BRIEF COMMUNICATION

MODIFIED UREMIC RAT MODEL – A TOOL FOR UREMIC STUDIES IN RATS

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ABSTRACT

Experimental model of chronic renal failure in rats have been described by many authors and has also been widely used in various studies. Many of these methods used highly sophisticated instruments which was difficult in our settings. The resection model was ideal in our experimental set-up, but this model had the risk of excessive bleeding and hypovolemia. In our study we used a combination of partial resection and ligation of the renal artery to create two models of stable uremia A and Moderate uremia B. Severe uremia. Both these models were compared with a sham operated group which served as controls. Following surgical procedure, the development of uremia was monitored by serial estimation of blood urea and serum creatinine levels that were measured at regular intervals (bi-weekly). From two weeks onwards the animals in the experimental group showed a significant elevation in the serum urea levels and a consistent elevation in the serum creatinine levels upto eight weeks when compared to the animals in the sham operated group. We established a modified method of producing renal failure which can be maintained for a period of six weeks. This model is simple, reproducible and less complicated that can be used for several studies relating to renal failure in the field of research.

KEY WORDS

Resection, Uremia, Chronic renal failure.

INTRODUCTION

Experimental models of renal failure in rats had been described by many authors (1-10). Many authors agreed that the severity of renal failure was graded by resection of renal parenchyma to various extents (2-3). We tried to repeat the same experimental models in our laboratory and found that most of the animals did not survive for more than twenty four hours after the procedure. We have standardized a modified renal failure model that is a form of the above described methods. Animals in our model survived for many weeks. We feel that the rat model standardized in our laboratory may be useful for

various studies which involve chronic renal failure of a long standing.

MATERIALS AND METHODS

Institutional Animal Ethics Committee (IAEC, KMC, Manipal) clearance was obtained before starting the experimental procedure. Wistar rats weighing 200-250g were used (n=9 in each group). All rats were inbred and maintained in normal laboratory conditions such as twelve hour dark and twelve hour light cycle, at 25°C, provided with standard rodent pellet diet and water ad libitum. The animals were anesthetized with pentobarbital (4mg/100g body weight, intraperitoneal). The abdominal area was sterilized and a midline incision was made. Two models of uremia were created i.e.

1. **Moderate Uremia:** The vessels of the right kidney were ligated at the hilar region with sterile sutures. This produced total nephrectomy on right side. The lower pole of the left kidney was decapsulated. A clamp was placed diagonally along the lower pole of the left kidney

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and an area of one third of the total, distal to the clamp was resected (Figure 1A).

2. **Severe Uremia:** Total nephrectomy was done on right side as above. The lower pole of the left kidney was resected in the similar way as described under moderate nephrectomy. After this, the clamp was placed vertically and another one third of the total area was also resected (Figure 1B).

Sham Control: Sham operated animals served as controls. In these animals, a midline incision was done similar to experimental groups after anesthetization, kidneys were handled and placed back in their position, abdomen was sutured and animals were returned to their home cage for recovery.

Following surgical procedure, the development of uremia was monitored by serial estimation of serum urea and serum creatinine levels that were measured at regular intervals (bi-weekly) using an autoanalyser for the confirmation of uremia in both the groups.

The animals are grouped in our model as: Control group- Sham operated animals (SC); Experimental groups- Animals with moderate nephrectomy (MN), Animals with severe nephrectomy (SN)

Results were expressed as mean $\pm$ SEM. Comparison of urea and creatinine levels between the groups were done using one-way ANOVA. When the overall difference in one-way ANOVA was significant, post hoc test was used to find out the significance between and within groups.

RESULTS

Twenty seven animals were used for the study (nine animals in each group), of which all the animals survived for upto 4 months. Survival rate was 100% when proper care was taken during the surgical procedure. However, a few animals were

Figure A. Moderate uremia

Figure B. Severe uremia

Figure 1: Different grades of uremia created on rats

lost during the surgical procedure either due to an overdose of anesthesia or due to hypovolemic shock. Compared to the sham operated group, the animals in the experimental groups were less active. The results of serum urea and serum creatinine are analyzed and presented in Figures 2 and 3.

Figure 2: Serum creatinine levels (micromole/L) at various weeks in sham operated and uremic rats (*p= 0.05 compared with SC group)

Urea levels were not altered in the sham operated group during the entire period of eight weeks (Figure 3). But urea levels showed an increase in moderate nephrectomy group when compared to the sham group and the increase was more marked in the severe nephrectomy group. There was a progressive increase in the serum urea levels in both the groups which was statistically significant when compared with sham operated animals. Within the same group there was no significant progression in the urea levels. Blood creatinine levels were elevated after two weeks in both experimental

Figure 3: Serum Urea levels (mmol/L) at various weeks in sham operated and uremic rats (*p= 0.05, **p=0.01, *** p= 0.001 compared with SC group)

groups when compared to the sham operated animal (Figure 2). In the subsequent weeks the elevations in the creatinine levels were not statistically significant.

DISCUSSION

Many models of nephrectomy were described earlier (1-10). Many of these methods used highly sophisticated instruments which was difficult in our settings due to high cost of these instruments like the electro coagulation(8) and cryosurgery(9). Infarction method which is widely used involves time consuming microsurgery and studies demonstrate the formation of collateral blood vessels bypassing the ligation after infarction (10, 11). So the resection model was ideal for our study. In our experimental setting we found that the animals did not survive with the resection models described by earlier researchers. We found that initially the animals did not survive the sectioning of renal parenchyma due to excessive bleeding. In order to minimize bleeding, we minimized the number of times the renal tissue was resected. With this we could achieved a 100 % survival rate. So we found that a combination of ligation of the renal artery and resection was able to establish uremia with an increased survival rate in our study.

We did not use normal control group since the animals in the sham operated group were healthy and with normal urea and creatinine levels. Although the animals of experimental groups were less active than that of sham group, they appeared healthy even after extreme loss of renal function. This may indicate that the animals can still be active and healthy with very minimal renal tissue atleast during the initial stages of uremia.

Both kidneys were handled through one single midline incision during the resection unlike in other studies where the second kidney was handled after a week. This initially produced a stage of acute renal failure, but over a period of time we noticed that the urea and creatinine levels remained elevated thus establishing a chronic stage of renal failure and uremia.

Progressive resection of renal tissue led to a progressive increase in urea and creatinine levels by which we developed two models of stable uremia namely the moderate and severe group. We found that the increase in urea levels within the same group was not significant which signifies that urea levels

were stabilized after two weeks of renal resection. There is a consistent elevation of serum creatinine in both the experimental groups which was similar to an earlier study (2).

We established a modified method of producing renal failure that can last for more than eight weeks in rats. It is a method which is simple, reproducible and less complicated that can be done in many laboratories. Our models of renal failure may be used for several studies relating to the renal failure in the field of research.

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