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Systematic Review / Meta-analysis

A scoping review of the role of ascorbic acid in modifying fluid requirements in the resuscitation phase in burn patients

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ABSTRACT

Background: Accurate fluid resuscitation in burn patients is the main therapy in improving clinical outcomes. The standard target is to provide adequate end-organ perfusion, taking into consideration the possible risks of fluid creep and over-resuscitation. Anti-oxidant therapies, especially vitamin C, have been evaluated as an adjuvant therapy in resuscitating burn patients in the acute phase.

Methods: A scoping search in PubMed and Google Scholar was done using the search terms "ascorbic acid" "burn patients", "vitamin C", "burn", and "fluid requirements". They were either searched individually or in combination. All relevant articles, of any study design (published till mid-October 2021), were included and narratively discussed in this paper.

Results: Ten articles were reviewed in this paper. Through these articles, we provided in detail the beneficial effects of vitamin C on burn patients in reducing fluid requirements in the resuscitation phase. Additionally, we summarized the pathophysiology of vitamin C in this entity, shedding light on the potential adverse effects and the importance of conducting similar clinical trials.

Conclusion: We cannot deny the beneficial effects of vitamin C on burn patients. Therefore, each burn center should conduct clinical trials until reaching, at the end, an evidence-based guideline providing a clear protocol in terms of its administration and dosage, aiming to minimize possible adverse effects.

1. Introduction

Accurate fluid resuscitation in burn patients is the cornerstone in improving clinical outcomes. The golden goal is to provide adequate end-organ perfusion, taking into consideration the possible risks of fluid creep and over-resuscitation; which in turn may lead to several morbidities like pulmonary and cerebral oedema besides compartment syndromes [1,2]. Postburn increased capillary permeability is mainly caused by the excess production of numerous inflammatory mediators besides the resultant redundant reactive oxygen species (ROS) which have a significant role in this entity due to the ROS-induced endothelial damage to lipids and proteins of cell membranes [1,2].

Anti-oxidant therapies have been evaluated as ROS scavengers in reducing this increased permeability. Vitamin C and E, selenium, and glutathione are the prominent studied antioxidants [1,2]. Numerous published papers have highlighted the positive roles of vitamin C in burn patients in reducing fluid requirements in the resuscitation phase. The primary purpose of this review is to show the beneficial effects of vitamin C on burn patients in reducing fluid requirements, taking into consideration other possible discussed benefits and related adverse effects, as a secondary purpose of this review.

2. Methods

2.1. Literature search

A scoping search in PubMed and Google Scholar was performed using the search terms: "ascorbic acid" "burn patients", "vitamin C", "burn", and "fluid requirements". They were either searched individually or in combination. All relevant articles, of any study design (published till mid-October 2021), were included and narratively discussed in this review.

2.2. Scoops and criteria

The primary objective of this review is to show the beneficial effects of vitamin C on burn patients in reducing fluid requirements in the resuscitation phase, taking into consideration other possible discussed

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benefits and related adverse effects, as a secondary purpose of this review. We also aimed to review the evolvement of the principals of decision-making regarding the possibility of inserting the recommendation of high-dose vitamin C infusion in the acute phase of resuscitation in the practical guidelines for burn patient management.

The inclusion criteria include: any study design, English language, paper with an object of discussing the role of vitamin C in modifying fluid requirements in the acute phase of resuscitation in burn patients, and studies on only human subjects. All the included papers were tabulated and discussed narratively.

