Official title of the study:

Effects of vitamin C administration on extravascular lung water in patients with severe features of preeclampsia: a randomized, placebo-controlled trial

NCT ID: not yet assigned

Date: 02/20/2018

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RATIONALE

Risk of fluid over-resuscitation is high in preeclampsia due to endothelial dysfunction and resulting increased vascular permeability (1). The Confidential Enquiry into Maternal Deaths in the UK reported six maternal deaths between 1994 and 1996 due to adult respiratory distress syndrome (ARDS) that appeared to be related to poor fluid management in women with preeclampsia (2). On the basis of these reported deaths, recommendations on limiting intravenous fluids to not more than to 80 ml/hour (or 1 ml/kg/h) have been made (3). Nevertheless, preeclampsia remains the leading cause of pulmonary edema in the peripartum period (4). Moreover, in some preeclamptic patients higher rates of intravenous fluid administration may be necessary to adequately correct tissue hypoperfusion.

Zieleskiewicz et al. were the first to demonstrate that lung ultrasound (LUS) can be used to objectively evaluate increased extravascular lung water (EVLW) in patients with preeclampsia (5). Ambrozic et al. recently confirmed these results and showed that the amount of EVLW assessed by LUS is increased in preeclamptic patients compared to healthy controls and that it decreases rapidly in the first four days following delivery (6).

It has been reported that administration of high-dose ascorbic acid (vitamin C) reduces vascular permeability in animals (7-9). In 2000, Tanaka et al. reported an RCT involving 37 patients with major burns (>30% body surface area) randomized regarding whether or not to receive an infusion of IV vitamin C, 66 mg/kg/h for the first 24 hours of hospitalization. Patients in the vitamin C group required less fluid resuscitation, had higher urine output, and developed less wound edema. This translated into improved oxygenation and less time on mechanical ventilation among the vitamin C group (average of 12 vs. 21 days of ventilation, p=0.03) (10). In 2002, Nathens et al. randomized patients shortly after admission to a surgical ICU to no therapy vs. a combination of enteral vitamin E plus IV vitamin C 1000 mg/8h until ICU discharge. The primary endpoint was a composite of pneumonia or ARDS. Although there were trends towards fewer pulmonary complications among patients treated with antioxidants, these did not reach statistical significance (the study was underpowered due to low rates of respiratory complications). However, patients treated with vitamins E and C

fared better on a variety of secondary endpoints including less time on the ventilator and less multiorgan failure (11).

In women with established preeclampsia, there is evidence of oxidative stress and decreased concentrations of vitamin C (12). An initial RCT on prophylactic supplementation with oral antioxidants, including 1g vitamin C daily, showed a significant reduction in preeclampsia (8 percent vs. 17 percent) in high-risk pregnancies (13). Subsequent large RCTs have, however, reported no significant reduction in the risks of preeclampsia, intrauterine growth restriction, or the risk of death or other serious outcomes in infants associated with oral vitamin C supplementation (14,15).There are no studies to date on use of higher dose IV vitamin C administration for reduction of capillary leak and consequently EVLW in patients with severe forms of preeclampsia. Given the safety (see below) and low costs of vitamin C this could be a promising approach to increase fluid tolerance in these patients. If vitamin C reduces vascular permeability in preeclampsia patients to the same degree that it seems to reduce vascular permeability in other conditions, such as burns, it could reduce the risk of pulmonary complications associated with this disease. At the same time, vitamin C therapy could allow safe additional fluid administration in patients with preeclampsia who are fluid responsive and in whom further increases in preload would be beneficial for preventing end-organ damage such as pre-renal acute kidney injury.

Safety of vitamin C

Safety of vitamin C has been well established even at high doses. For example, none of the above studies reported any adverse event, despite the use of very high doses by Tanaka et al. (1.6 grams/kg over 24 hours) (10). One potential concern regarding vitamin C is that it may be metabolized into oxalic acid, leading to calcium oxalate nephropathy. This doesn't seem to be a significant problem for several reasons:

- Oxalate formation is a dose-dependent toxicity. This has rarely been reported from short courses of IV vitamin C, but only at much higher doses (>40 grams/day) (16).
- In 2014, Fowler et al. published a phase I safety trial of vitamin C in patients with severe sepsis. Their prospective RCT involved patients with severe sepsis in a medical ICU. 24 patients were randomized to receive placebo, low-dose vitamin C (12.5 mg/kg IV/6hr), or high-dose vitamin C (50 mg/kg IV/6hr). The primary endpoint was safety and tolerability, with no adverse events noted (17).

- Recently Marik et al. published a before-after study investigating the impact of treating sepsis with a combination of thiamine 200 mg IV/12hr, Vitamin C 1.5 g/6hr, and hydrocortisone 50 mg IV/6hr. Mortality was substantially reduced in patients receiving vitamin C (p<0.001). Moreover, vitamin C use correlated with *improved* renal outcomes (the rate of dialysis was reduced from 33% to 10%, p=0.02) (18).

Another concern which has been raised is that vitamin C at extremely high doses may have a pro-oxidant effect. This was shown not to occur even at a dose of 7.5 grams IV daily (19).

OBJECTIVE

The objective of the study is to determine whether administration of vitamin C (1.5g/6 hours) in the first three days post-partum reduces the amount of EVLW assessed by LUS in patients with preeclampsia with severe features.

