THE EFFECT OF THYROXIN ON THE RENAL FUNCTION OF ASPHYXIATED NEONATES

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Abstract

Thyroxin has been shown to have a beneficial effect on renal function in cases of pending renal failure in animal studies[1-5] . Studies of the use of thyroxin in humans in pending renal failure are scarce. The aim of this study was to assess the effect of oral thyroxin on the renal function of asphyxiated neonates who often have renal impairment.

A randomised controlled trial was conducted. Two groups of 15 term asphyxiated neonates were studied. Thyroxin (50 μg) was given on day 1, 2 and 3 of life for the treatment group and placebo was given for the control group. Renal function was studied on day 1 and day 4 of life

The two groups were not statistically significant different for gestational age, birthweight, severity of asphyxia, pregnancy or delivery complications, fluids administered and drugs used. There was no significant difference in urine output, creatinin clearance and fractional excretion of sodium on day 1 but there was a trend towards a worse renal function on day 1 in the treatment group. The creatinin clearance (Cl_{creat}) was significantly better in the treatment group on day 4 ($p = 0.017$) . Urine output and fractional excretion of sodium on day 4 were better in the treatment group but the differences did not reach statistical significance (p of 0.14 and 0.057 respectively). Statistical analysis on the differences between day 4 and day 1 showed statistical significance only for Cl_{creat} : Cl_{creat} day 4 - Cl_{creat} day 4 was 52.6 (+/- 32.4)for the thyroxin group and 7.3 (+/- 7.8)for the controls ($p= 0.006$).

These data support that thyroxin may have a significant beneficial effect on the renal function in patients with perinatal asphyxia. Thyroxin may be proven useful in future for patients with pending renal failure.

Introduction

Birth asphyxia and kidney function :

Birth asphyxia remains one of the major perinatal problems. Neurological sequelae can be extensive and care of the new-born with asphyxia is primarily directed towards a reduction in the neurological morbidity. However the brain is not the only organ affected by asphyxia. There is often a significant degree of other organ involvement[6] : asphyxiated babies have often multiple organ failure. Organs, other than the brain which are most frequently affected are the kidneys, the gastro intestinal tract (necrotising enterocolitis, transient rise in liver enzymes),the heart and the lungs .

The kidney function has been studied in asphyxiated neonates. Up to over 40 percent of children with perinatal asphyxia have renal impairment[6,7] and almost all of the severe cases. Generally the medulla is the first affected since that part of the kidney has under normal conditions a very limited blood supply. Tubular dysfunction is a consequence of this medullar hypoxia, often presenting as problems with sodium reabsorption.

This kind of tubular dysfunction may also have its effects on the glomerular function resulting in a decrease in glomerular filtration rate (tubulo-glomerular feedback). A good estimate of the glomerular filtration rate can be made by measuring the creatinin clearance.

As a result of this combined glomerular and tubular dysfunction, the urine output is generally low in the first few days of life of asphyxiated children.

Most authors however found that the impairment of renal function is transient in most cases. However azothaemia and disturbances of the fluid balance could aggravate the cerebral damage, which is the main determinant of the final outcome for the patient.

Thyroxin and acute or impending acute renal failure:

Thyroxin has been proven in several animal studies to be effective in treating and reverting pending acute renal failure. There are several papers demonstrating renal protective effects of thyroxin administered to animals with experimentally induced nephrotoxic (gentamicin, uranyl nitrate,...) renal failure[1-4].

Further animal studies[4,5] have been reported, using hypoxic ischaemic models of acute renal failure and each of those studies was capable of demonstrating a positive effect of thyroxin on renal function. Some of them used daily doses for several days, others were using a single dose at the moment of maximal expected renal injury. The renal function was improving in terms of urine output, glomerular filtration rate and urinary fractional sodium reabsorption.

Human studies on the use of thyroxin in acute or pending acute renal failure are quite scarce. Straub has reported a few uncontrolled studies[8,9] on the use of thyroxin in children with renal failure, mentioning resumption of urine output in all studied subjects within two days of thyroxin administration. There is one study[10] reporting a randomised controlled trial of thyroxin therapy in babies with asphyxia. This study

was showing a beneficial effect of thyroxin on glomerular filtration rate and tubular function.

Aim of this study

The aim of this study was to evaluate the effect of thyroxin on the renal function in asphyxiated term neonates.

Materials and methods

A placebo controlled randomised trial was conducted..

Subjects

Two groups of 15 term asphyxiated neonates were studied. The patients were allocated to one group or the other according to a computer generated random table. Asphyxia was defined as having an Apgar score at 5 minutes of less than 7 and a first pH showing a bicarbonate level of less than 18 mmol / litre. Only term babies were included in the study (babies born with gestational age of 38-42 weeks). Babies with congenital abnormalities were excluded from the study.

