Glucotoxicity in Peritoneal Dialysis –
The Present Solutions

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ABSTRACT
Peritoneal Dialysis is a form of Renal Replacement Therapy (RRT) that is delivered to the patients with End Stage Renal Disease (ESRD) who cannot survive with medical line of management alone. PD was first performed in 1920 by Ganter’s in Germany. The concept of Continuous Ambulatory Peritoneal Dialysis (CAPD) was later developed by Popovich and Moncrief in 1977, subsequently there was an enormous development in the understanding of peritoneal membrane anatomy and physiology, development of newer catheter designs and insertion techniques which lead on to a great success of peritoneal dialysis. Glucose based peritoneal dialysis solution was used widely due to its low cost, easy availability and heat stability. But the impact of glucose on peritoneum and cardiovascular system raised a controversy. Recent evidences have proved its significant peritoneal glucotoxicity resulting in a progressive decline in peritoneal dialysis efficacy. The evolution of amino acid and Icodextrin based peritoneal dialysis solutions have significantly reduced both local and systemic effects of conventionally used glucose based solutions and have significantly improved survival of patients on peritoneal dialysis.

KEY WORDS: PD; Peritoneal Dialysis, ESRD; End Stage Renal Disease, RRT; Renal Replacement Therapy.

Introduction
Peritoneal dialysis is a form of Renal Replacement Therapy (RRT) offered to patients with underlying Chronic Kidney Disease (CKD) who cannot sustain on only medical line of management. Renal transplantation remains the best form of renal replacement therapy offering a good quality of life.

In developing countries due to late presentation, delay in diagnosis of the underlying disease and improper medications leads to an increased burden of Chronic Kidney Disease. Diabetes Mellitus remain the commonest cause of CKD in India. By 2025, India would have 7.3 crore Diabetic and 2 crore CKD patients.

Glucose based dialysis solution was used extensively worldwide due to its easy availability, low cost, heat stability, and no acute toxicity on absorption. Glucose was used as an osmotic agent in the peritoneal dialysis solution. Since it undergoes slow absorption into systemic circulation as well produce local effect over the peritoneum, the efficacy of peritoneal dialysis slowly declined.

The concept of glucotoxicity slowly emerged
by virtue of which the newer glucose free dialysis solutions were invented, thereby reducing the use of traditionally available glucose based solutions.

1. The Proposed Mechanism of Glucotoxicity

The glucose which is used as an osmotic agent undergoes systemic absorption to a significant extent leading to 320 - 640 Kcal/day of extra calories, which in Diabetics worsen the glycemic status (Fig:01). The carbohydrate load favours visceral fat deposition and dyslipidaemia[1] (Fig:02).

The peritoneal membrane dysfunction occurs due to various mechanisms which ultimately results in an accelerated inflammation, fibrosis, angiogenesis, apoptosis and necrosis. (Fig. 3) The most important factors being,

1. Osmotic stress over the peritoneal membrane
2. Increased generation of protein kinase C through Polyol pathway
3. Increased expression of TGF – β1 and VEGF

3. Recent advances

To overcome the local and systemic effect of traditionally available glucose based solutions, over the last few decades many newer solutions were formulated of which the Amino acid based solutions and Icodextrin based solutions gained popularity and are widely available as an effective alternative solutions.

3.1 Amino Acid solutions

The only marketed solution contains 1.1% amino acid. The average molecular weight of the amino acids is 126. Approximately 65% of them are absorbed in to the systemic circulation during 4 – 6h of peritoneal dwell which is enough to replace the approximately 5-8 g/day of protein and 3 g/day of aminoacids that are lost in non-aminoacid PD exchanges.

The increased uptake is probably due to the lower average molecular weight of the amino acids and to amino acid-induced vasodilation.

Drawbacks

1. Amino acid solutions can only be used once daily since a higher number of bags favors acidosis and increases urea.
2. In addition, the methionine load from the dialysate may significantly increase plasma homocysteine levels.

3.2 Icodextrin solutions

Icodextrin is a mixture of high molecular weight, water soluble glucose polymers isolated from corn starch. Molecular weight of icodextrin polymers ranges 1,638-45,000 Daltons. Icodextrin consists of Polysaccharide polymers of D-glucopyranose linked by alpha (1-4) and alpha (1-6) glucoside bonds.

