Impact of Intravenous Vitamin C Megadose on the Quality of Life of Terminal Cancer Patients (an Observational Analytical Study)

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ABSTRACT

Background

Our observational study was conducted to assess the impact of intravenous megadose vitamin C on the quality of life (QoL) of terminal cancer outpatients experiencing side effects of cancer therapies (radiotherapy, chemotherapy, surgery and/or hormonotherapy).

Methods

We asked doctors in two medical centres in Bogota in Colombia to identify cancer patients who are both experiencing side effects from conventional treatments and have been prescribed high dose intravenous Vitamin C (HDIVC) as part of their treatment. The HDIVC protocol used with terminal cancer patients in the Bogota medical centres uses 140 grams of HDIVC over 7 days.

The medical centre doctors explained the study to identified patients, sought consent, and asked patients to fill out the European Organisation for Research and Treatment of Cancer questionnaire EORTC-QLQ C30 version 3 (QLQ-30) before their HDIVC treatment. 22 patients were entered into the study, 19 completed. Our observational study compared the pre and post HDIVC QLQ-30 data for these 19 patients.

The collected QLQ-30 raw data was scored according to EORTC guidelines and also arranged into 5 categories; Domestic activity, Everyday (Routine) activity, Emotional activity and General QoL (Patient Score). The summed results of the raw data for each of these categories are presented and a percentage change for QoL results after HDIVC treatment is given.

Results

For the QLQ-30 scale scores significant improvements in QoL ($p < 0.01$) were observed for: Global health status/QoL, Physical functioning, Role functioning, Emotional functioning, Social functioning, Fatigue, Pain, Insomnia, and significant improvements in QoL ($p < 0.05$) were observed for: Nausea and vomiting, Dyspnoea, Appetite loss. For the raw data the mean ± SD percentage change improvements in QoL observed were: Domestic activity (20.99 ±33.53), Routine activity (30.98 ±22.40), Emotional activity (33.22 ±21.18), Sum of Domestic + Routine + Emotional (31.49 ±18.21), General QoL (100.21 ±140.86).

Conclusions

Overall the application of high dose intravenous Vitamin C had a significant positive effect on patients' quality of life in all categories. No significant side effects to high dose intravenous Vitamin C administration were reported.

Keywords

Cancer treatment and side effects Intravenous Vitamin C Megadose Quality of Life EORTC QLQ-30 Observational Study

Background

There is significant literature that supports the relationship between pharmacological consumption of vitamin C and the health of animals and humans [1]. It is now well established that megadoses of Vitamin C have functions well beyond its early classic use in treating scurvy. Apart from its well established role in the hydroxylation reactions including proline and lysine in the formation of the collagen [2], cholesterol [3] and some hormone formation [4], the epigenetic switching of methylated cytosine in the promoter region of genes [5], it is also well established that ascorbic acid acts as a strong antioxidant and free radical scavenger decreasing inflammation in numerous disease processes including sepsis [6], burns [7] and cancer [8]; it also increases the absorption of inorganic iron through reduction of ferric ion to ferrous [9].

A typical HDIVC dose used in treatment and research for over two decades has been 60 grams [10]. More recently a wide variety of doses and dose schedules have been used. A recent review in 2014 [11] details several studies examining multiple doses and

dose schedules that show that Vitamin C has significant effects on inflammation in cancer, and that Vitamin C is typically very depleted in cancer patients undergoing standard treatments.

The use of HDIVC in conjunction with medical cancer treatments in clinical research and treatment is now becoming widespread. A review by Klimant et al. (2018) [12] discusses Vitamin C deficiency in cancer, benefits in QoL and management of side effects with HDIVC in cancer patients, reduction in inflammation in cancer patients, and reviews dose ranges and some of the understood mechanisms for HDIVC in cancer.

Since the proposal by the twice Nobel prize-winner Linus Pauling about the efficacy and necessity of administering megadose Vitamin C intravenously (approx. 10 grams per dose) - rather than just orally - to improve the outcome of cancer patients, researchers studying Vitamin C in cancer have continued seeking to find the appropriate doses of vitamin C, especially delivered intravenously in this pathology [13]. The patient cohort included in the Pauling and Cameron cancer study in general had not received any significant cytotoxic therapy nor radiotherapy which may have resulted in more significant immune stimulation post megadose intravenous Vitamin C [14]. The pharmacokinetics of higher concentrations of Vitamin C achievable in the blood stream through intravenous administration compared with oral administration are well established [15].

The Quality of life (QoL) concept first appeared in 1948, when the World Health Organization (WHO) defined "health" as complete physical, mental and social well-being; superseding an older concept of health as the absence of disease or infirmity. The current definition, although criticized because of the difficulty of defining and measuring well-being, remains an ideal. Later, the term quality of life (QoL) evolved from a purely conceptual definition to a series of scales. This new definition measures the general perception of the individual. A commonly used tool to measure QoL in cancer patients is the European Organisation for Research and Treatment of Cancer questionnaire EORTC-QLQ C30 version 3 (QLQ-30) [16] . The QLQ-30 is scored into scales that measure functionality, pain and disability and emotional scales that are influenced by personal experiences and the expectations of a person [17].