3. Results

In this review, we followed the checklist of the "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews" [3]. The selection process is explained by the PRISMA flow diagram (see

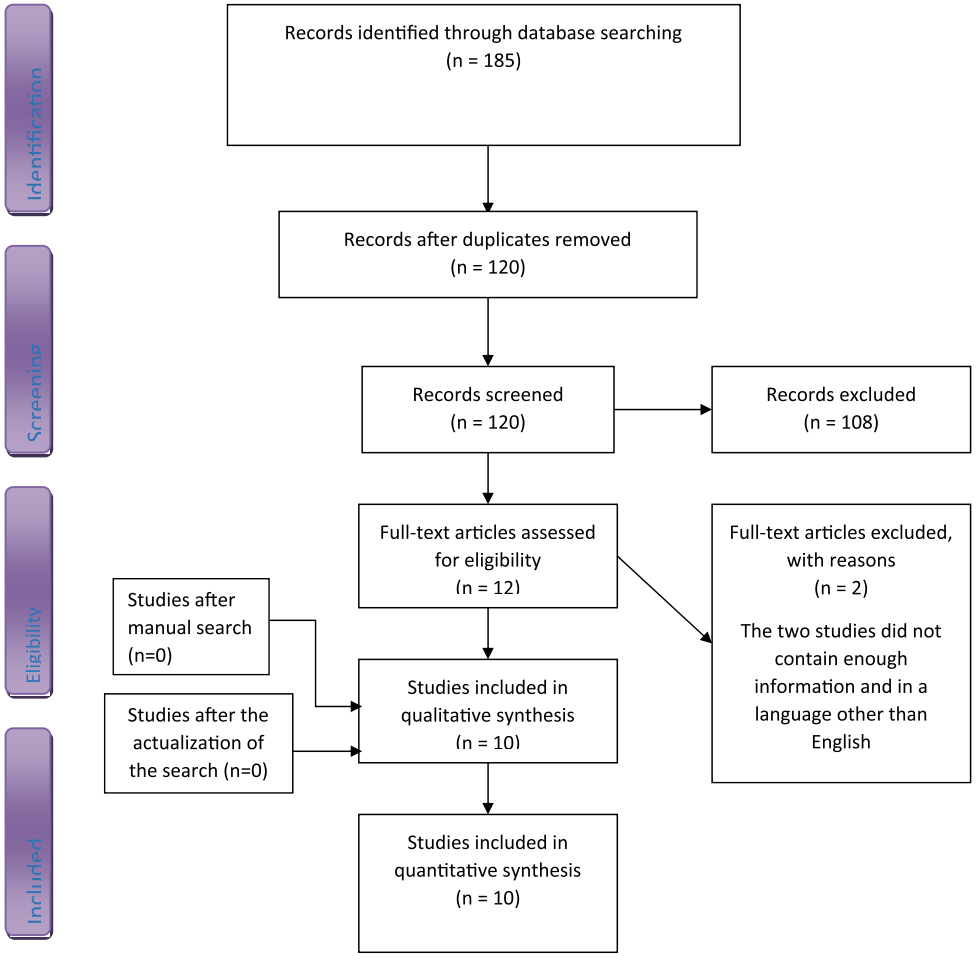

Fig. 1. PRISMA 2020 flow diagram explains the selection process.

Fig. 1). The medical literature search identified 185 articles. According to our inclusion criteria, of them, 10 articles and reports were eligible for inclusion in this scoping review. The summary of the included articles is shown in Table 1.

4. Discussion

4.1. Pathophysiology and interpretation of results

Vitamin C has been studied more than other anti-oxidants in post-burn injuries, because of its various mechanisms in reducing both fluid requirements and wound oedema. Mainly, its mechanisms include regeneration of vitamin E, ROS scavenging, decreasing of lipid peroxidation, and inhibition of collagen denaturation, and therefore, adding intravenous vitamin C as an adjuvant therapy in resuscitating burn patients in the acute phase has been seriously taken into consideration [1,2]. Pre-clinical studies applied on animals - especially on guinea pigs-have reported the clinical advantages of high-dose vitamin C infusion in decreasing total intravenous fluid requirements in thermal injuries. Most of those studies cited a dose of (14.2 mg/kg/h) to achieve this utility [1,2]. Consequently, clinical studies on humans have begun. To the best of our knowledge, only few studies have evaluated the role of vitamin C as an adjunct in burn resuscitation [1,2].

