

Vitamin C and Prevention of Reflex Sympathetic Dystrophy in Case of Surgical Procedure for Programmed Knee Surgery

Jean-François Cazeneuve*

Clinique Victor Pauchet, 2, avenue d'Irlande, 80000 Amiens, France

***Corresponding Author:** Jean-François Cazeneuve, Clinique Victor Pauchet, 2, avenue d'Irlande, 80000 Amiens, France.

Received: June 18, 2018; **Published:** July 06, 2018

Abstract

Introduction: Complex regional pain syndrome type I (CRPS-I) is a significant complication in osteoarticular pathology, whether surgery has been undertaken or not. Intake of vitamin C appears to be the only preventative factor. This study seeks to show evidence that the liposomal conditioning of vitamin C is more effective than taking vitamin C in its usual form.

Patients and methods: Two series of patients, one took vitamin C in liposomal form and the other in conventional form. Comparison was made between both groups which were identical in number and were the same average age. The type of surgery was performed in the same one centre by the single surgeon using the same Operative techniques procedures and the same implants.

Results: After a one-year follow-up, the group taking the liposomal form did not experience any CRPS-I whereas the group that was administered traditional vitamin C form saw five cases of CRPS-I. All the follow up was documented by PET bone scanning.

Conclusion: 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.

Keywords: *Vitamin C; Reflex sympathetic dystrophy; Prevention*

Volume 2 Issue 3 July 2018

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Summary

Reflex sympathetic dystrophy is a major complication for orthopaedic surgery. Its pathogenesis is related to lipid peroxidation which causes vascular endothelial cells, increasing capillary permeability. Vitamin C is a natural antioxidant. Liposomal vitamin C is a specific packaging which allows for almost complete digestive absorption. Our protocol deals with 44 women scheduled to undergo knee surgery. These patients were divided into two equal-numbered groups.

The first series received two 500 mg liposomal vitamin C pills per day before, during and after surgery without developing reflex sympathetic dystrophy and the second one was given conventional vitamin C (likewise two 500 mg pills once a day before, during and after surgery): however, five cases of reflex sympathetic dystrophy were recorded. If the prescription of vitamin C is a breakthrough in the

Citation: Jean-François Cazeneuve. "Vitamin C and Prevention of Reflex Sympathetic Dystrophy in Case of Surgical Procedure for Programmed Knee Surgery". *Orthopaedic Surgery and Traumatology* 2.3 (2018): 332-337.

prevention of sympathetic dystrophy, we believe that the liposomal packaging is a very promising addition to a multimodal prophylaxis for orthopaedic surgery.

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 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 44 patients divided into two 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 unicompartamental 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 twenty times or with rachi-anaesthesia performed in twenty-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.

The first group of patients had a history of Complex Regional Pain Syndrome Type 1 (CRPS-1), documented under a bone scanner, half having developed in a benign post-traumatic context and the other half in operations such the ablation of synovial cysts, carpal tunnel surgery or osteotomy of the first metatarsal for hallux valgus treatment. All of them 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, with no history of Complex Regional Pain Syndrome Type 1 (CRPS-1), 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). 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 ($p < 0.05$) pain syndrome. 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 was observed on patients who received a ligamentoplasty in compliance with Kenneth-Jones, but half of them showed patellar signs and clinical antero posterior laxity.

Patients who received unicompartmental joint replacement surgery all had good XR-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 scans requested for this first group have never revealed recurrence or occurrence of a complex regional type 1 pain syndrome.

The results analysis of the second group reveals the occurrence of five complex type 1 pain syndromes confirmed by PET bone scanners. Two cases 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 two cases during the implantation of a total knee prosthesis. The other complications were in line with and proportionally the same as the first group (Table 1).

Scheduled knee surgery on 44 women aged from 30 to 55 years old	Liposomal vitamin C n = 22 2 capsules of 500 mg daily during 28 days Average age 44 years		Conventional vitamin C n = 22 2 capsules of 500 mg daily during 28 days Average age 44 years	
Casuistry	Number of cases operated	SDRC 1	Number of cases operated	SDRC 1
Transposition of the anterior tibial tuberosity	5	0	5	2
Ligamentoplasty LCA according to Kenneth-Jones	5	0	5	1
Internal unicompartmental prosthesis for centralized osteoarthritis	6	0	6	0
Total prosthesis for eccentric osteoarthritis	6	0	6	2

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

Studies	Conventional Vitamin C		Placebo		Liposomal Vitamin C		Risk Ratio
	Events	Total	Events	Total	Events	Total	
1999 Zollinger	4	52	14	63			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			0	22	X^2 : 4.537 d.d.l : 2 $p < 0.05$
Total		312		287		22	621
Total Events	25		38		0		63

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

Discussion

Complex Regional Pain Syndrome remains a frequent postoperative complication [1]. It is distributed differently according to the different series [7-10]. Its frequency can reach 37 percent [11]. Contrary to commonly accepted notions, psychological and constitutional factors cannot explain its occurrence [2, 12-14]. 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 Aim., *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, Aim., *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 by voluntarily choosing specific fields and high-risk pathologies has shown that vitamin C in its liposomal form seems even more effective than the vitamin C usually administered to prevent the occurrence of a regional type1 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. This liposomal conditioning does not cause intolerance leading to a prescription. Currently and systematically, for patients at risk, we prescribe the intake of a 500mg 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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