Effect of on-line hemodiafiltration on serum tumor necrosis factor in pediatric hemodialysis patients

Thesis

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By

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Abstract

Background: Hemodiafiltration (HDF) is a form of renal replacement therapy. Tumor necrosis factor (TNF) is proinflammatory cytokine and has been reported to be elevated in adults with ESRD on hemodialysis.

Objective: To compare TNF levels and dialytic change between conventional hemodialysis and on-line hemodiafiltration.

Methods The study included 2 groups of pediatric patients (<15 years of age) with ESRD; group I (n=16) treated with on-line HDF and group II (n=20) with conventional low-flux hemodialysis. Plasma TNF was measured for all patients at the beginning and termination of a dialysis session.

Results: TNF levels in patients treated with online HDF (106.2 +/- 57.5 pg/mL) were lower than in those on conventional HD (180.5 +/- 71.7 pg/mL); p=0.002.

Both groups had significantly higher levels than controls. Post-dialysis values were 82.1 +/- 36.1 pg/mL and 179.1 +/- 83.5 for HDF and HD respectively, both reflecting insignificant reductions (p=0.17 & 0.98).

Conclusion: In children with ESRD, online HDF is associated with lower plasma concentrations of proinflammatory cytokines (as TNF) than conventional HD.

Key words: cytokines–ESRD –hemodialysis-online HDF.

Contents

Abbreviation

- AAMI: Advancement of Medical Instrumentation.
- ACE: Angiotensin-converting enzyme.
- AFB: acetate-free biofiltration.
- APRIL: proliferation-inducing ligand.
- AVF: Arteriovenous fistula.
- AVG: Arteriovenous graft.
- BAFF-R: B-cell activating factor family receptor.
- BCMA: -cell maturation antigen.
- BUN: blood urea nitrogen.
- Ca P: calcium phosphorous product.
- Ca: calcium.
- CFU: colony forming units.
- CKD: Chronic kidney disease.
- CRDs: cysteine-rich domains.
- CRH: corticotropin releasing hormone.
- CRP: C-reactive protein.
- $C_{UF:}$ ultrafiltration coefficient.
- DBP: diastolic blood pressure.
- DOPPS: Dialysis Outcomes and Practice Patterns Study.
- ECD: extracellular domain.
- eGFR: estimated glomerular filtration rate.
- ESA: erythropoiesis stimulating agents.

- ESRD: End-stage renal disease.
- ELISA: enzyme linked immunosorbent assay.
- EU: Endotoxin Units.
- GFR: Glomerular filtration rate.
- HB: hemoglobin.
- HDF: Hemodiafiltration.
- HF: Hemofiltration.
- ICD: intracellular domain.
- IRS-1: insulin receptor substrate-1.
- K/DOQI: Kidney Disease Outcomes Quality Initiative.
- *Kt*/*V:* dialyzer urea clearance (*K*) per unit time (*t*) of the dialysis session divided by urea volume (*V*) of distribution.
- LAK : lymphocyte-activated killer.
- LT: lymphotoxin (LTα, LTβ).
- LVMI: left ventricular mass index.
- NK: natural killer.
- PDUR: postdialytic urea rebound.
- PGE2: prostaglandin E2.
- PKC: protein kinase C.
- PLT: platelets.
- PO4: phosphorous.
- PTFE: polytetrafluoroethylene.
- QOL: quality of life.
- RDA: recommended daily amounts.
- SBP: systolic blood pressure.
- SIRS: Systemic Inflammatory Response Syndrome.

- sTNFR: soluble form of TNF receptors.
- TACI: transmembrane activator and calcium modulator and cyclophilin ligand interactor.
- TIBC: total iron binding capacity.
- TLC: Total leucocytic count.
- TMD: transmembrane domain.
- TMP: transmembrane pressure.
- TNF: Tumor necrosis factor.
- TNFR: tumor necrosis factor receptor.
- TNFR1: TNF-receptor type 1.
- TNFR2: TNF-receptor type 2.
- TNFRSF: Tumor necrosis factor receptor superfamily.
- TSAT: transferrin saturation.
- UF: ultrafiltration
- UKM: Urea kinetic modeling
- USRDS: The United States Renal Data System
- VSMCs: vascular smooth muscle cells
- VUR: Vesicoureteric reflux

List of Tables

List of figures

Introduction

Chronic kidney disease (CKD) is an increasingly common worldwide public health problem (***Choi et al., 2009***). Chronic hemodialysis is one of the main therapeutic options for end-stage renal disease (ESRD) ***(van der Heijden et al., 2004).***

Blood contact with the dialysis membrane has been documented as a major cause of cytokine activation and release. Although haemodialysis-related acute manifestations associated with cytokine release, such as fever and hypotension, are now infrequent; a variety of consequences of chronic low-grade inflammatory state have been recognized or proposed. These include malnutrition, atherosclerosis, cardiovascular disease, erythropoietin-resistant anemia and even a higher mortality rate. Increased cytokine production/ activation may also be responsible for bone remodelling and the aggravation of β2 microglobulin amyloidosis. (***Gill et al., 2007***). By virtue of age, life expectancy and active growth, patients with pediatric-onset ESRD are likely to be more significantly affected by these consequences (***Canaud, 2007***).

