

Research Article

Prevention of Reflex Sympathetic Dystrophy and Vitamin-C in Programmed Knee Surgery; A Prospective Randomized Trial

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Clinique Victor Pauchet. 2, avenue d'Irlande. 80000 Amiens, France*Abstract****Background**

Complex regional pain syndrome type I (CRPS-I) is a significant complication in operated osteoarticular pathology and may adversely affect patient's quality of life. Vitamin C is an anti-oxidant and a neuro-modulating agent. Intake of vitamin C appears to be the only preventative factor. The objective of this study seeks to assess the effectiveness of liposomal conditioning of vitamin-C in reducing reflex sympathetic dystrophy and to show evidence that it is more effective than taking vitamin C in its usual form.

Methods

Three series of patients undergone for identical pathologies the same surgery performed in the same centre by a single surgeon using the same operative techniques and the same implants. The first group took vitamin C in liposomal form. The second one took classical vitamin C tablets. The third one received placebo pills. Comparison was made between both groups which were identical in number and were the same average age. Results were compared and analysed at the end of 1 year.

Results

After a one-year follow-up, the group taking the liposomal form showed improvement of functional outcome as compared to the classical vitamin C and placebo groups.

Conclusions

The intake of vitamin C in a liposomal encapsulation represents a breakthrough in the prevention of the occurrence of a CRPS-I particularly on scheduled osteo-articular knee surgery risk areas.

Key Words: Vitamin C; Reflex sympathetic dystrophy; Prevention

Introduction

Complex Regional Pain Syndrome Type 1 (CRPS-1), formerly called algodystrophy, neuro-algodystrophy or shoulder-hand syndrome, remains one of the major complications of osteoarticular surgery according to Camelot et al. [1]. Its occurrence is related to the toxic effects of the oxidation of free radicals on the endothelial permeability of the microcirculation, causing protein and fluid losses [2]. Ascorbic acid has the effect of recovering these excess free radicals in the extracellular medium, and acts as a prophylactic antioxidant [3]. In 2002, in the footsteps of Zollinger et al. [4], we had published encouraging results as to the preventive nature of vitamin C upon occurrence of a complex type 1 regional pain syndrome after fracture of the distal radius treated by surgery [5]. These results were confirmed by a systematic review and a recently published meta-analysis [6]. Only 10% conventional vitamin C is absorbed. Since 2014, we have used liposomal vitamin C in scheduled knee surgery (Goldman® Laboratories LTD, London, UK). Liposomal encapsulation uses European phosphatidylcholine, extracted from natural sunflower lipids and non-GMO cultures; it is also known as lecithin. The active substance is encapsulated in a structured spherical composition of phospholipids. This new matrix assembly called liposome protects the active substance when in direct contact with the gastric juice of the stomach and the digestive enzymes of the intestine. The patent

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technology makes it possible to design the optimal size for each liposome to ensure that the active substance is properly released into the cells of the body. Thus, the content of each liposome is fully absorbed when it reaches the level of the gastrointestinal system and it retains all its intrinsic properties.

The aim of this prospective and mono-centric comparative study is to find out if the liposomal form represents a breakthrough compared to the form conventionally used in the prevention of the occurrence of a complex type 1 regional pain syndrome in programmed knee surgery.

Material and Methods

From 2014 to 2017, we treated 66 patients divided into three identical groups in number and whose average age was 44 years, ranging from 30 to 55 years for planned knee surgery also divided into five transpositions of the anterior tibial tuberosity, five ligamentoplasties of the Kenneth-Jones type, six unicompartmental internal prostheses for centralized osteoarthritis and six total prostheses for eccentric osteoarthritis. All of them benefited from a truncular block associated with general anaesthesia performed thirty times or with spinal anaesthesia performed in thirty-four cases. The treatment was performed in a single centre by a single surgeon using the same pathways, the same surgical techniques and the same implants.

