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REVIEW OPEN ACCESS

Vitamin C for the Treatment of Depression in Cancer Patients: A Literature Review

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Abstract

Introduction: One in two Canadians will be diagnosed with cancer in their lifetime and one in four will experience depression during their diagnosis. The cause of depression during cancer could be related to psychological, social, inflammatory, or immunological factors. Vitamin C can exert an effect on oxidative stress levels, adrenal function, and immune function and may have a role in the treatment of both cancer and depression. Vitamin C levels can affect neurotransmitter levels and its ability to increase quality of life in cancer patients, as well as relieve other cancer-related symptoms such as pain, has been documented.

Methods: A systematic literature search was completed to identify all studies that assessed changes in depression symptom severity in patients receiving intravenous vitamin C treatment. The databases utilized include PubMed, Medline Complete, CINAHL Plus, Web of Science, Cochrane, and PMC. The inclusion criteria were: human participants with confirmed cancer of any type and stage, intravenous vitamin C treatment, with or without conventional treatment and with or without additional oral vitamin C dosing, and assessment of depression.

Results: Out of 152 unique articles analyzed, four observational studies evaluate depression symptoms as part of an assessment of quality of life in cancer patients undergoing intravenous vitamin C treatment. All four studies reported improvement in mood.

Discussion: The four included studies assessed the role of intravenous vitamin C in the treatment of depression in cancer patients. These studies confirmed previous research reporting improved quality of life and other cancer-related benefits (i.e. decreasing fatigue and pain). All four studies noted a decrease of depression in cancer patients which are summarized in Table 1. The included studies all evaluated safety and reported no significant adverse effects associated with the treatment.

Conclusion: The current literature suggests that intravenous vitamin C could potentially have a beneficial effect on levels of depression in patients with cancer; however, more research is needed. Prospective clinical trials using validated assessment tools to capture changes in depression and control groups are needed to further study the potential role of this therapy in the treatment of depression in cancer patients.

Keywords: vitamin c; cancer; depression; intravenous; ascorbic acid; mental health; mood; naturopathic medicine; naturopathy

Introduction

One in two Canadians will receive a diagnosis of cancer in their lifetime and one in four of them will experience depression during their diagnosis [1]. Chronic stress is common in cancer patients, leading to increased levels of catecholamines, which are associated with higher rates of depression [2]. Despite its prevalence, depression in cancer patients is often misdiagnosed [2]. The cause of depression during cancer is often multifactorial and may include psychological, social, and immunological factors as well as inflammation related to cancer or treatments [2]. Not only does depression in cancer patients significantly reduce quality of life (QoL), but it is also associated with higher levels of anorexia, fatigue/sleep issues, as well as an increased number of days in the hospital and the number of resources used, leading to greater health-related expenses [2, 3]. Studies have associated increased depression with increased metastasis and worse survival outcomes [4, 5]. Cancer patients with depression are more than twice as likely than people without cancer to die by suicide [6]. Consequently, there is a need to reduce the burden of depression among cancer patients.

Cancer and depression share some common pathophysiologic characteristics, such as decreased immune function and altered adrenal function, and vitamin C could possibly play a beneficial role in the treatment of both [2, 7]. Not only are cancer patients at an increased risk for depression, but depression can cause chronic stress, which

may have implications in the pathogenesis and progression of cancer [7-9]. Chronic stress increases epinephrine, which is known to suppress the immune system, and sustained elevation of levels may potentially contribute to carcinogenesis [7]. In-vitro and in-vivo studies demonstrated that vitamin C decreases chronic stress-induced cancer cells, indicating that vitamin C possibly plays a role in the reduction of tumour growth via this mechanism [7]. Vitamin C is also vital for adrenal function, which plays a crucial role in depression via the hypothalamic-pituitary-adrenal (HPA) axis, making it essential to have sufficient levels for emotional well-being [10, 11].