First, Tanaka et al., 2000, in Japan have revealed in their randomized clinical trial (RCT) on burn patients ((with >30% total body surface area (TBSA) burns)) a significant reduction in the vitamin C group fluid requirements in the first 24 h for about 45% ($p < 0.004$) with a 66 mg/kg/h dose of vitamin C besides decreasing in lipid peroxidation and improvement in respiratory function estimated by improvement in partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) ratios, with fewer ventilator days ($p = 0.03$). Furthermore, fasciotomies in vitamin C group have been performed less, too. This result, concerning the fluid requirement, goes with what Tanaka and his colleagues reported in 1991 in their clinical experimental model on guinea pigs. On the other hand, there was no significant difference in mortality rate, and possible side effects of this high dose of vitamin C have not been studied [1,4].

Later, in 2011, in USA, Kahn et al. showed in their retrospective chart review that vitamin C infusion (66 mg/kg/h) in burn patients (>20% TBSA) may reduce the overall resuscitation fluids in the first 24 h for about 25% ($p < 0.05$); in addition, vitamin C group urine output increased causing a reduction in the net balance of fluid ($p < 0.05$), besides no increased risk of renal failure has been reported. On the other side, no improvement in neither respiratory function nor mortality rate was observed [1,2,5].

After that, Pakraftar et al., 2011, in USA also demonstrated in their retrospective chart review that fluid requirements were less in the vitamin C–treated patients with a dose of 66 mg/kg/h in burn patients (>25% TBSA) [5]. Next, Tanwar et al., 2018, in India showed in their RCT that when a high-dose vitamin C (66 mg/kg/h) is administered as an adjuvant therapy in resuscitating burn patients in the first 24 h, this reduces fluid requirement in the first 24 h ($P < 0.001$), increases urine output ($p = 0.006$), decreases fluid retention in body ($p = 0.046$), and finally, lowers the malondialdehyde levels presenting the antioxidant effect of vitamin C in burn patients (>35% TBSA) [6].

Finally, Nakajima et al. conducted a nationwide cohort study in 2019 in Japan to estimate the effect of high-dose vitamin C therapy on severe burn patients. They found that vitamin C therapy was associated with a reduced mortality rate when used under a minimum threshold of 10 grams (g) within the first 2 days of admission ($p = 0.006$). On the contrary, mortality rate has not shown a significant difference when applying a threshold of 24 g ($p = 0.068$). Concerning fluid requirements, their study showed contrariwise a larger (under the 10 g minimum threshold of vitamin C) or similar (under the 24 g minimum threshold) total fluid volume within 1, 3, and 7 days of admission [8].

Table 1
Shows a summary of the articles included in this scoping review.

