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Renal toxicity induced by Nicotine in male Albino rats –an experimental study.

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Abstract

Introduction:

Nicotine, a nitrogen containing chemical is the principal alkaloid contained in tobacco and is believed to be the primary reason for cigarette smoking in many people as they derive satisfaction and pleasant sensation from inhaling nicotine. Nicotine is readily volatile and dibasic in nature. Nicotine, the main alkaloid contained in tobacco is highly addictive potent parasympathetic stimulant.

Methods:

36 male albino rats were divided into three groups Group 1; control group (n=6) fed on normal diet like gram,vegetables and normal tap water. Group 2; study group (n = 24). The group 2 was further divided in to 2A and 2B. Group 2A; (n =12) normal diet and nicotine solutions 5mg/10ml. Group2B; (n =12) normal diet and nicotine solutions 7.5mg/10ml.

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Results and observations:

The cytotoxic effects in kidney appeared in the form of cellular inflammation, tubular casts and tubular dilatation. Thus nicotine negatively influences renal morphology. **Conclusion:** The findings of our study clearly revealed that changes induced in micro-anatomy of kidney in male albino rats were directly related with dosage and duration of nicotine administration and considering the similarity between human kidney and male kidney of albino rats, the therapeutic administration of nicotine in human population should be studied vigorously by more experimental studies.

Keywords: Nicotine, kidney, microscopic changes,cellular inflammation,tubular dilatation.

Introduction

Nicotine, a nitrogen containing chemical is the principal alkaloid contained in tobacco and is believed to be the primary reason for cigarette smoking in many people as they derive satisfaction and pleasant sensation from inhaling nicotine[1]. Nicotine is the main component of tobacco smoke and failure to quit smoking is virtually attributed to its addictive potential, which is similar to that of opium and alcohol[2]. Nicotine is named after tobacco plant nicotiana tobaccum. It was believed to give protection against plague[3]. It is produced in the roots of the plant and accumulates in the leaves and is also found in smaller amounts in other members of the Solanaceae family of flowering plants.[4,5,6] Nicotine is readily volatile and dibasic in nature.[7] Nicotine, the main alkaloid contained in tobacco is highly addictive potent parasympathetic stimulant. An average tobacco rod contains 10–14 mg of nicotine and on average about 1–1.5 mg of nicotine is absorbed systemically during smoking.[8,9] In lesser doses, it acts as stimulant while high amount (50-100mg) can be harmful.[10] However cigarettes not only contain nicotine also contains other toxic, carcinogenic, mutagenic, growth retardative and immunosuppressive

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compounds such as polycyclic aromatic hydrocarbons, cyanide, carbonmonoxide.[11] Nicotine has a relatively high toxicity in comparison to many other alkaloids such as caffeine, which has an LD50 of 127 mg/kg when administered to mice[12]. It constitutes approximately 0.6-3% of the dry weight of tobacco, and is present in the range of 2–7μg/kg in various edible plants.[13] Nicotine is also present in common foods like tomatoes, potatoes, egg plant, cauliflower, green pepper, capsicum and leaves of coco plant. Eggplant is richest in nicotine and contains nicotine in concentration of 100ng/g. The LD50 of nicotine is 50 mg/kg for rats and 3 mg/kg for mice, 30–60 mg (0.5–1.0 mg/kg) can be a lethal dosage for adult humans[14.] At environmental levels of 5 mg/m3, nicotine is immediately dangerous to life and health[15]. Smoking can lead to nephrosclerosis, which is damage to the small arteries that supply the kidneys. Nicotine can also contribute to glomerulonephritis. Both of these conditions can lead to chronic kidney failure, warns a 2004 report in the "Journal of the American Society of Nephrology." Smoking has also been linked to a faster progression of diabetic nephropathy, states the "Journal of the American Medical Association." Even though quitting smoking cannot reverse the damage that has already been done, it may help to slow the progression of this condition.