Cancer patients frequently experience nutritional deficiencies due to a variety of reasons ranging from lack of appetite, changes in taste, and decreases in mental well-being, to increased biological demands associated with cancer and chemo/radiotherapy [12-17]. These nutritional deficiencies have substantial implications for disease progression, with some studies citing an approximated 30% increase in mortality in malnourished cancer patients [12]. Nutritional deficiencies are common in cancer patients regardless of their body mass index, including overweight patients where obesity can potentially mask malnutrition [18]. In a 2019 study of palliative cancer patients, authors Vollbracht et al. sought to determine nutritional status and found vitamin C deficiency (defined as serum below 4.5 mg/L) in 45.2% of patients, as well as deficiencies of vitamin D3 (93.5%), B6 (48.4%), and B1 (25.8%) [19]. When a patient undergoes surgery, chemotherapy, or radiation, there is an increased demand by the body for vitamin C as it plays an integral role in several different biological and psychological mechanisms [15, 17, 20-23]. Thus, nutritional deficiencies have important implications among cancer patients.

Vitamin C deficiencies have significant implications in synthesizing the neurotransmitters serotonin, norepinephrine, and dopamine, which play an important role in the pathogenesis of depression [24-26]. Multiple studies have shown that patients with depression have significantly decreased vitamin C levels [19, 27, 28]. Khanzode et al. demonstrate that individuals with major depression have significantly increased levels of oxidative stress markers, such as serum superoxide dismutase (SOD), increased serum malondialdehyde (MDA), and decreased plasma vitamin C levels [29]. Therefore, the antioxidant effects of vitamin C in non-cancerous cells are a potential mechanism of action for a possible antidepressant effect [3, 29]. In a double-blind, experimental study, Zhang et al. demonstrated that oral vitamin C administration to acutely hospitalized patients significantly improved depression [30]. In the double-blind, placebo-controlled pilot study, Amr et al. found that 1 g of oral vitamin C per day alongside fluoxetine significantly reduced depression as compared to fluoxetine with placebo [31]. These studies suggest that vitamin C supplementation may be useful in the treatment of depression and that further study of its use in the treatment of depression among cancer patients is warranted.

Vitamin C is a versatile nutrient in the body that was first isolated in 1928 and has since been subject to many different studies to explore its various applications and mechanisms [24]. Humans lack the enzyme gulonolactone oxidase, which is integral to endogenous vitamin C synthesis; as such, deficiency is common in humans when demands are not met through dietary sources or supplementation [24]. Linus Pauling was among the first to provide intravenous vitamin C (IVC) to cancer patients in the 1970s [32]. Preliminary evidence suggests that administration of this nutrient by this route may be associated with reduced tumour growth as well as improvement in other cancer-related symptoms [32]. Studies have shown that high-dose IVC is safe and has beneficial cancer-related effects such as increased survival times, decreased tumour growth, increased QoL, increased efficacy of conventional treatment, decreased cancer symptoms, and decreased side effects from conventional cancer treatment [32]. Therefore, addressing deficiency through IVC may play a vital role in managing and treating cancer and reducing depression among patients. This literature review aims to establish this by examining the use of IVC treatment in managing depression in cancer patients.

IVC administration results in increased serum levels 25 to 100 times higher than with oral administration for a minimum of four hours; this is largely due to the limitations of oral route administration, such as the limited capacity for enteric absorption coupled with renal excretion rates [33-35]. IVC produces an exponentially higher serum status of vitamin C for a sustained period of time as compared to oral route administration [34]. The resulting increase in serum vitamin C is utilized by GLUT glucose transporters, which are upregulated in tumour cells and lead to substantially higher concentrations within tumours than in non-cancerous tissue [32]. This upregulation of vitamin C intake in tumour cells accounts for some of the increased metabolic demand for vitamin C in cancer patients; this is why achieving substantially higher serum status is necessary through IVC application as it bypasses the limitations of enteric absorption rates [32]. The pro-oxidant effects of high cellular levels of vitamin C increase hydrogen peroxide, which has been demonstrated to be oncolytic while being neutral to non-cancer cells due to the presence of catalase [32, 36-38]. The reduction of catalase capacity in cancer cells is substantial with some studies noting a two-fold difference in metabolism [39]. In short, several authors have suggested there is an increased metabolic demand for vitamin C in people with cancer; this may have implications in mental health due to vitamin C's role in neurotransmitter synthesis.