In each group, there was no history of Complex Regional Pain Syndrome Type 1 (CRPS-1). The first took a capsule of liposomal vitamin C at 500 mg, in the morning and evening, one week before surgery, one during the day of surgery and lastly, during the first 21 post operation days. In the second group, the surgery was performed under the standard vitamin C framework with a daily intake of 500 mg in the morning and evening for 28 days (starting 7 days before the operative procedure, on the day of the surgery and ending twenty-one days after surgery). In the third group, the placebo was taken daily in the morning and the evening for 28 days (7 days before surgery, on the day of surgery and twenty-one days after the surgical procedure). Patients were reviewed monthly during the first trimester and then every three months during the first postoperative year. The main objective was to monitor whether CRPS-1 developed and to document the one-year follow-up.

To evaluate the comparability study of the two groups, the quantitative data were compared by the Student's test and the qualitative data by the Chi [2] tests.

Results

For the first group, there was no discontinuation of liposomal vitamin C due to intolerance. The one-year follow-up showed no complex regional type 1 pain syndrome ($p < 0.05$). Moreover, we did not find any major loco-regional complications such as hematoma, deep infection, post-fall fracture, dislocation or general thromboembolic or cardio-neurovascular type. Two-thirds of the patients who had undergone anterior tibial tubercle transposition admitted feeling no improvement during the long follow-up. No instability or antero-posterior laxity was observed on patients who received a ligamentoplasty in compliance with Kenneth-Jones, but half of them showed patellar signs. Patients who received unicompartmental joint replacement surgery had good X-rays and clinical results at the end of the one-year follow-up. Lastly, one third of the patients who benefited from a total prosthesis of the knee presented a stiffness, whereas a second third showed moderate mechanical pain chart. The scintigraphy requested for this first group have never revealed occurrence of a complex regional type 1 pain syndrome.

The results analysis of the second group reveals the occurrence of three complex type 1 pain syndromes confirmed by scintigraphy. One case occurred on a follow-up of a transposition of the anterior tibial tuberosity, one case during a ligamentoplasty carried out according to Kenneth-Jones and finally one cases during the implantation of a total knee prosthesis. The other complications were in line with and proportionally the same as the first group.

The analysis of the third group shows five complex type 1 pain syndromes confirmed also by scintigraphy. Two cases occurred after a transposition of the anterior tibial tuberosity and two cases after implantation of total knee arthroplasty. The other complications were in line too with and proportionally the same as the first group (Table 1).

Table 1 :Description of the series and resultswith $p < 0.05$ (X^2 to 4.537 for d.d.1 to 1).

Scheduledkneesurgeryo 66 womenagedfrom 30 to 55 yearsold	Liposomalvitamin C (n=22). 2 capsules of 500 mg dailyduring 28 days. Averageage of 44 years	Conventionalvitamin C (n=22). 2 capsules of 500 mg dailyduring 28 days. Averageage of 44 years	Placebo pills (n=22). 2 pillsdailyduring 28 days. Averageage of 44 years.
Casuistry	Number of cases operated and SDRC 1	Number of cases operated and SDRC 1	Number of cases operated and SDRC 1
Transposition of anterior tibial tuberosity	5 / 0	5 / 1	5 / 2
Ligamentoplasty LCA according to Kenneth-Jones	5 / 0	5 / 1	5 / 0
Internal unicompartimental prosthesis for centralizedarthritis	6 / 0	6 / 0	6 / 0
Totolknee replacement for eccentricarthritis	6 / 0	6 / 1	6 / 2

Table 2 :Statistical analysis of three randomized controlled trials and our presentseries.