It is apparent from several previous studies that high dose vitamin C improves QoL in cancer patients. Cameron and Pauling in 1976 [14] demonstrated that megadose intravenous Vitamin C (typical dose 10 g) along with oral Vitamin C not only improved the quality of life of cancer patients but on average increased the length of survival. Vollbracht et al. in 2011 [18] studied the effect of 7.5 g of intravenous Vitamin C weekly on the QoL of cancer patients receiving standard tumor therapy and aftercare. The intensity score for symptoms was close to twice as high in the placebo group compared to the IVC group. Ou et al in 2017 [19] conducted a pharmacokinetic and QoL study in China on patients receiving electro-hyperthermia along with high dose intravenous Vitamin C for advanced non-small cell lung cancer. They saw significant improvements in EORTC QLQ-30 physical function scores and symptom scores for all high dose ranges of intravenous Vitamin C tested; 1.0 g/kg, 1.2 g/kg and 1.5 g/kg – 60 to 90 grams of Vitamin C for a 60 kg person. Takahashi et al. [20] in 2012 observed the use of a high dose Riordan protocol - dose adjusted after the third day of IVC treatment for each patient to reach a plasma Vitamin C concentration of 350 mg%, typically approx. 140 g IVC per week. The study was conducted in multiple centres in Japan and saw dramatic increases in overall EORTC QLQ-30 QoL scores in a group of 60 patients after 2 and 4 weeks of HDIVC treatment. Yeom et al. in 2007 [21] used 10 g IVC in 2 doses 3 days apart in cancer patients and measured the change in QoL with the QLQ-30 questionnaire. They found a significant improvement in QoL in multiple function and symptom scales. Carr et al. [11] reviewed several trials and case studies reporting positive effects by HDIVC on QOL in cancer patients with or without chemotherapy. They note that the typical limitations in QoL studies of HDIVC in cancer are that; the studies do not use a placebo control, the studies do not examine dose ranging effects, and the studies do not measure the duration of effectiveness of a dose. Bazzan et al. in 2018 [22] retrospectively examined the effects of HDIVC on 86 patients of the Thomas Jefferson University Hospital over a 7-year period. They found that overall HDIVC was safe, well tolerated and was effective at improving QoL for these patients.

Vitamin C megadose therapy has been safely used for over 50 years in developed countries as a complementary medical treatment for cancer. We prospectively observed the effects of intravenous vitamin C therapy on the quality of life in a group of Colombian patients with advanced cancer, for whom conventional oncological treatments were producing side effects. Our aim was to observe the effects of high dose Vitamin C on our population and see how it compares with other results from around the world.

METHODS

This is an observational, analytical, prospective and comparative study (patients fill out a questionnaire both pre and post treatment). The questionnaire is the European organization for research and treatment of cancer quality life EORTC QLQ-C30 version 3 [16].

Human Right Statements and informed consent All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study.

COLLECTION OF BASIC INFORMATION

(Patient Questionnaire)

The most validated method used today worldwide to measure QoL has been developed by the European Organisation for Research and Treatment of Cancer and is called EORTC QLQ-C30 version 3 [16].

The EORTC is an international organization in which investigators from different countries participate in cancer research; in this case with a special emphasis on QoL of patients who suffer from cancer [17].

Our reference population is adult outpatients in the city of Bogota (Colombia) with any malignant cancer diagnosis receiving conventional treatments including chemotherapy, radiotherapy and/or hormone/therapy.

Suitability for treatment and consent All patients receiving HDIVC at the Bogota medical centres are tested that they are medically fit to receive HDIVC prior to treatment. This includes checking for contraindications and completing tests for a) Serum chemistry profile with electrolytes, b) Complete blood count (CBC) with differential and c) Red blood cell G6PD (must be normal). All patients receiving HDIVC have signed consent forms.

We asked the medical centre doctors to identify suitable outpatients according to inclusion and exclusion criteria:

Inclusion Criteria

- Adult (18 years old or older)
- External ambulatory patient (outpatient) with a 5 year (or less) active malignant cancer diagnosis being treated with chemo, radio, hormone therapy, or surgery.
- Individual who can read, understand and answer the EORTC QLQ-C30 questionnaire version 3.
- No evidence of G6PD deficiency nor abnormal kidney function.

Exclusion Criteria

- Under 18 years old.
- Be hospitalized (inpatient)
- Not being treated with chemotherapy, radiotherapy and/or hormone therapy.
- Not able to read, understand and answer EORTC QLQ-C30 questionnaire version 3.