Despite preliminary evidence and possible mechanisms, there currently are no studies synthesizing the research related to the effects of IVC on depression levels in patients with cancer. This literature review aims to

identify and integrate the findings of studies that have assessed depression levels in patients receiving IVC treatment for cancer, identify gaps, and put forward recommendations for further research.

Methods

This literature review analyzed all available studies on the effect of IVC on depression in cancer patients. The search strategy was executed using PubMed, MedLine Complete, CINAHL Plus, Web of Science, Cochrane, and PMC databases in May 2020. Authors searched "IVC," "Intravenous Vitamin C," "Vitamin C" and "Ascorbic Acid" in conjunction with "Depression" and "Cancer." This review includes both prospective and retrospective studies. Bibliographies of relevant articles were searched for additional publications not identified in the original search.

The criteria of inclusion were the following: human participants with confirmed cancer of any type and stage, IVC treatment, with or without conventional treatment (chemotherapy, radiation, and/or surgery) and with or without additional oral vitamin C dosing, and assessment of depression. This review excludes preclinical studies (e.g. animal or *in vitro*), non-English publications, and literature reviews and/or opinion articles.

Results

The search strategy identified 152 scholarly articles. Of these, four observational studies met the criteria for inclusion. Table 1 summarizes these studies.

The populations of the included studies were all adults with a variety of different kinds of malignant cancer diagnoses and stages, including stage IV terminal cancer and stages IIa-IIIb breast cancer (refer to Table 1). In all four studies, researchers found a benefit of IVC on depressive symptoms associated with cancer and/or cancer therapy. The authors of all four studies do not include data on supplemental mental health support for patients. In the Yeom et al. study, authors examined the impact of IVC and oral vitamin C supplementation on 39 patients with terminal cancer diagnoses (less than six months life expectancy) where the treatment goal was an improvement in QoL scores[40]. Two doses of 10 g IVC per day for three days with concurrent 4 g oral route vitamin C per day for one week were found to significantly improve the scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[40]. Analysis revealed significant improvement in all five functional scales (physical, role, emotional, cognitive, and social) and significant improvement in several symptom scores such as fatigue, nausea/vomiting, and appetite loss; other symptom improvements include pain and in sleep disturbance [40].

Similarly, Takahashi et al. used a combination of oral vitamin C and IVC and reported a significant improvement in EORTC QLQ-C30 scores at two weeks compared to baseline and an even greater significant improvement at four weeks in 60 patients with malignant cancers[41]. This study also reported significant improvements in all five functional scales, which includes emotional function as well as fatigue, insomnia, pain, and constipation [41].

Our review included two retrospective studies, Bazzan et al. and Vollbracht et al. [3, 42]. In the Bazzan et al. study, authors identified cases where patients received either IVC alone, IVC and chemotherapy, or chemotherapy alone [42]. Bazzan et al. reported significant improvement in pain and fatigue; additionally, six out of seven patients reported improved mood (the last remained unchanged) [42]. In the Vollbracht et al. study, authors sought to explicitly examine the impact of IVC on symptoms caused by chemotherapy and radiotherapy with regards to depression as well as fatigue, sleep disorders, and loss of appetite [3]. As a result, Vollbracht et al. found a significant reduction in depression scores ($p=0.017$) in patients with stages IIa-IIIb breast cancer undergoing IVC with concomitant conventional treatments [3].

Discussion

The four included observational studies assessed the role of IVC for depression in cancer patients. These studies confirmed previous research in reporting improved QoL and other cancer-related benefits (i.e. decreasing fatigue and pain) [3, 40-42]. All four studies noted a decrease of depression in cancer patients [3, 40-42]. In the Takahashi et al. study, 5% of the IVC patients experienced a transient worsening in QoL scores graded as "minimally worse", while adverse events were minimal and did not result in patients withdrawing from the study [41]. The included studies all evaluated the safety of IVC and reported no significant adverse effects associated with IVC, which is critical when considering any intervention as a proposed treatment. These findings of safety have been replicated in numerous trials and are summarized in several meta-analyses and systematic reviews [3, 28, 30, 32, 40-43]. The consistency of these findings further supports the feasibility of future studies into IVC and its potential role in the treatment of depression in cancer patients.