The rat kidneys are reddish brown in colour and are covered by a thin connective tissue capsule that is adherent to sub capsular connective tissue. The histological section of each kidney shows, outer cortex and inner medulla. The cortex and medulla are arranged into more pyramidal shape called renal pyramids, the apex of each pyramid is called renal papilla. The basic unit of the rat kidney is the nephron, each nephron can be subdivided into number of distinct parts in the cortex and medulla. Nephron consists of Renal Corpuscle (consisting of Glomerulus and Bowman's capsule), the proximal convoluted tubules, loop of Henle (consisting of ascending and descending limbs) and distal convoluted tubule. The cortex consists of Renal corpuscle, proximal convoluted tubules and distal convoluted tubules. The renal corpuscle is a round or irregular shaped structure formed of glomerulus which is

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enveloped by Bowman's capsule. The Bowman's capsule is formed of two thin cellular layers, the outer parietal and inner visceral layer. The parietal layer consists of a flat single layer squamous epithelium thus layer enclosing a narrow space, the urinary space which is continuous with the lumen of proximal convoluted tubule. The visceral layer is surrounded by the glomerular capillaries. The medulla of the kidney is formed from collecting tubules, thick and thin parts of the loop of henle.

Aims and Objectives

The main aim of the study was to study the effect of graded doses of oral nicotine on microanatomy of kidney of male albino rats.

Material and methods

The present randomised Controlled trial (RCT) was conducted in the Post graduate department of Anatomy Government Medical College Srinagar, after obtaining the ethical clearance from the institutions ethical committee. The study was done to see the changes in microanatomy of kidney in male albino rats once graded doses of oral nicotine were administered. 36 male Albino rats weighing on an average 150- 200 grams were taken from the Animal house of Govt. Medical College Srinagar for the present study.

Inclusion Criteria

Apparently healthy albino rats with an average weight of 150 to 200 gm.

Exclusion Criteria

Albino rats weighing less than 150 and more than 200gm and showing less physical activity and weight loss.

Preparation of various study components and diet schedule of all groups of rats for 24 weeks of study:

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Group 1: control group (n= 12) Fed on normal diet like gram, vegetables normal tap water. *Group 2*: study group (n = 24) The group 2 was further divided in to 2A and 2B.Group 2A; (n =12) normal diet and nicotine solutions 5mg/10ml. Group 2B; (n =12) normal diet and nicotine solutions 7.5mg/10ml.

Nicotine solutions with concentration of 5mg/10 ml and 7.5mg/10ml were prepared using tap water and nicotine hydrogen tartrate. All the groups of rats were kept under uniform husbandry conditions in separate iron cages. The animals were sacrificed in four sittings. The first three sittings were done with duration of four weeks between each sitting and the last sitting was done after stopping the drug for four weeks .Three animals were sacrificed from each group in every sitting and lastly the tissues were processed and histological changes were recorded. In each sitting rats were sacrificed after anesthetizing them with chloroform. The limbs of each rat was fixed on boards with pins, a midline abdominal incision was given. Kidneys were identified, dissected out, cleaned and were put in dishes containing formaldehyde. These tissues were processed manually for block making using standard histological techniques. Sections measuring 5-6 micrometers were cut and fixed on glass slides.

Observations and results:

No significant macroscopic changes were seen at any week after the drug administration, while as microscopic changes were observed.

Microscopic changes:

1. Inflammatory Infiltrates

	Inflammatory infiltrate in Kidneys

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	Absent	Mild	Moderate	Severe
Control (1)	12	0	0	0
	100.0%	0.0%	0.0%	0.0%
Low Dose (2A)	3	6	3	0
	25.0%	50.0%	25.0%	0.0%
High Dose (2B)	3	3	3	3
	25.0%	25.0%	25.0%	25.0%

Table 1: Distribution of severity of Inflammatory infiltrate in Kidneys of the three groups.