Patients with the following cancers were recruited into our study; Breast cancer, myoepithelial carcinoma, ovarian cancer, kidney carcinoma, non-Hodgkin's lymphoma, pleural mesothelioma, pleomorphic sarcoma, gastric carcinoma, stomach adenocarcinoma, brain macroadenoma, lung cancer, frontal lobe astrocytoma, transverse bowel cancer, ductal adenocarcinoma, bladder carcinoma, womb cancer

INTRAVENOUS VITAMIN C USED BY THE BOGOTA CLINICS

Vitamin C as Sodium Ascorbate solution. Each vial contains 100mL, with 11.2 grams of Sodium Ascorbate for injection equivalent to 10 grams ascorbic acid. Manufacturing laboratory: Biological Therapies, Victoria Australia Registered in Colombia INVIMA 2016M-0012358-R1 In the Bogota medical centres cancer patients who receive HDIVC are given a standard protocol. The protocol is based on the work of Drs. Riordan and Hunninghake et al. [23] but is modified for use in Colombia. The protocol we observed was used by the medical centre doctors (H. Prieto, S. Rojas, R. Leudo) trained in injectable nutrients therapies.

An online version of the original Riordan protocol is maintained by the Riordan Clinic [24]. It states that " Research and experience have shown that a therapeutic goal of reaching a peak-plasma concentration of ~20 mM (350–400 mg/dL) is most efficacious. (No increased toxicity for post-IVC plasma vitamin C levels up to 780 mg/dL has been observed.) The first post-IVC plasma level following the 15-gram IVC has been shown to be clinically instructive: levels below 100 mg/dL correlate with higher levels of existent oxidative stress, presumably from higher tumor burden, chemo/radiation damage, hidden infection, or other oxidative insult, such as smoking."

In Colombia post-IVC plasma vitamin C levels measurements to determine the oxidative burden are not available (at May 15th, 2016). Since 2013 medical centre doctors have been utilizing the European patented Vit C test (Free Radical Analytical System 4, Evolvo Italy TM); It is relevant to mention that the Regulatory Body in Colombia, INVIMA, has only approved a concentration of 100mg/mL for IVC. For the above-mentioned reasons the American Riordan Protocol has been adjusted to Colombian conditions (test and concentration).

Products

- Sodium Ascorbate Solution: vial 11.2 g in 100 ML (equivalent to 10 gr of Ascorbic Acid) (Biological Therapies, Australia) – various amounts used on each occasion between 15g and 50g equivalent ascorbic acid.
- 100 ml of Water for Injection.
- Magnesium Sulfate: 10 ml ampoule of Mg So4 al 20% (2.5 gr x 10 ML) (Ryan Laboratorio, Colombia)

ADMINISTRATION OF IVC (DOSAGES): 14 VIALS = 140GRAMS IN 5 DOSES

Contraindications, precautions and potential side effects are outlined in detail in Riordan´s Protocol (24). After completing an oxidative stress test (Free Radical Analytical System, FRAS 4) and after patients have completed the Pre-HDIVC QLQ-30 questionnaire, the administering physician begins with a series of three consecutive IVC infusions at 15, 25, and 50-gram dosages.

Following the first three IVCs, the patient is scheduled to continue with a 25-gram IVC dose twice a week.

Day 1:

Vitamin C IV 15 g (1.5 vials of Sodium Ascorbate equivalent to 15g of ascorbic acid) in 150 cc of SSN (or LR). IV infusion rate of 0.5-1.0 g x min (15-30 min) + 1 CC of Magnesium Sulfate. Total Volume = 301 cc

Day 2:

Vitamin C IV 25 g (2.5 vials of Ascorbate) in 250 cc of SSN (or LR). IV infusion rate of 0.5-1.0 g x min (25-50 min) + 2 CC of Magnesium Sulfate. Total Volume = 502 cc

Day 3:

Vitamin C IV 50 g (5 vials of Ascorbate) in 500 cc of WFI. IV infusion rate of 0.5-1.0 g x min

(50-100 min) + 4 CC of Magnesium Sulfate. Total Volume = 1004 cc

Day 4: (3 days after day 3)

Vitamin C IV 25 g (2.5 vials of Ascorbate) in 250 cc of SSN (or LR). IV infusion rate of 0.5-1.0 g x min (25-50 min) + 2 CC of Magnesium Sulfate. Total Volume = 502 cc

Day 5: (2 days after Day 4)

Vitamin C IV 25 g (2.5 vials of Ascorbate) in 250 cc of SSN (or LR). IV infusion rate of 0.5-1.0 g x min (25-50 min) + 2 CC of Magnesium Sulfate. Total Volume = 502 cc

Final course of action:

Oxidative stress test completed (FRAS4), Post-HDIVC QLQ C30 questionnaire Note= Oral vit C 1 gram every 6 hours during break days after Day 3 is advisable.

The post HDIVC questionnaire was answered by 19 outpatients. The outpatients' quality of life (QoL) was measured using the QLQ-C30 questionnaire, both three days before and three days after application of HDIVC.

