints included: analgesic drug consumption, length of hospital stay, delay to return to normal activity and patient satisfaction.

Results:



In preliminary tests, skin and deep (3 cm) temperature measurements were as follows: pre- and postoperative temperatures remained stable and nearly equivalent (33.4±1.7°C vs 34.3±1.4°C) in the control group. In the treated group, the initial pre-compress temperature ranged from 5 to 8°C (mean: 6.2 ± 1.7°C). After application of the cold compress, the skin temperature decreased from 32.4±1.2°C to 12,9° °±1.2°C in the first thirty minutes , and to a mean value of 10,8° ± 1.8°C after 2 hours. Deep tissue measurements showed a similar profile. After removing the cold compress, skin temperature increased quickly (20 minutes) from 11.3±1.6°C to 23.4±3.0°C, and then had a progressive linear return to near base-line values (35.6 ± 2.3°C) after two hours. One hundred and eight patients were included from September 2010 to December 2011. The two study groups were comparable with respect to pre- and intra-operative characteristics. There was no difference concerning operative time (36.3±14.0 vs 39.6±7.2 minutes) and early (one-week) complications, although there was a non significant reduced incidence of hematoma and ecchymosis (0/54 versus 4/54) for the cold compress group. Analgesic drug consumption was significantly (p=0.01) reduced. During the day of surgery and the first postoperative day, the visual analogue scale was significantly lower after cooling. There was a non-significant reduction in length of hospital stay (150 ± 37 versus 210 ± 47 min), and time to return to normal activity was shorter in the cold compress group, without additional expense.At one week, patient's satisfaction was similar in the two groups .

Conclusion:

For open inguinal hernia repair performed in the ambulatory setting, immediate pre- and post operative surgical site cooling, targeting a controlled temperature between 12°C and 15°C significantly reduced postoperative pain,, analgesic drug consumption and resulted in improved immediate outcomes. This technique is safe, simple, easy to use, inexpensive and well tolerated by the patient.

Key words: Inguinal hernia repair, cooling, ambulatory surgery, pain, analgesics

Hernia surgery performed in the ambulatory setting is widely implemented worldwide, and when performed skilfully, can result in excellent outcomes. Immediate postoperative pain and local complications may, however, negatively affect outcomes. Several studies [1,2] have shown the benefit of postoperative skin cooling to reduce wound pain and edema. A number of theories have been put forward to explain the mechanism by which application of an ice pack may attenuate tissue injury and act as a local analgesic. This includes reduction of tissue metabolism and induction of vasoconstriction, that may reduce the production of inflammatory cytokines, and reduce edema and bleeding [3]. Several studies [4,5] have been performed to establish the critical level of tissue cooling required to induce specific effects; a local temperature of 10 to 12°C is needed to lower the tissue metabolic enzyme activity and to reduce nerve conduction velocity.
Our hypothesis was that cold therapy, applied by local sterile frozen ice compress care (Alkantis France) on the surgical site, before and after open inguinal hernia repair, would reduce immediate postoperative pain and bleeding. For this reason, we conducted a prospective randomized trial, comparing treatment with cooling versus standard therapy in patients with primary open unilateral hernia repair.
In a preliminary study, thorough measurements of skin and deep tissue temperature had been performed in volunteers, in order to evaluate exactly the level and evolution of temperature change with and without cooling.

PATIENTS AND METHODS

The Paris XIII University Ethical Committee approved all aspects of the study protocol. Written informed consent was obtained for all patients before enrolment in the trial. The type of local care used was selected at random on the day of surgery

Study design and patients

The device used in the present study (*Alkantis France*) is a sterile, disposable, polypropylene skin compress, with a small compound and filtrated sachet of water (22 µ), and is ready to use following at least 90-minutes of refrigeration. Compress size is 18x10 cm and weight is 150 g. The compress can be kept at -4°C (photo 1). It is easy to use, fixed by a strap, and provides a dry and sterile cooling (post operative) between 5°C and 12°C for 2 to 3 hours. It can be prepared several days in advance..Contraindications to use include Raynaud's syndrome, cryoglobulinaemia and allergy to cold.