Icodextrin is derived from corn starch which on enzymatic hydrolysis yields malto dextrin, which is further subjected from membrane fractionation to get Icodextrin (Fig. 4).

3.3 Metabolism and Mechanism of action of Icodextrin

Icodextrin on systemic absorption yields oligosaccharides the most abundant being Maltose. Maltose on entering the cell, with the help of intracellular maltase gets converted to Glucose. The conversion of Maltose to Glucose occurs within the cell (Fig. 5).

Icodextrin has an osmolality of 282 – 286 mOsmol/l, which is similar to that of plasma (Iso Osmolar).

Icodextrin induces ultrafiltration through the process of colloid osmosis, in which fluid flow across a semipermeable membrane occurs in the direction of the relative excess of impermeable solutes, rather than along the osmolarity gradient.
4. Therapeutic Benefits of Icodextrin based dialysis solution

4.1 Ultrafiltration with Icodextrin in CAPD

Mistry CD et al in 1997 observed that the net ultrafiltration with Icodextrin was over 500ml with both 8hours and 12hours dwell, which was sustained even at the end of 20th week. The net ultrafiltration with Glucose based solution was lesser than 200ml with 8hours dwell and approximately 100ml with 12hours dwell, which was statistically lesser than that achieved with icodextrin solution. Hence fluid removal was much superior with icodextrin solution[3].

By virtue of good Ultrafiltration, wolfson et al in 2002 observed that the pedal edema was significantly reduced and there was minimal weight gain when compared to those on dextrose solution.

4.2 Impact of Icodextrin on Blood Pressure

Woodrow G et al (Fig. 6) in 2000 observed that both the Systolic Blood Pressure and Diastolic Blood Pressure was well controlled with Icodextrin solution. The SBP which was 142.1 mm Hg with dextrose solution was reduced to 122.9 mm Hg with Icodextrin solution at the end of one month (p < 0.02). Similar observation was found in DBP which was 83.1 mm Hg with dextrose solution and 76.8 mm Hg with Icodextrin solution[4] (p= 0.08).

4.3 Urea and Creatinine Clearance with Icodextrin

Wolfson et al in 2002 showed that in CAPD, 7.5% icodextrin was shown to provide significantly greater small solute clearance during long overnight dwell (8-hour) exchanges compared to 2.5% dextrose (Fig. 7). Superior clearance was noted at both 2- and 4-week evaluations (p <0.05). The improvement in solute clearance was related to greater ultrafiltration and secondary solute drag experienced by icodextrin-treated patients[5],

4.4 Absorption of Carbohydrate with Icodextrin

Mistry C et al in 1997 showed that the carbohydrate absorption with 7.5% Icodextrin was less than 20% as compared with 80% absorption with 3.65% Glucose solution[2]

4.5 Impact of Icodextrin on Insulin secretion and insulin sensitivity

Amici et al in 2001 (Fig. 8) documented that the hyperinsulinemia was significantly lower with icodextrin solution than dextrose solution which was statistically significant (p = 0.02). With icodextrin solution Insulin Sensitivity was much better than with Dextrose solution by HOMA index[6], which was statistically significant (p = 0.04).

An increase in insulin sensitivity favors a good glycemic control in diabetic patients undergoing PD.
4.6 Beneficial effect of icodextrin on Lipid Profile

Gokak et al in 1998 (Fig. 9, 10) demonstrated a significant beneficial effect of icodextrin over dextrose solution in lipid lowering. The Total Cholesterol, LDL Cholesterol and Triglycerides was significantly lowered at the end of 6 months[7] and a similar observation was also made by Bredie et al in 2001.

4.7 Impact on Quality of Life

Wolfson et al in 2002 demonstrated a Better Quality of life among icodextrin group which was 30% as compared to 4% with dextrose group at the end of 52 weeks[5].

Conclusion

- Icodextrin solution is Iso osmolar ; 282 – 286 m Osmol/lit.
- Causes significant reduction in SBP & DBP.
- Achieves good urea/creatinine clearance.
- Reduces hyperinsulinaemia
- Achieves good glycaemic control.
- Has favorable outcome on lipid profile.
- Virtually free from glucotoxicity.
- Sustains ultrafiltration.
- Enhances peritoneal membrane viability and sustains peritoneal dialysis.
- Improves Quality of Life.

References

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