ENTERING THE QLQ-30 DATA INTO DATABASE CATEGORIES

The QLQ C-30 TABLE A questionnaire was converted into specific category groups for entry into a database:

- Domestic Activity
- Everyday Activity
- Emotional Activity
- General Quality of Life

DATABASE VARIABLES

62 variables are defined as follows:

a. Start: variable 1 and variable 2 describe the patient as pre QLQ-30 or post QLQ-30.

b. General Data: Covers the identification variables of the patients – diagnosis – status – value of laboratory tests used by external doctors (Pharmanex Biophotonic Scanner 3 and Free Radical Analytical System, FRAS 4). Variables 3 to 11.

c. Inclusion Criteria: Covers variables 12 to 18 and describes how the inclusion criteria are fulfilled.

d. Exclusion Criteria: Covers variables 19 to 26 and describes how the exclusion criteria are fulfilled.

e. Date EORT: variable 27 specifies when (the date) EORT was taken pre and post application of the Riordan protocol.

f. Domestic Activity: Covers variables 28 to 33 which include the first five questions of the QLQ-C30 that categorized as "Domestic Activity". Variable 33 describes the total score of this category.

g. Every day (Routine) Activity: Covers variables 34 to 48 which include questions 6 to 19 of the QLQ_C30 that are categorized as "Routine Activity". Variable 48 describes the total score to this category.

h. Emotional activity: Covers variables 49 to 59 of the QLQ-C30 that are categorized as "Emotional Activity". Variable 58 describes the total score of this category, variable 59 is the total score of the 3 categories.

i. General evaluation: variables 60 to 62 "General evaluation". Variable 62 describes the total score of this category.

All patients fulfilled the inclusion / criteria.

SCORING THE QLQ-30

The European Organisation for Research and Treatment of Cancer has published procedures for scoring the QLQ-30 (25).

We have presented the Scored data (the QLQ-30 Scales) for pre and post HDIVC and also presented a percent change statistic calculated on the raw data for pre and post HDIVC.

QLQ-30 SCALES

The procedure is to combine the QLQ-30 data into 15 scales, calculate a raw score for each scale (the average of all elements in the scale), then calculate an adjusted score ranging from 0 - 100 for each scale (the "Score").

In the QLQ-30 scores the following apply:

- For the general QoL scale a higher score = a higher QoL
- For the functional QoL scales a higher score = a higher QoL
- For the symptom QoL scales a higher score = a lower QoL, i.e. worse symptoms

RAW DATA

A scale with a score ranging from 0 – 100 is not suitable for our percent change descriptive statistic. The adjusted Score for each patient will on several occasions produce a value of zero which produces a "divide by zero" error in percent change calculations. Rather than adjust this further we chose to use the raw data only for our percent change calculations.

The raw data will never contain a zero. Data presented in our 5 categories; Domestic activity, Routine activity, Emotional activity, Sum of these three, and the General QoL are all sums of raw data.

Questions 1 – 28 in the QLQ-30 all have 4 possible responses:

Not at All A Little Quite a Bit Very Much

1 2 3 4

For questions 1 - 28 a low number in the raw data represents a higher QoL.

Questions 29 – 30 in the QLQ-30 all have 7 possible responses:

1 2 3 4 5 6 7

Very Poor Excellent

For these two questions a high number in the raw data represents a higher QoL.

RESULTS

No significant side effects to HDIVC administration were observed.

QLQ-30 SCORES

The QLQ-30 data was sored according to the EORTC manual (25).

Wilcoxon signed rank tests were used to determine statistical significance.

Table 1: Results. QLQ-30 scores

HDIVC 140 g in 1 week

EORTC QLQ-30 Score ± SD

	Pre	Post	P value
Global scale			
Global health status/QoL	41 ± 25	70 ± 16	**
Functional scales			
Physical functioning	66 ± 25	87 ± 11	**
Role functioning	48 ± 28	79 ± 21	**
Emotional functioning	43 ± 35	80 ± 18	**
Cognitive functioning	74 ± 26	85 ± 18	
Social functioning	46 ± 31	82 ± 25	**
Symptom scales			
Fatigue	63 ± 23	24 ± 18	**
Nausea and vomiting	28 ± 33	9 ± 17	*
Pain	55 ± 33	25 ± 20	**
Dyspnoea	40 ± 36	14 ± 20	*
Insomnia	61 ± 39	18 ± 30	**
Appetite loss	42 ± 40	16 ± 23	*
Constipation	32 ± 36	19 ± 30	
Diarrhoea	9 ± 19	14 ± 17	
Financial difficulties	56 ± 42	23 ± 33	

DESCRIPTIVE STATISTICS

(Percent Change)

Domestic Activity (4 possible responses for each question):

Our category Domestic Activity covers the first 5 questions (1 to 5) of the QLQ-C30 questionnaire. Each of these questions has a range from 1 – 4, so the possible sum of the raw data ranges from 5 - 20, where 5 is the highest QoL (excellent QoL), and 20 is the lowest QoL (very poor QoL).