In a preliminary study, 20 healthy, non-obese (BMI <25 kg/m^2) volunteers (medical students, nurses, and doctors) agreed to undergo, for a 2-hour period, repeated (every 15 minutes) skin and deep temperature measurements in the inguinal area, before, during and after local cooling. Local skin and deep (3 cm) temperature was easily evaluated with an infrared electronic thermometer (Thermo Flash Lx260T®; infrared no contact tests approved clinically ASTH 1965 – 1998 [2003]) that immediately measures temperature from 0° to 45°C.

In the clinical study, patients, from 18 to 65 years of age with primary unilateral inguinal hernia could be enrolled. After informed consent was obtained, the patients were randomised and underwent sutureless "Lichtenstein – like " hernia repair using a self-adhering mesh (*Adhesix® Laboratoire Bard)* .
Exclusion criteria were: bilateral or recurrent inguinal and femoral hernia, EHS (European Hernia Society) classification [6] L3H3, emergent case, age less than 18-year old, pregnancy, unable to obtain informed consent; peripheral neuropathy, cryoglobulinaemia, Raynaud's syndrome, associated surgery, obesity (BMI ≥ 30 kg/m^2), insulin-dependant diabetes mellitus, hepato-cellular disease, drug or alcohol addiction, psychiatric pathology, regular use of analgesic drugs, steroids, immunosuppressive agents or anticoagulant therapy, contraindication to ambulatory surgery care .

In the treated group, the sterile frozen skin compress was applied on the surgical site starting at least 30 minutes before surgery. It was removed a few minutes prior to skin incision. At the end of the procedure, immediately after skin closure, a second sterile cooling device was placed directly on the surgical site for a minimum of 2 hours.
Preoperative data were collected prospectively , including in a data-base hernia history,demographic characteristic , physical and professional activity level, European Hernia Society (EHS) classification [6], American Society of Anaesthesiologist (ASA) classification, and the presence of co-morbidities and risk factors (e.g.: hypertension, prostatitis, smoking). The type of anaesthesia used was at the discretion of the surgeon and anaesthesiologist. Antithrombotic and antibiotic prophylaxis were used according to professional guidelines. The surgical skin site was prepared (shaving, cleaning, antiseptic) in according to hospital protocol. The use of local intra-operative anaesthetic such as Naropeine® (*Astra Zeneca France*) was not permitted during the trial. Skin was closed with a running absorbable intradermal suture. Analgesic drugs, using the WHO classification was systematically proposed to the patients and used if necessary. The protocole included : Bi- profenid® (Ketaprofene) *Laboratoire Sanofi Aventis France*) 100 mg systematically one pill morning / evening and Xprim® (*Laboratoire Sanofi Aventis France*) Tramadol 37,5 mg + Paracetamol 325 mg) : 3 pills every day (each 8 hours) . Consumption evaluation scale was from 0 to 5 per day (number of pills used ' if needed , by the patient each day .