STUDIES	ConventionalVitamin C		Placebo		Liposomal Vitamin C		Risk Ratio
	Events	Total	Events	Total	Events	Total	
1999 Zollinger	4	52	14	63	0	22	0.35 (0.12, 0.99)
2007 Zollinger	2	114	10	99			0.17 (0.04, 0.77)
2014 Ekrol	14	124	14	125			1.01 (0.50, 2,03)
2018 Cazeneuve	5	22	4	22	0	22	X^2 : 4.537 d.d.1 : 2 $p < 0.05$
Total		312		309		22	643
Total Events	25		42		0		67

Discussion

Complex Regional Pain Syndrome remains a frequent postoperative complication [1]. It is distributed differently according to the different series [7,8,9,10]. Its frequency can reach 37 percent [11]. Contrary to commonly accepted notions, psychological and constitutional factors cannot explain its occurrence [2,12,13,14]. In fact, the experimental study of Van der Laan et al. [2] shows the toxicity of free radicals released during soft-tissue contusion that increase the vascular permeability of striated muscle to macromolecules thereby decreasing circulating proteins and fluids [15]. Matsuda et al. [3] observed the beneficial effect of vitamin C in high doses, which reduces leakage of liquids and proteins thanks to its antioxidant and protective action against capillary endothelium, red blood cells and leucocytes [16].

Regarding prevention efficacy, systematic review of the literature associated with a meta-analysis performed by Aïm et al. [6] found only three randomized controlled trials. Two series are in favour of the preventive character of vitamin C intake to offset the occurrence of CRPS-1 [4,17] whereas one study shows no benefit

from administration of vitamin C as a preventive measure [18]. Chronologically, in 1999, Zollinger et al. [4] showed in a study on two series of patients that vitamin C administration in the event of reduced and immobilized distal radius fracture prevented the development of a Complex Regional Pain Syndrome type 1. In 2002, we reported in a retrospective sequenced study that daily intake of one gram of vitamin C for 45 days in distal radius trauma enabled reducing the rate of complex regional pain syndrome type 1 from 10 to 2.1. % [5]. In 2004, Reuben et al. [19] concluded that only vitamin C has proven effectiveness in preventing the development of Complex Pain Syndrome type 1 in scheduled orthopaedic surgery. To conclude, in 2009, Besse et al. [20] confirmed the preventive effect of vitamin C in Complex Regional Pain Syndrome type 1, on ankle and foot surgery. These again are retrospective studies.

Regarding the dosage to be prescribed, in 2007, Zollinger et al. [17] showed that intake of doses below 500 mg are ineffective. In 2013, Shibuya et al. [21] demonstrated through a meta-analysis the beneficial effects and non-toxicity of high-dose vitamin C in the prevention of Complex Regional Pain Syndrome 1 for lower limb trauma. In 2017,

Aïm et al. [6] using a systematic review and a meta-analysis of only placebo-controlled randomized trials, concluded that taking 500 mg of vitamin C daily for 50 days tended to reduce pain syndrome by half. This refers to oral intake of vitamin C, as only 10% of the ingested dose is absorbed.

With reference to the usefulness of liposomal encapsulation: in 2017, Sabesan et al. [22] indicated that liposomal encapsulation used in shoulder surgery anaesthesia to deliver constant doses of bupivacaine for 72 hours provided excellent control of postoperative pain by drastically reducing opioid consumption. Our study has shown that vitamin C in its liposomal form seems even more effective than the vitamin C usually and the placebo administered to prevent the occurrence of a regional type 1 pain syndrome and no case was found throughout the one-year follow-up with $p < 0.05$ (Table 2). The liposomal envelope provides protection against acidic gastric juices and intestinal enzymes thus allowing almost complete absorption, without denaturing the active ingredient.

Conclusion

This prospective and mono-centric comparative study demonstrates that over one-year liposomal encapsulation form of vitamin C provides better prevention of a Complex Regional Syndrome type 1 in programmed knee surgery rather than the conventionally used form and the placebo. This liposomal conditioning does not cause intolerance leading to a prescription. Currently and systematically, we prescribe the intake of a 500 mg capsule of liposomal vitamin C, in the morning and the evening, seven days before the operation, the day of the operation and for twenty-one days afterwards.

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