In our Domestic Activity category, we observed that 4 out of 19 patients replied that their QoL was impaired (20.99%), 3 patients replied their QoL did not change at all (15.78%), and 12 patients replied their QoL improved (63.15%).

The greatest improvement in QoL was 66.67%; and the greatest decrease in QoL was 57.14%; with a general average of (positive= Improvement in QoL) 21% Routine Activity (4 possible responses for each question):

Our category Routine Activity covers questions 6 to 19 of the QLQ-C30 questionnaire. Each of these questions has a range from 1 – 4, so the possible sum of the raw data ranges from 14 - 56, where 14 is the highest QoL (excellent QoL), and 56 is the lowest QoL (very poor QoL)

In our Routine Activity category, we observed that 2 out of 19 patients replied that their QoL was impaired (10.5%) and 17 patients replied their QoL did improve (89.5%).

The greatest improvement in QoL was 63.83%; and the greatest decrease in QoL was 25.00%; with a general average of (positive= Improvement in QoL) 30.98%

Emotional Activity (4 possible responses for each question):

Our category Emotional Activity covers questions 16 – 28 of the QLQ-C30 questionnaire.

Each of these questions has a range from 1 – 4, so the possible sum of the raw data ranges from 13 - 52, where 13 is the highest QoL (excellent QoL), and 52 is the lowest QoL (very poor QoL).

In our Emotional Activity category, we observed that 1 out of 19 patients replied that their QoL was impaired (5.2%) and 18 patients replied their QoL did improve (94.8%).

The greatest improvement in QoL was 66.67%; and the greatest decrease in QoL was 6.25%; with a general average of (positive= Improvement in QoL) 33.22%

General (Sum of Domestic, Routine & Emotional):

A combination of the 3 categories Domestic, Routine and Emotional covers questions 1 to 28 of the QLQ-C30. The summed raw data ranges from 28 to 112, where 28 is the highest

QoL (excellent QoL) and 112 is the lowest QoL (very poor QoL).

We observed that 1 out of 19 patients in the study replied that their QoL was impaired (5.26%), none replied their QoL did not change at all, and 18 patients replied their QoL did improve (94.8%).

The greatest improvement in Qol was 65.26%; and the greatest decrease in Qol was 2.08%; with a general average of (positive= Improvement in Qol) 31.49%

Final QoL (Patient Score – 7 possible responses for each question):

For questions 29 - 30 of the EORTC QLQ-C30 questionnaire,

the possible score ranges from 2 to 14, where 14 is the highest QoL (excellent QoL) and 2 is the lowest QoL (very poor QoL)

The greatest improvement in QoL was 500%; and the greatest decrease in QoL was 20.00%; with a general average of (positive= Improvement in QoL) 100.21%

Table 2: Results. Sums of raw data for each patient in each category

Category	Domestic			Routine			Emotional			General (Sum)			Patient Score		
Patient	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ
CA003	11	5	54.55	35	22	37.14	25	9	64.00	71	36	49.30	10	10	0
CA004	9	7	22.22	31	16	48.39	28	14	50.00	68	37	45.59	7	12	71
CA005	5	6	-20.00	22	16	27.27	15	12	20.00	42	34	19.05	8	11	38
CA006	5	5	0.00	21	18	14.29	11	9	18.18	37	32	13.51	8	12	50
CA007	17	8	52.94	49	28	42.86	36	18	50.00	102	54	47.06	2	10	400
CA008	11	6	45.45	28	21	25.00	13	12	7.69	52	39	25.00	6	10	67
CA009	7	8	-14.29	46	17	63.04	29	15	48.28	82	40	51.22	2	12	500
CA010	18	6	66.67	47	17	63.83	30	10	66.67	95	33	65.26	6	12	100
CA011	13	5	61.54	41	22	46.34	28	14	50.00	82	41	50.00	4	12	200
CA012	13	6	53.85	39	25	35.90	30	16	46.67	82	47	42.68	4	11	175
CA013	5	5	0.00	30	14	53.33	12	9	25.00	47	28	40.43	11	14	27
CA014	12	9	25.00	37	30	18.92	22	21	4.55	71	60	15.49	3	8	166
CA015	11	10	9.09	31	32	-3.23	24	15	37.50	66	57	13.64	10	8	-20
CA016	7	7	0.00	32	26	18.75	26	25	3.85	65	58	10.77	10	8	-20
CA018	12	7	41.67	31	18	41.94	27	21	22.22	70	46	34.29	6	10	67
CA019	10	7	30.00	33	18	45.45	15	9	40.00	58	34	41.38	6	12	100
[illegible]															
CA021	7	11	-57.14	24	21	12.50	21	11	47.62	52	43	17.31	12	10	-17
CA022	7	8	-14.29	24	30	-25.00	17	11	35.29	48	49	-2.08	10	10	0
Average			20.99			30.98			33.22			31.49			100.21
SD			±33.53			±22.40			±21.18			±18.21			±140.86
Highest value			66.67			63.83			66.67			65.26			500
Lowest value			-57.14			-25.00			-6.25			-2.08			-20

Pre = Pre HDIVC, Post = Post HDIVC, %Δ = percent change. A positive number for %Δ values in all categories means an improvement in QoL.