Hemodiafiltration (HDF) is a form of renal replacement therapy which combines standard hemodialysis with hemofiltration, a therapy that removes toxins by ultrafiltration of plasma water and uses a replacement fluid to keep the patient in fluid balance (***Whalen, 2008***)**.**

On-line HDF for treatment of ESRD has been introduced into clinical practice in the late 90s. The most important technical and regulatory challenges were the safety and microbiological quality of the substitution/replacement fluid. **(*Guth et al., 2003*)** This has resulted in the concept of "ultrapure dialyzate" where patient

contact with endotoxins and other pyrogenic or bacteria-derived substances should be negligible **(*Ledebo, 1999*).**

Online-HDF may be associated with lower proinflammatory cytokines release than conventional HD.

Tumor necrosis factor (TNF) is the main cytokine associated with endotoxin release, has been implicated in various acute cytokine release syndromes including systemic inflammatory response syndrome (SIRS) and septic shock; and has been reported to be elevated in adults with ESRD on hemodialysis (***Vaslaki et al., 2000***).

Aim of the work

To determine the serum TNF-alpha level in pediatric patients with ESRD undergoing regular hemodialysis;

And to compare TNF levels and dialytic change in TNF between conventional hemodialysis and on-line hemodiafiltration.

End stage renal disease (ESRD)

Definition:

Chronic kidney disease (CKD) is characterized by an irreversible deterioration of renal function that gradually progresses to end-stage renal disease (ESRD). CKD has emerged as a serious public health problem, as the incidence of the CKD in children has steadily increased ***(Levey & Coresh, 2003).***

Kidney Disease Outcomes Quality Initiative (K/DOQI) working group of the National Kidney Foundation of the United States (2003) defined CKD as evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least three months, with or without a decreased glomerular filtration rate (GFR), as defined by a GFR of less than 60 mL/min per 1.73 m^2.

Incidences and prevalence:

CKD is frequent, it increases with age, and affects one person out of 10 in the general population, and only 4 per 100,000 will reach end-stage renal disease (ESRD) ***(Noël & Landais, 2012).***

The incidence and rate of progression to ESRD are equal in both sexes, although obstructive uropathies are more common in males ***(Ardissino et al., 2003***).

Stages of CKD:

Table (1): Stages of CKD:

Stage	Description	GFR	Metabolic consequences
-	At increased risk	Higher than 90 (with risk factors for chronic kidney disease)	-
1	Kidney damage (early) with normal or elevated GFR	90 or higher	-
2	Kidney damage with mildly decreased GFR (early renal insufficiency)	60 to 89	Parathyroid hormone level begins to rise (GFR of 60 to 80).
3	Moderately decreased GFR (moderate kidney failure)	30 to 59	Calcium absorption decreases (GFR below 50). Lipoprotein activity declines. Malnutrition develops. There is onset of left ventricular hypertrophy and/or anemia (erythropoietin deficiency).
4	Severely decreased GFR (pre-end-stage kidney disease)	15 to 29	Triglyceride concentration begins to rise. Hyperphosphatemia or metabolic acidosis develops. There is a tendency toward hyperkalemia.
5	Kidney failure (end-stage kidney disease (uremia)	< 15 (or dialysis)	Azotemia develops

(National Kidney Foundation: K/DOQI, 2003).

Estimation of the GFR gives a rough measure of the number of functioning nephrons. A reduction in GFR implies progression of the underlying disease ***(O'Hare et al., 2006).***

The current ***K/DOQI guidelines (2003)*** state that estimates of GFR is the best overall indices of the level of kidney function. The reference range of GFR in young adults is 120-130 mL/min/1.73 m^2. However, the reference range of eGFR is much lower in early infancy, even when corrected for body surface area, and subsequently increases in relationship to body size for up to 2 years. Hence, the eGFR ranges that are used to define the 5 CKD stages apply only to children aged 2 years and older (***Hellerstein et al., 2004)***.

The eGFR can be estimated from the constant k, plasma creatinine (PCr) (in mg/dL), and body length (L in cm) according to the Schwartz formula, as follows:

GFR = (k X L) / PCr (***Schwartz et al. 1976***).

The value of "k" is different at different ages: k = 0.4 (preterm infants), 0.45 (full-term infants), 0.55 (aged 2-12 y). Therefore, all children with CKD should have an eGFR calculated (***Donadio et al., 2004***).

Cockcroft-Gault another method were used to measure GFR but it is commonly used in adults.

The Creatinine Clearance Rate (CCR)

CCR = [140 - Age (yr)] x weight

S. Creatinine x 72 (*Michels et al., 2010).*