INCLUSION CRITERIA

Consecutively admitted patients with singleton pregnancies complicated by preeclampsia with severe features will be included in the study at hospital admission. Severe features of preeclampsia will be defined using the American College of Obstetricians and Gynecologist Task Force on Hypertension in Pregnancy recommendations (table) (20).

Inclusion criteria: Singleton pregnancy with severe featutes of preeclampsia (any of the following)

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than $100x10^9$/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration greater 97 µmol/L or a doubling of the serum creatinine concentration in the absence of other renal disease)

- Pulmonary edema
- New-onset cerebral or visual disturbances

STUDY PROTOCOL

All patients will be managed in a high dependency setting. Fluid intake and urine output will be assessed hourly. Intravenous fluids will be limited to 80 ml/h, and neither additional fluids nor diuretics will be routinely administered.

After written informed consent, patients will be randomized into two groups. They will receive either 1,5g of IV vitamin C in 100 ml 0.9% NaCl within 30 min of delivery and then every 6 hours for the first 72 hours post-partum or placebo (100 ml of IV 0.9% NaCl within 30 min of delivery and then every 6 hours for the first 72 hours post-partum) (Figure).

Randomization will be performed in a 1:1 ratio using a computer generated randomization sequence. The randomization codes will be kept at the pharmacy department as will be the preparations (vitamin C and normal saline). Physicians and patients will be blinded to the type of medication administered by nurses who will prepare and administer the study medications.

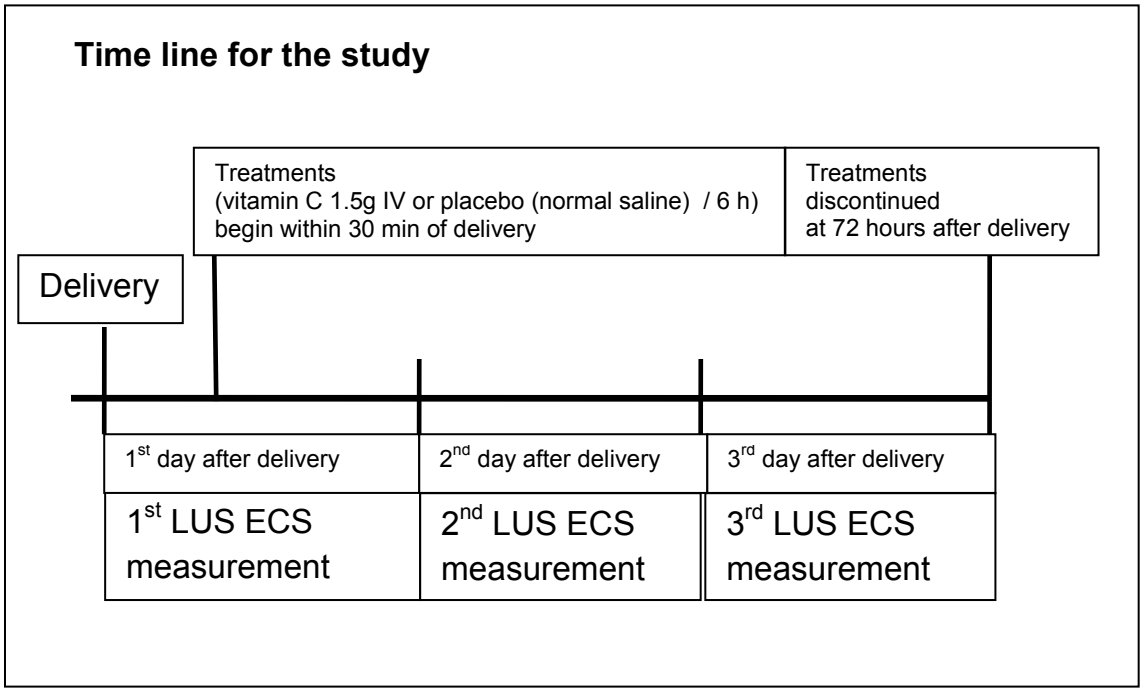

Figure: Time line of the study; *LUS lung ultrasound; ECS Echo Comet Score*

STUDY OUTCOME

The primary outcome studied will be the Echo Comet Score (ECS) at days 1, 2, and 3 following delivery in the vitamin C vs. placebo group. Mann Whitney U-test will be used for comparing ECS between the two study groups (vitamin C vs. placebo)

Lung ultrasound assessment will be performed once daily in the first three days following delivery. The amount of EVLW will be determined by the ECS obtained by summing the number of B-lines or "comet tails" found on each of the 28 chest wall areas. In addition to the 28 region technique, the ECS using the more clinically applicable 8 anterior region technique will also be documented.

SAMPLE SIZE CALCULATIONS

Sample size was calculated using data from Tanaka et al., who showed a reduction in fluid volume requirements in burn patients (a marker of vascular permeability) of 46% (5.5 ml/kg vs. 3.0 ml/kg indexed by burn size) associated with vitamin C treatment (10). We have recently found an average ECS on the first day following delivery of 13 (with a standard deviation of ± 7) in patients with severe features of preeclampsia not treated with vitamin C (6). To discern a decrease of 46% in ECS between the study (vitamin C) and placebo groups we would require a minimum sample size of 17 patients per group, which was calculated using a desired power of 0.80 and an alpha of 0.05.

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