STATISTICS ANALYSIS OF THE RAW DATA

22 patients who fulfilled the requirements of inclusion criteria were recruited for the present study. 19 patients completed. The QLQ-C30 questionnaire was completed before and after doctors administered HDIVC to all 19 patients.

A starting (base) line was used to compare the outcome of the QLQ-C30 questionnaire before and after the external doctor's administration of HDIVC (data not published). A Chi square Test was used for analysis, and for expected frequencies under 5, a Fisher exact test was used to compare qualitative variables.

For our analysis, we selected as a Pre-HDIVC group: Patients on cancer allopathic therapies undergoing secondary effects and we selected as a Post-HDIVC group: the same Patients after HDIVC administration.

For the Chi square and Fischer exact tests of association:

HYPOTHESIS

Megadose intravenous vitamin C significantly improves the quality of life in patients with any malignant cancer diagnosis who are receiving conventional medical treatments including chemotherapy, radiotherapy and/or hormone therapy; where these patients have secondary effects that may affect their quality of life; and are evaluated by the QLQ-C30 questionnaire.

NULL HYPOTHESIS

Megadose intravenous vitamin C does not affect the quality of life in patients with any malignant cancer diagnosis who are receiving conventional medical treatments including chemotherapy, radiotherapy and/or hormone therapy; and are evaluated by the QLQ-C30 questionnaire.

A descriptive statistic was used to adjust the results of the QLQ-C30 questionnaire for each of the categories measuring changes in the quality of life (if there were any). The results were recorded as a percentage change, comparing the pre and post HDIVC raw scores for each patient in each category.

The alfa error was 0.05 in all analyses.

The statistics package EPIDAT 4.1 was used for all analyses. When zeros cause problems with calculation Epidat adds the standard error 0.5 to all cells. This happens because all our 2x2 tables have a "Pre-HDIVC" group containing 19 patients with secondary effects and 0 patients with absence of secondary effects.

Table 3: Analysis of association between HDIVC administration and improvement in QoL

Category	QoL Improved?			OR	IC 95.0%			Chi²		
Domestic	No	Yes	Total						Result	p=
Pre-HDIVC	19	0	19	65.000000	3.403853	1241.240294	(Woolf)	Pearson	16.4103	0.0001
Post-HDIVC	7	12	19		5.467030	-	(Cornfield)	Yates	13.7892	0.0002
Total	26	12	38	Fisher Exact:	One tailed: p=0.0000		Two tailed: p=0.0000			
Routine	No	Yes	Total						Result	p=
Pre-HDIVC	19	0	19	273.000000	12.246978	6085.501072	(Woolf)	Pearson	29.1919	0.0000
Post-HDIVC	2	17	19		18,373506	-	(Cornfield)	Yates	25.8586	0.0000
Total	21	17	38	Fisher Exact:	One tailed: p=0.0000		Two tailed: p=0.0000			
Emotional	No	Yes	Total						Result	p=
Pre-HDIVC	19	0	19	481.000000	18.405655	12570.103971	(Woolf)	Pearson	32.4812	0.0000
Post-HDIVC	1	18	19		26.796892	-	(Cornfield)	Yates	28.9724	0.0000
Total	20	18	38	Fisher Exact:	One tailed: p=0.0000		Two tailed: p=0.0000			
General (Sum)	No	Yes	Total						Result	p=
Pre-HDIVC	19	0	19	481.000000	18.405655	12570.103971	(Woolf)	Pearson	32.4812	0.0000
Post-HDIVC	1	18	19		26.796892	-	(Cornfield)	Yates	28.9724	0.0000
Total	20	18	38	Fisher Exact:	One tailed: p=0.0000		Two tailed: p=0.0000			
Patient Score	No	Yes	Total						Result	p=
Pre-HDIVC	19	0	19	81.000000	4.201687	1561.515591	(Woolf)	Pearson	18.5714	0.0000
Post-HDIVC	6	13	19		6.700994	-	(Cornfield)	Yates	15.8242	0.0001
Total	25	13	38	Fisher Exact:	One tailed: p=0.0000		Two tailed: p=0.0000			

Association Chi squared results for all categories are above the critical value (for one degree of freedom) and all p values are < 0.05, therefore we reject the null hypothesis.

Fisher Exact Test results for all categories have a p value < 0.05, therefore we reject the null hypothesis.

In all categories administration of HDIVC showed a statistically significant association between HDIVC treatment and improvement in QoL scores.