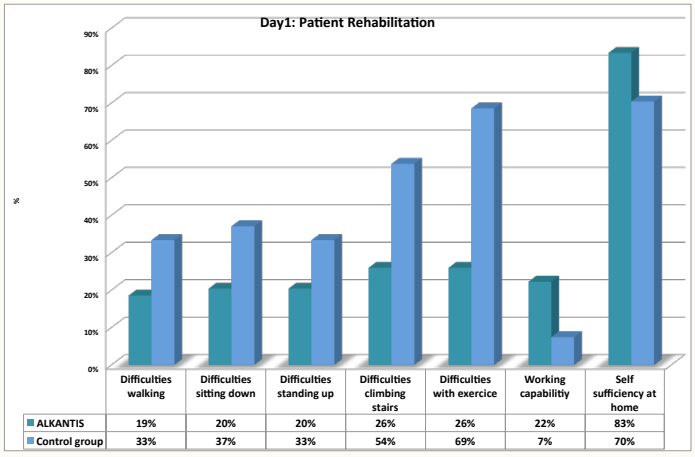
Study end points

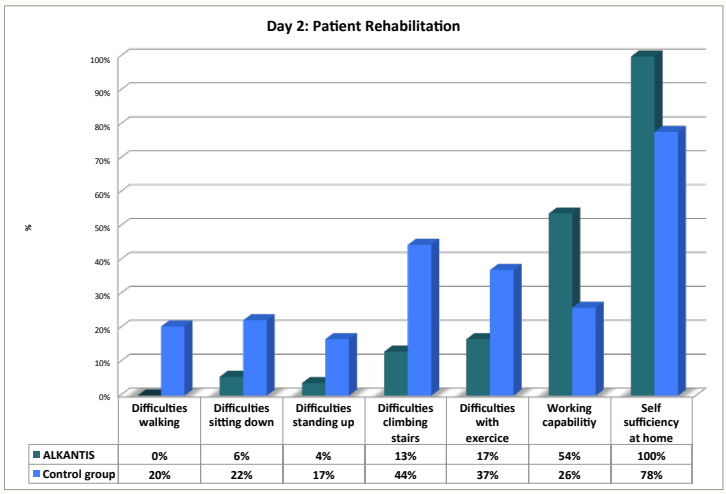
The primary endpoints were:

1) **Pain** was assessed during the early hospitalization period (at 2 hours, and before discharge) and after discharge (at home) during the first two postoperative days, at regular time points: 6, 12, 24 and 48 hours post operatively.. The evaluation of pain , using a visual analogue scale (VAS) , was conducted by Unit's nurses during hospitalization – as is the case with all patients who are operated on –and by patients themselves in a self evaluayion after having been trained to do so .

2) **Early complications** (at one week): Ecchymosis, hematoma, skin leakage, wound sepsis, seroma,,and mesh infection.

The secondary endpoints were: Operative time and hospital stay (in minutes); uses of the WHO class I-II analgesic drugs during the first two days follow up period, time to return to normal activity, incidence of adverse events, cost savings, patient's satisfaction as determined with a 0-100 scale (100=very satisfied) .





Statistical Analysis

The minimum number of patients in each study group was calculated based on the reduction of pain incidence (during the first two post operative days) from 21% , as observed in the litteraure in the first 48 hours after ambulatory open hernia repair(11) to 5% or less , would be significant.
With assumption a power test of 80% and alpha level of 0.05 , we calculated showing that 50 patients were needed in each group study . The final patient number per group was 62 to anticipation of possible "losses"

All statistical analysis were performed using.the S A S (version 9.2) software package . The results are reported with 95% confidence intervals and a 5 % level of significance . Descriptive statistics were used to characterize patient groups, and mean (standart deviation) or median value (range of values) depending of the type of data and a normal data distribution in the interval scale .Qualitative data were summarized using frequency tables (frequency and percentage) and were analysed qualitatively . Frequency distribution were compared using the CHI-sqared test .

The study was approved by the APHP Paris Hospital Institution review board , under the control of the Statistical Unit .

Results

Preliminary skin and deep tissue (3 cm) temperature measurements in volunters had shown homogeneous temperature change for each study condition. In the control group, pre and postoperative temperature (evaluated in the operating room) remained stable averaging 33.4±1.7°C and 34.3±1.4°C, respectively. The initial temperature of the device before use ranged between 5° and 8°C (mean: 6.2±1.7°C). During preoperative cooling, skin temperature decreased regularly from 32,4+-1,2°C to 12,9±1.2°C at thirty minutes , and decreased slowly to 10.8 ±1.8°C at two hours. Deep (3cm) temperature measurements followed a similar profile with a mean higher temperature of 2.5 ± 1.7°C. After removing the device, skin temperature increased quickly (over 20 minutes) from 11.3±1.6°C to 23.4±3.6°C in a progressive linear fashion up to near normal values (33.6±2.3°C) at two hours.

One hundred and twenty five patients were included in the study between September 2010 and December 2011.Incomplete feed back provide by some of them (17 : 9 in the control group and 8 in the cooling group) ,demonstrate that the initial population size of 125 was reduced to 108 in order to obtain complete and usable information .