Methods

The babies in the treatment group received 50 μg of thyroxin (crushed tablet mixed with 1 cc of water for injection through Riles tube) on day 1,2 and 3. The babies in the control group received placebo (glucose) in a similar way.

Complications during pregnancy and delivery were recorded in a standardised way. The clinical condition of the baby and postnatal complications and therapies provided were similarly recorded

Renal function was measured on day 1 and day 4 of life of the babies included in the study. Urine output was expressed in ml/kg/h. Electrolytes (Na, K, Ca, P and Mg),. urea and creatinine were measured in serum and urine. From these values creatinine clearances and fractional excretions were calculated using standardised formulas.

The results were computed and processed with Epi-info and Kruskal Willis H. test was used for statistical analysis.

Results.

Treatment group and control group did not differ significantly for the baseline characteristics of the patients in each of the groups. The number and severity of complications during pregnancy and delivery were similar for both groups. The distribution of the mode of delivery was also comparable for both groups. The gestational age, birth weight, sex, parameters correlating with the severity of asphyxia and the mean BP on day 1 were also comparable

There were also no significant differences in fluid management or drug therapy between the 2 groups.

The results of the renal function tests are given in table 1.

There was no significant difference between the 2 groups for urine output, creatinin clearance and fractional excretion (FE) of sodium on day 1 but there was a trend towards a worse renal function in the treatment group. The creatinin clearance was significantly better in the treatment group on day 4 ($p = 0.017$) . Urine output and fractional excretion of sodium on day 4 were better in the treatment group but the differences did not reach statistical significance (p of 0.14 and 0.057 respectively). When the differences between day 4 and day 1 within the same group were compared for the tested parameters, statistical significance was only found for the creatinin clearance (Cl_{creat}) : Cl_{creat} day 4 - Cl_{creat} day 1 was 52.6 (+/-32.4)for the thyroxin group and 7.3 (+/- 7.8)for the controls ($p= 0.006$)

	thyroxin (n)	SD	placebo (n)	SD	p value
Cl_{creat} day 1/1.73m^2	5.55 ml/min (8)	3.4	12.6 ml/min (10)	10.0	0.13
Cl_{creat} day 4/1.73m^2	58.38 ml/min (8)	34.6	17.4 ml/min (8)	14.09	0.017
Urine output day 1	0.7 ml/kg/h (11)	0.5	1.2 ml/kg/h (13)	0.9	0.14
Urine output day 4	2.4 ml/kg/h (10)	0.3	1.8 ml/kg/h (8)	0.5	0.070
FE_{Na} day 1	2.0 % (9)	2.4	1.9 % (11)	2.06	0.96
FE_{Na} day 4	0.4 % (7)	0.4	1.2 % (8)	0.9	0.056

Table 1 : renal function parameters on day 1 and on day 4

Due to technical problems such as not enough blood in the sample, problems with urine collection or laboratory factors not every patient in this study got full results for every parameter. The number of observations for each parameter within each group is indicated between brackets (n).

Discussion

The results of this study are suggesting that thyroxin is capable of improving renal function in neonates suffering from asphyxia

The urine output is considerably less (but not statistically significant) in the treatment group on day 1 than in the control group. However on day four the urine output is a lot better in the treatment group when compared to the control group, just not reaching significance. Similarly the creatinin clearance is lower in the treatment group than in the control group on day 1 (not significant) but on day four it is significantly better for the treatment group than for the control group.

The fractional excretion of sodium can be seen as a parameter for assessing the tubular functions. There was no difference on day one but on day four there was a clear trend towards a lower fractional excretion of sodium and thus a better tubular function on day four in the treatment group.

The relatively high standard deviations may be due to the relatively small number of observations. Larger studies may prove more convincingly the effect of thyroxin on renal function in asphyxiated subjects.

Asphyxiated neonates can be considered to be in impending acute renal failure and, as in previous studies also demonstrated, thyroxin may prevent the development to overt acute renal failure. The mechanism of action of thyroxin on the kidney has been studied as well. In studies where the renal cortical sodium-potassium ATP-ase was

measured, there was a very marked increase in activity of this enzyme in the renal tubular cells.

This effect of thyroxin on the sodium-potassium ATP-ase, maybe mediated by effects on alkaline and acid phosphatases, is assumed to be responsible for the positive effects of thyroxin on renal function. This increase in sodium-potassium ATP-ase results in an increase in tubular reabsorption of sodium in the proximal tubules, thus restoring the main function of the proximal tubuli[6]. Through the mechanism of tubulo-glomerular feedback the glomerular filtration increases subsequently as well.

Conclusion

This study suggest that thyroxin has a positive effect on renal function in asphyxiated neonates. Other studies have shown similar effects on renal function in patients with impending renal failure.

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