Domestic activity:

X 2 = 16.41; Yates Correction = 13,78, IC 95% {3.40 – 1241.24}; p = 0.0002 & Fischer Test p = 0.0000.

Routine Activity:

X 2 = 29,19; Yates Correction = 25,85, IC95% {12,24 – 6085,50}; p = 0,0000 & Fischer Test p = 0,0000.

Emotional activity:

X 2 = 32,48; Yates Correction = 28,97, IC 95% {18,40 – 12570,10}; p = 0,0000 & Fischer Test p = 0,0000.

Combined Domestic + Routine + Emotional Activities:

X 2 = 32,48; Yates Correction = 28,97, IC 95% {18,40 – 12570,10}; p = 0,0000 & Fischer Test p = 0,0000.

Overall patient score:

X 2 = 18,57; Yates Correction = 15,82, IC 95% {4,20 – 1561,51}; p = 0,0001 & Fischer Test p = 0,0000.

Our data suggests a strong association between HDIVC intervention and improved QoL in all categories.

DISCUSSION

Ours is an observational study looking at the effect of HDIVC on the QoL of cancer outpatients receiving treatment in two integrative medicine centres in Bogota. HDIVC is commonly used in these centres with cancer patients who are also receiving standard therapies. The HDIVC doses used are more typical of the high doses being used in current clinical trials and aim to achieve high blood levels of Vit C.

Many studies have reported improved QoL in cancer patients with HDIVC. Klimant et al. [12] in 2018 have reviewed the use of HDIVC in cancer treatments and give recommendation for an effective but conservative use of HDIVC in combination with chemotherapy.

Studies investigating the effect of HDIVC, including QoL studies, have used a large range of doses from as little as 7.5 g up to 150 g of IVC with a variety of dosing schedules employed.

However very few studies have been formal QoL studies measuring QoL using a variety of validated questionnaires. Some other previous QoL studies have examined lower dose IVC; doses of 7.5 grams weekly [18] and 10 grams (2 doses 3 days apart) [21], doses that are much lower than the typical dose being used in current clinical trials and the Bogota medical centres. Three other QoL studies have examined a higher dosage schedule. Ou et al. in 2017 [19] used 1.0, 1.2 or 1.5 grams/kg, Takahashi et al [20] in 2011 observed the Riordan protocol, approx. 140 grams/week, and Bazzan et al. [22] in 2018 observed a wide range of doses and schedules in a hospital, ranging from 50 – 150 grams per dose). Three previous studies (Ou et al. [19] high dose, Takahashi et al [20] high dose and Yeom et al [21] lower dose) have used the QLQ-30 for measuring pre and post HDIVC in cancer patients.

Our results compare favourably with results from previous QLQ-30 studies.

Table 4: EORTC QLQ-30, comparison of global health status

HDIVC EORTC Score ± SD						
Study	Current study		Yeom 2007 (21)		Takahashi 2012 (20) (after 4 weeks)	
	Pre	Post	Pre	Post	Pre	Post
Global health status/QoL	41 ± 25	70 ± 16	36 ± 18	55 ± 16	45 ± 28	61 ± 24

Our results also compare favourably with studies that have used different methods for comparing QoL (Vollbracht et al 2011 [18], Bazzan et al (22) 2018)

Ours is not a dose ranging study. We have not asked the medical centres to modify their treatments, QoL is not their only reason for treatment. We have not collected data on the effects of different doses or HDIVC protocols on QoL.

The Riordan protocol used in the USA [24] is titrated for each patient to achieve a 350 mg% blood level of Vit C at around day 3 of the protocol. Some patients require considerably more IVC than average to reach these levels, some require considerably less. So, the total amount of Vit C administered over the period of the protocol can vary quite a bit from patient to patient. In clinical experience in Colombia, the amount of HDIVC required to achieve high blood levels is on average lower than that in the USA. Also, the Bogota medical centres routinely test for G6PD deficiency and adequate kidney function in all patients prior to IVC treatment as outlined in the Riordan protocol [24]. G6PD deficiency is uncommon in our Colombian population and appears to be more common in the USA and some other countries. We are aware then of some differences in our population compared to G6PD levels in the USA.

LIMITATIONS OF THE STUDY

This is an observational study. Associations have been measured between high dose Vitamin C administration and changes in quality of life. We have sought to gain preliminary data for the effectiveness of Vitamin C administration in our population, with a view to adequately sizing a future clinical trial into Vitamin C and QoL in cancer patients. This study has not answered the open questions remaining about the use of high dose Vitamin C in QoL, we have not observed or measured: the effect of dose ranging on different cohorts, the duration of effectiveness of a dose, the use of a placebo control.

CONCLUSION

We have had encouraging results from our observational study. In both the EORTC QLQ-30 scores and a percent change descriptive statistic we observed that HDIVC was associated with a significant improvement in reported QoL.