Study ID	Place or professional society	Study design or article type	Primary objective "fluid requirements"	Other documented related findings
Tanaka et al., 2000 (4)	Japan	A randomized clinical trial	- A significant reduction in the vitamin C group fluid requirements in the first 24 h for about 45% ($p < 0.004$) with a 66 mg/kg/h dose of vitamin C on burn patients ((with >30% total body surface area (TBSA) burns))	- Decreasing in lipid peroxidation and improvement in respiratory function estimated by improvement in partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) ratios, with fewer ventilator days ($p = 0.03$). - Fasciotomies in vitamin C group have been performed less. - There was no significant difference in mortality rate
Kahn et al., 2011 [5]	USA	A retrospective review	Vitamin C infusion (66 mg/kg/h) in burn patients (>20% TBSA) may reduce the overall resuscitation fluids in the first 24 h for about 25% ($p < 0.05$)	- No increased risk of renal failure has been reported. - No improvement in neither respiratory function nor mortality rate was observed
Pakraftar et al., 2011 [6]	USA	A retrospective review	-Fluid requirements were less in the vitamin C–treated patients with a dose of 66 mg/kg/h in burn patients (>25% TBSA)	
Tanwar et al., 2018 [7]	India	A randomized clinical trial	- They showed in their RCT that when a high-dose vitamin C (66 mg/kg/h) is administered as an adjuvant therapy in resuscitating burn patients in the first 24 h, this reduces fluid requirement in the first 24 h ($P < 0.001$) on burn patients with (>35% TBSA)	This high dose of vitamin c: - increases urine output ($p = 0.006$). - decreases fluid retention in body ($p = 0.046$). - lowers the malondialdehyde levels presenting the antioxidant effect of vitamin C in burn patients
Nakajima et al., 2019 [8]	Japan	A cohort study	- Their study showed contrariwise a larger (under the 10 g minimum threshold of vitamin C) or similar (under the 24 g minimum threshold) total fluid volume within 1, 3, and 7 days of admission.	- They found that vitamin C therapy was associated with a reduced mortality rate when used under a minimum threshold of 10 g (g) within the first 2 days of admission ($p = 0.006$). - On the contrary, mortality rate has not shown a significant difference when applying a threshold of 24 g ($p = 0.068$).
Jeschke et al., 2020 [9]	Canada, USA, and Netherthelands	A narrative review	- Consider high dose of vitamin C in the fluid resuscitation phase (0–48) hours	
Siddiqi et al., 2021 [10]	USA	A narrative review	- Patients who were given vitamin C exhibited a decrease in fluid requirement in 42% of the studies when compared to controls.	- Vitamin *C*- group patients exhibited: a decrease in wound healing time (in 35% of studies), a decreased rate of post-burn infections (in 28% of studies), and a reduction of oedema (in 14% of studies).

4.2. Dosing

Recommended daily intake dose of vitamin C is about 80–100 mg, in addition, daily oral doses of vitamin C of almost 10 g appear to be well-tolerated, and that's because of its high water solubility in addition to its low metabolism [1,2]. The accurate dose of vitamin C in burn resuscitation has not been determined yet. As mentioned before, preclinical studies on animals have cited the dose of 14.2 mg/kg/h to achieve the efficacy in reducing total fluid requirements. No clear justification why mostly all authors had chosen the dose of 66 mg/kg/h in their clinical trials which is equal to a total dose of 110 g of vitamin C in a 70-kg patient in 24 h [1,2].

4.3. Potential adverse effects

However, vitamin C is extremely hydrophilic and is promptly excreted by kidneys, lots of concerns of high-dose vitamin C supplementation have been raised [1,2]. Based on postmortem examinations of a limited number of reported cases, this high dose of vitamin C in burn patients caused a calcium oxalate nephropathy, leading to a clinical acute kidney injury [10]. To date, this adverse effect has been documented in only 6 reports [10], so this adverse effect must be taken into consideration while using this high dose of vitamin C in burn patients.

Additionally, as the excess amounts of vitamin C are excreted by the kidneys, resultant osmotic diuresis, which may worsen the acute kidney injury, has been reported. But monitoring of urine output, hematocrit, hemodynamics, serum osmolality, and urine osmolality would be the golden key to avoid such complication [1,2]. Lastly, there is no accuracy of point-of-care glucose measurement during infusion of high-dose vitamin C, which can be easily solved through using usual laboratory measurements [1,2].

5. Conclusion

Vitamin C is a promising antioxidant candidate that has been evaluated in burn studies. Without any doubt, the current enthusiasm about the high-dose vitamin C infusion is well justified, based on the fact that many clinical trials, to date, have demonstrated the beneficial role of vitamin C after thermal injury in decreasing total resuscitative volumes.

At the same time, we should take care of possible adverse effects due to this high dose of vitamin C. Therefore, each burn center ought to conduct such trials until reaching, at the end, an evidence-based guideline providing a clear protocol in terms of its administration and dosage, aiming to minimize possible adverse effects.

Provenance and peer review

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Consent

Not applicable-no human subjects or research participants' data were utilized or collected.

Author contribution

Amjad Soltany: manuscript preparation in all phases. Maen Al Aissami: revised the final version of the manuscript critically and gave the final approval.

Registration of research studies

Not applicable-no human subjects or research participants' data were utilized or collected.

Guarantor

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