Outside of cancer research, low levels of vitamin C (i.e. scurvy) is common in adults with depression [44-48]. However, not all of the research on vitamin C deficiency and mood reflected these same results [49, 50]. Oral vitamin C supplementation may improve mood in acutely hospitalized patients, healthy young adults [30, 51]. While most studies measuring the effects on mood with vitamin C supplementation show at least a trending improvement, a small 2015 clinical trial did not show any significant changes in major depressive disorder and suicidal behaviour when treated with oral vitamin C adjuvant with citalopram versus citalopram alone [52]. However, another trial that combined 1 g of oral vitamin C with fluoxetine in a pediatric population significantly decreased depression symptoms as compared to fluoxetine plus placebo [31].

Table 1. Human studies of high-dose vitamin C in the treatment of cancer-associated depression

Author and Year	Methodology	Sample size	Cancer Type(s)	Dose of vitamin C	Concomitant Therapy	Depression Scale Used	Outcome for Depression	Other Outcomes
Yeom 2007 [40]	Prospective Observational Study	39	Stage IV terminal cancer (estimated survival less than 6 months)	Two doses of 10 g IVC per day for three days with concurrent 4 g oral route vitamin C per day for one week	None; however, all had previously completed standard of care treatment	EORTC QLQ-C30	Patients had significantly increased scores in emotional function after IVC therapy ($p<0.005$).	Significant improvements in QoL/global health scale as well as improvements in sleep, fatigue, N/V, pain, appetite loss and cognitive function ($p<0.005$). Patients had significantly increased scores for physical, cognitive, and social function, post-IVC therapy ($p<0.005$). No patients ceased IVC due to adverse effects.
Takahashi 2012 [41]	Prospective Observational Study	60	Any cancer with malignant tumours	Riordan IVC protocol: 1st dose 12.5-15 g; 2nd dose 25 g; 3rd dose 50 g; 4th and additional dosing was calculated to maintain serum concentrations of 350-400 mg/dL. As well, vitamin C oral intake of 2-4 g daily	No limitations were placed (i.e., patients were allowed to engage in ongoing standard of care therapy)	EORTC QLQ-C30	There was a significant improvement in emotional function at four weeks ($p<0.05$).	Significant QoL improvements from baseline demonstrated an average 8.6-point increase at week 2 ($p<0.05$) and a 16.8-point improvement at week 4 ($p<0.01$) There were significant improvements in physical, role, cognitive, and social function at four weeks ($p<0.05$). There were significant reductions in fatigue and insomnia at 4 weeks compared to baseline ($p<0.01$) by nearly 50%; as well as significantly decreased pain and constipation ($p<0.05$). No patients ceased IVC due to adverse effects.
Vollbracht 2011 [3]	Retrospective Observational Study	125	Breast cancer (stages IIa-IIIb)	Standard therapy + IVC (7.5 g Pascorbin once weekly)	Standard chemotherapy and radiation	3-point scale to assess the intensity of complaints (0=no complaints, 1=mild complaints, 2=severe complaints).	The IVC (n=53) treatment group had significantly reduced scores of depression ($p=0.017$).	There were significant reductions in cancer- and chemo/radiation- associated side effects during the adjuvant stage, such as fatigue ($p=0.004$), sleep disorders ($p=0.005$), and loss of appetite ($p=0.046$). The authors do not document any adverse effects associated with IVC. There were no significant interactions between IVC and adjuvant therapy ($p=0.255$ for chemotherapy and $p=0.905$ for radiotherapy).
Bazzan 2018 [42]	Retrospective Observational Study	86 (32 IVC only; 54 had IVC and chemotherapy)	Variety of different types and stages	At least 5 doses of 50-150 g of IVC given over 2-3 hours	Chemotherapy (different kinds)	3-point scale to assess the efficacy of IVC (improved, stable or worse) during the adjuvant therapy and aftercare phases.	6 of the 7 patients that had mood disturbances* reported significant improvement and the last patient reported mood stability.	The most common adverse events related to IVC were temporary nausea and local discomfort at the site of injection. All adverse events reported in the IVC alone group were associated with less than 3% of the total number of infusions. Patients also reported improvements in fatigue and pain while receiving IVC.