The two study groups (54 each) were comparable according to pre- and intraoperative data (Table 1). The study population was composed of 104 males (96%) and the median age was 53±15 years. Mean BMI was 24.6±3.1 kg/m^2. At admission, 50 patients (47%) had an ASA score of I, 55 patients (50.9%) had a score of II and the remaining 2% had a score of III. The preoperative comorbidity prevalence rate was 10.2%. Forty-two patients (39%) reported no professional activity (30% retired and 9% unemployed), while 38 (36%) were manual workers and 28 (26%) had sedentary professional activity. Thirty-four (32%) reported active participation in sports. The mean duration of the hernia was 1.5 ± 1.9 years In accordance with the protocol, all hernias (55 right side, 45% left side) were defined as primary.. The types of hernias, according to the EHS classification, are reported in Table 1.

General anaesthesia was used in 100% of the cases. The median size incision was 6.3±1.4 cm and the mean “skin to skin” operating time was 36,6 .±16.8 minutes. During the surgical procedure, the ilio-inguinal (94%), ilio-hypogastric (76%) and genital branch of the genito-femoral (68%) nerves were observed by the surgeon in 92 patients (85%). Nerves were preserved in 88 cases) (95,6%) and cut in 4 cases. The technique performed for hernia repair was the equivalent of the Lichtenstein technique using a self adhering mesh (lightweight [32 g] polypropylene, coated with a biochemical absorbable glue) Adhesix® Laboratoire Bard
According to the study protocol, intra-operative local infiltration of buvicaïne (Naropeine® : Astra Zeneca) was not performed. According to professional recommendations, the patients did not receive any prophylactic antibiotics or anticoagulation. There were no intraoperative complications.
There was no difference regarding the operative time (36,3± 14 min vs 39.6± 7,2 min) between the study groups. Hospital stay was not significantly reduced in the experimental group (150±37 min vs 210±47 min,) . The rate of early local complications (one week) was comparable, although there were fewer hematomas and decreased ecchymosis in the treated group (0/54 versus 4/54; (ns). There was no sepsis or skin leakage. Analgesic drug consumption (analgesic/anti-inflammatory,scoring between 0 to 5) was significantly (p=0.01) reduced in the treated group during the first two post-operative days (Table 2), with a significantly lower VAS pain score, at the different time points (6, 12, 24 and 48 hours) (Table 3). In the treated group, 90% of the patients had no pain (VAS=0) on the first day after surgery: this percentage was significantly (p=0.01) higher than in the control group. The mean VAS was significantly lower, with less analgesic drug consumption (p=0.01). These findings were similar on the second post operative day. The percentage of patients returning to normal activity was higher in the treated group (8 questions with answer “yes or not” at day 1 and day 2) (Table 4). None of the treated patient displayed “side effects” and all patients were very satisfied (ns) in the two groups (97±2,6 vs 95 ± 4,1).

Discussion

Lichtenstein's technique for inguinal hernia repair is recognized as an efficient and safe method with a low recurrence rate, and is considered the "Gold Standard" [7], performed in the ambulatory surgery setting. Bay-Nielsen et al (8) have pointed to early and long-term pain as major adverse outcomes after hernia repair . Numerous contributing factors have been described. Recently, we have shown in a prospective study using the principles of the Lichtenstein technique, the safety and efficacy of a "self adhering" mesh (lightweight 32g/m^2) coated with resorbable chemical glue in terms of early outcomes [9].