For the QLQ-30 scale scores significant improvements in QoL ($p < 0.01$) were observed for; Global health status/QoL, Physical functioning, Role functioning, Emotional functioning, Social functioning, Fatigue, Pain, Insomnia and significant improvements in QoL ($p < 0.05$) were observed for: Nausea and vomiting, Dyspnoea, Appetite loss.

Out of the 19 patients evaluated in the categories Domestic Activity, Routine Activity and Emotional Activity, only one did not report improvement in their quality of life and 18 patients

reported improvement (94.73%). All statistical tests in these categories showed a strong association between HDIVC treatment and improvement of QoL in our study population.

Overall the administration of HDIVC had a significant positive effect on patients' quality of life. Further trials into HDIVC on QoL in cancer cohorts are warranted.

LIST OF ABBREVIATIONS

EORTC: European Organisation for Research and Treatment of Cancer

QLQ-30: EORTC QLQ-30 version 3 questionnaire

HDIVC: High dose intravenous Vitamin C

QoL: Quality of Life

WHO: World health Organisation

SSN (or LR) : Normal Saline or Ringer's Lactate

X 2 : Chi squared test

IV: Intravenous

FRAS4: Free Radical Analytical System

DECLARATIONS

Ethics approval and consent to participate (translated from Spanish)

Re: IMPACT OF INTRAVENOUS VITAMIN C MEGADOSE ON THE QUALITY OF LIFE OF

TERMINAL CANCER PATIENTS. (An Observational Analytical Study)

Dear Doctor,

The Ethical Committee in Biomedical Research CEDIFF has received and reviewed the information dated 13 April 2019. In accordance with to the ACT 07 this Committee confirms that:

The request that was submitted before the commencement of the observational study:

"IMPACT OF INTRAVENOUS VITAMIN C MEGADOSE ON THE QUALITY OF LIFE OF

TERMINAL CANCER PATIENTS. (An Observational Analytical Study)"

Will not require further assessment by any Ethics Committee because the methods applied to the study are of no risk.
This response is generated accordance to Resolution 8430 of 1993 Health Ministry, ACT 11, a) relating to: Studies Risk classification.

Cediff Ethical Committee guarantees the observational study adheres to the following international rules related to biomedical research in human beings:

- Nuremberg Code 1947;
- Helsinki declaration WHO. 1964 and further revisions;
- Belmont Report, national commission report for human beings of biomedical research and behaviour 1979;
- Universal declaration about bioethics and human rights UNESCO 2005.

Furthermore, the study also adheres to the following national regulations:

- Resolution 8430 (1993), Resolution 3823 (1997), Resolution 2378 (2008) and all relevant updated topics issued by INVIMA or Health and Social protection Ministry

Sincerely Yours,

Yinneth Milena Pérez Rubio

President

Comité de Ética en Investigación Biomédica Cediff

CONSENT FOR PUBLICATION

All data has been de-identified. Individual patients are referred to by an identification number or patient code. Patients have signed a consent form for publication. No patient identifiable data is included in the publication or associated tables.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

HG has received research grants from Biological Therapies comprising of IVC vials supplied free of charge for this study. HG owns stock in Drug company Grupo Gales SAS which imports Vitamin C from Biological Therapies to Colombia.

CC declares that he has no competing interest.

GG declares that she has no competing interest.

FUNDING

Biological Therapies, AUSTRALIA

A Division of Orthomolecular Medisearch Laboratories Pty Ltd. A.C.N. 006 897 856. Manufacturers & Distributors of Parenteral & Oral Nutritional Supplements. Suite 5, 20-30 Malcolm Road (PO Box 702) Braeside VIC 3195 Australia Tel (61) 3 9587 3948; Fax (61) 3 9587 1720
Web www.biologicaltherapies.com

Biological Therapies provided free of charge the Vitamin C used in this study, registered in Colombia INVIMA 2016M-0012358-R1

AUTHOR'S CONTRIBUTIONS

HG, CC and GG designed the study.

CC prepared the data tables for the study and conducted the analyses once data was complete at patient no. 22. CC prepared the interpretations of the data in Spanish.

HG prepared the original manuscript and translated all materials from Spanish into English.

This study has not been published in Spanish.

ACKNOWLEDGEMENTS

LOCAL ASSISTANTS

Mr. Jhon Cantor, Statistical Analysis Assistant, Grupo Gales

Ms Astrid Llorente, Head of Nursing, Grupo Gales

Ms Mónica Padilla Pinzón, Nurse Assistant, Grupo Gales.

Ms Sandra Villagrán, Pharmacist, Grupo Gales.

JC, AL, MPP and SV provided logistics and support for the study.

EXTERNAL DOCTORS

Dr Helber Prieto Epidemiologist, Specialist in Occupational Health/Medicine, SCMPO (The

Colombian Society of Preventive Medicine).

Dr Santiago Rojas, Palliative Care, Colombia

Dr Rocio Leudo, Dentist, Colombian Odontological College, Colombia

HP, SR and RL were observed in clinical practice

HP provided support for statistics analysis

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