Table made using Microsoft Word. *Mood Disturbances are not the same as depression. QoL: Quality of life. IVC: Intravenous vitamin C. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30. N/V: Nausea/vomiting. These four included studies resulted from reviewing 152 unique scholarly articles

Considering the Yeom 2007 study where cancer patients took oral vitamin C in addition to IVC, it would be helpful for future studies to assess the effects of depression using the PHQ-9 by comparing IVC in cancer patients with and without oral supplementation [40].

Other nutrients with evidence to potentially improve mood in adult cancer patients include isoquercetin and omega-3 fatty acids, using the PHQ-9 and EORTC QLQ-C30, respectively [53, 54]. However, more data from well-designed, adequately controlled and powered studies is needed to determine if these agents are efficacious in cancer patients with depression.

In terms of dosing, the included studies use varying doses of IVC ranging from 7.5 g to 100 g per administration, with several studies using additional oral dosing. Previous clinical research has found tolerability of IVC dosages up to 1.5 g per kg of body weight [3, 55]. There is no definitive guideline that sets apart high-dose from low-dose vitamin C supplementation; however, a review of the literature reveals a common understanding that low-dose vitamin C refers to dosages typically in the 1-5 g range as these are the general limitations on enteral administration due to bowel tolerance; while high-dose vitamin C refers to dosages over 5 g and are synonymous with serum status levels that are only achievable through parenteral administration [20, 32]. Alternative distinguishing characteristics could be related to the safety implications of dosing, such as the requirement for glucose-6-phosphate dehydrogenase testing in dosages greater than 15 g as a deficiency in this enzyme with high doses of vitamin C can result in hemolytic anemia [32]. Other contraindications include renal failure, hemochromatosis, and oxalate calculus [3].

It is important to note key differences between the studies, such as cancer staging and timing of IVC interventions with conventional therapies. One limitation of using the EORTC QLQ-C30 is that it only captures overall QoL and while a subdomain assesses emotional function, it lacks validation for the assessment of depression. However, research does exist that draws an association between EORTC scores and depression, such as a 2009 study of colorectal cancer patients that correlates those who scored over 17 points on the Beck Depression Inventory with substantially lower EORTC scores [56].

One strength of this review is the employment of a systematic search strategy to ensure the identification of all relevant studies. Another strength is that the same validated questionnaire, EORTC QLQ-C30, was used in two studies, which aids in the comparison of the findings [40, 41]. Conversely, a limitation of this review is that two of the four studies were retrospective and only one study had a control group; making direct comparison of findings difficult [3, 40-42]. In future studies, it is crucial that a validated tool, such as the PHQ-9, Hamilton Depression Rating Scale, or the Beck Depression Inventory, is used in order to adequately assess the impact treatment has on depression symptoms [57].

Conclusions

The current literature suggests that IVC could potentially have a beneficial effect on levels of depression in patients with cancer; however, more research is needed. The studies completed to date lack an assessment tool designed to capture changes in depression severity. Prospective clinical trials using validated assessment tools and control groups are needed to further study the potential role of this therapy in the treatment of this highly prevalent and disabling condition.

List of Abbreviations Used

IVC: Intravenous vitamin C
QoL: Quality of Life
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core-30
EORTC: EORTC QLQ-C30
PHQ-9: Patient Health Questionnaire-9
HPA: hypothalamic-pituitary-adrenal

Conflicts of Interest

The authors declare that they have no competing interests.

Ethics Approval and/or Participant Consent

No research ethics board review was required for the purpose of a systematic literature review.

Authors' Contributions

JAK: Made substantial contributions to the background research and the literature review process, assessed for inclusion and exclusion criteria, drafted the manuscript, and gave final approval of the version to be published.
ESE: Made substantial contributions to the background research, analyzed, and synthesized the results of the included studies, drafted the manuscript, and gave final approval of the version to be published.

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