We routinely used this prosthesis for patients included in the trial. Ambulatory hernia surgery is recommended in the EHS guidelines [7] Outcomes after ambulatory surgery are correlated with the risk of early complications, specifically bleeding (hematoma) and the possibility of uncontrolled pain, during the first two post-operative days. Inguinal hernia repair is a painful ambulatory surgery, with almost half of patients describing moderate to severe pain post-operatively [10]. The incidence of severe pain was evaluated to be 21% in the first 48-hours post ambulatory surgery [11] and pain control has been shown to improve postoperative recovery [12]. Also, poor pain control can lead to the development of chronic pain. Several pain control methods have been suggested including: use of analgesic drugs (antalgic, anti-inflammatory), and intraoperative infiltration of xylocaïne [7]. Current therapeutic strategies for the management of postoperative pain management are mostly dependent on opioid analgesics and NSAIDs. Placebo-controlled studies have shown that NSAIDs reduce postoperative pain and limit the use of additional analgesics after inguinal hernia repair [13]. Administration of a COX-2 selective non steroidal anti-inflammatory drug prior and following outpatient inguinal herniorraphy improves functional outcomes when compared with placebo and increases patient satisfaction yet the use of COX inhibitors is associated with thrombotic complications [14]. The risk profile for COX-2 selective agents in terms of cardiovascular and renal systems requires a careful patient selection. The administration of local anesthetic agents into the surgical incision and surrounding wound bed is easy to perform and is low risk for patients. Pain ratings and opioid requirements are reportedly decreased following a single dose wound infiltration of a long acting local anesthetic following inguinal herniorraphy, when compared to saline infiltration [15]. Cryotherapy is a widely used technique in the immediate care of traumatic injury, protocols for postsurgical rehabilitation and treatment of pain [4]. A number of studies have been performed to establish the critical level of tissue cooling (13°6 C) required for specific effects (localized analgesia). To reduce nerve conduction velocity by approximately 10%, a temperature of 12.5°C is requiredand to lower metabolic enzyme activity by approximately 50%, a tissue temperature between 10°C and 11°C is suggested [16-17]. Historically, gel packs have been criticized for being too stiff when frozen and therefore, unable to shape adequately to the body part on application. This lack of flexibility reduces the cooling effect, because the modality is not uniformly in contact with the skin. Alkantis®, used in the present study, is a sterile device, usable for postsurgical wound care, supple, covering exactly (18x12cm) of the surgical site needed for inguinal open hernia repair, overcoming the above mentioned disadvantage. The temperature measurements showed that the effective level of cooling (10-12°C) was obtained in about 30 minutes. Postoperatively, the cooling device (sterile) should be used during the entire rehabilitation period before living hospital. The tolerance was acceptable in 100% of the patients (weight 180 g) with a high level of satisfaction concerning pain control (95%).

Several investigators have reported intramuscular (IM) temperature at specific depths relative to subcutaneous adipose layer (19). With a 30-minute ice bag application to the thigh, 1 cm subadipose IM temperature has been reported to decline by 9.7°C, whereas 2 cm subadipose IM temperature reduction of 5°C and 8.4°C has been reported [20]. Thus, cooling of the operating site may be inefficient in obese patient. We speculate that adequate cooling may require a longer application time for obese patients.

In the present study, we recorded no adverse events in the treated group. Pain evaluated by VAS during and after the hospital stay, was decreased at all time points for the compress group . Furthermore, consumption of analgesic drugs was significantly reduced in the same group during the first two days after surgery. Patients were discharged from the ambulatory unit earlier (ns) than in the control group, and displayed a significantly (p=0.01) better rehabilitation at home with earler return to daily activities. Our results are in keeping with prior studies reported in the literature [20]. The effects of cooling have been also evaluated in a randomized trial using local anaesthesia for ambulatory hernia repair in the UK [21], with a significant reduction of pain after cooling of the operative site (4°C versus 22°C) for 5 minutes. Simultaneously, there is a risk of local tissue necrosis at this level of cooling. Although relatively unfrequent, groin hematoma following inguinal herniorraphy is a morbid complication with significant ramifications including mesh infection and hernia recurrence. Smooth et al [22] have shown that the crucial risk factor for groin hematoma for patients undergoing inguinal hernia repair is the preoperative coumadin therapy. In this situation, local cooling may reduce the risk of hematoma. Patients on coumadin therapy were excluded from the present trial. Application of the ice compress may have reduced the possible side effects of antalgic drugs ..

Conclusion

In open hernia repair, preoperative cooling of the operative site for 20 to 30 minutes, using the gel compress Alkantis ® significantly decreases early postoperative pain, resulting in a reduction of antalgic drug use. This approach is simple, easy to use, well tolerated, no-expensive, and safe. This cooling technique could be a reasonable alternative to intraoperative analgesic infiltration (dose related, allergies) and/or systematic use of analgesic drugs, which may have adverse effects.

Conflict of Interest :
Summative Disclosure Statement :

- GC declare conflict of interest directly related to the submitted work (Travel support , meeting registration)
- A V declare no conflict of interest
- L P declare no conflict of interest
- C V declare no conflict of interest
- C B declare no conflict of interest

It is important to note the effectiveness of the ALKANTIS cold therapy when applied from the Operating Room.

The sooner the Better!

When ALKANTIS is immediately applied onto the suture line and kept in place for a period of 24 h the beneficial effects for the patient is quantifiable for the next 24H and 48 h after the surgery.

The patient feels less pain, take less medication and is able to recover more quickly.
These benefits have a real economic impact for the hospital.

Prevent rather than treat!

Table 1 : Pre operative data

Number N	Cooling 54	No cooling 54	p- value ns
Male / Female	53/1	51/3	ns
Age (years)	52 ± 9.7	54 ± 8.2	ns
Comorbidity (%)	6/54 (11.1%)	5/54 (9.2%)	ns
ASA Score I Score II	23 28	27 27	ns ns
BMI Index (kg/m^2)	25.4 ± 4.1	23.4 ± 3.7	ns
Professional activity No (retired/Jobless) Manual work Sedentary	 21 18 15	 21 20 13	 ns ns ns
Type of Hernia (EHS) 1./L. P 1.M.P 2.L.P 2.M.P	 7 14 8 25	 6 12 6 30	 ns ns ns ns

Table 2 : Use of analgesic drugs

(during the first and second post operative days)

	Cooling N=54		No cooling N=54		P - value
	Patients[1]	* Pills[2]	Patients[1]	Pills[2]	
Day 1	22/54 (44%)	1.6	42/44 (77%)	2.3	p=001
Day 2	34/54 (62%)	2.1	41/54 (75%)	3.1	p=001

Patients[1] : number and percentage using Analgesic drugs

Table 3 : Evaluation of pain (VAS)

(during the first two post operative days)

	Cooling (N=54)		No cooling (N=54)		p- value
VAS (0 to 100)	Mean	(VAS=0)	Mean	(VAS=0)	
Return Ambu Unit	3.1 (0-18)	49 (90%)	11.2 (0.41)	41 (76%)	ns
Postop : 2 hours	3.4 (0-17)	47 (87%)	18.4 (052)	36 (66%)	p=0.01
Leaving hospital	4.6 (0-24)	47 (87%)	19.6 (048)	28 (51%)	p=0.01
Postop : 6 hours	12.7 (0.-31)	38(70%)	29.4 (0.-60)	10 (18,5%)	p=0.02
12 hours	19.8 (034)	18 (33%)	24.3 (11.-45)	0 (0%)	p=0.01
24 hours	14.2 (021)	14 (25%)	21.7 (17-52)	0 (0%)	p=0001
48 hours	10,2 (0-31)	23 (42,5%)	19,6 (0-53)	8 (14,8%)	p=0.01

VAS: mean and range at each control *VAS=0 : number of patients and percentage*

Table 4 : Return to normal activity

	Day I			Day II		
	Cooling N=54	No cooling N=54	p- value	Cooling N=54	No cooling N=54	p- value
Self sufficiency at home	45	38	ns	54	42	ns
Difficulties walking	10	18	0.07	0	11	0.5
Difficulties sitting down	11	20	0.5	3	12	0.01
Difficulties standing up	11	18	ns	2	9	0.02
Difficulties climbing stairs	14	29	0.01	7	24	0.01
Working capabily	12	4	0.01	29	14	0.01
Difficulties driving a car	Non authorized			6/38	12/42	0.01
Difficulties with exercice	14	37	0.01	9	20	0.01

Number of patients with positive answer to the question

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