	No.	Mean Rank	p value
Control (1)	12	9.50	
Low Dose (2A)	12	21.50	
High Dose (2B)	12	24.50	<0.001

Table 2: Comparison of severity of inflammatory infiltrate in Kidneys of the three groups using Kruskal-Wallis Test

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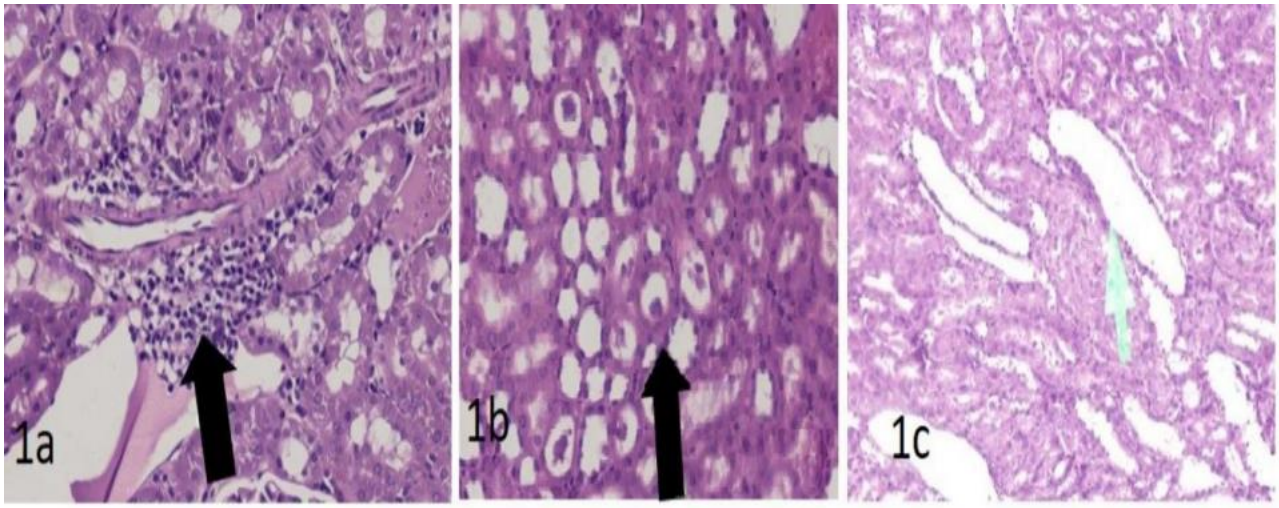

Figure 1: Micro photograph of Kidney after Nicotine administration.

1a: High Dose group at eight weeks showing parenchymal inflammation (40x).

1b: High Dose group at week 8 showing tubular casts at (20x).

1c: High Dose group at week 12 showing tubular dilatation (20x).

2. Tubular Casts

	Tubular casts in Kidneys		
	Absent	**Mild**	**Moderate**
Control (1)	12	0	0
	100.0%	0.0%	0.0%
Low Dose (2A)	3	6	3
	25.0%	50.0%	25.0%
High Dose (2B)	3	6	3
	25.0%	50.0%	25.0%

Table 3: Distribution of severity of Tubular casts in Kidneys of the three groups.

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	No.	Mean Rank	p value
Control (1)	12	9.50	
Low Dose (2A)	12	23.00	
High Dose (2B)	12	23.00	<0.001

Table 4: Comparison of severity of Tubular casts in Kidneys of the three groups using Kruskal-Wallis Test.

3. Tubular Dilatation

	Tubular dilatation in Kidneys	
	Absent	**Mild**
Control (1)	12	0
	100.0%	0.0%
Low Dose (2A)	9	3
	75.0%	25.0%
High Dose (2B)	6	6
	50.0%	50.0%

Table 5: Distribution of severity of Tubular dilatation in Kidneys of the three groups.

	No.	Mean Rank	p value
Control (1)	12	14.00	
Low Dose (2A)	12	18.50	

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High Dose (2B)	12	23.00	0.020

Table 6: Comparison of severity of Tubular dilatation in Kidneys of the three groups using Kruskal-Wallis Test.

Discussion

Nicotine, an organic compound, is the principal alkaloid of tobacco. In its pure form, nicotine is the colourless, odourless liquid with an oily consistency but when exposed to light or air, it acquires a brown colour and gives off a strong odour of tobacco. Nicotine's dependence results in substantial mortality, morbidity, and socioeconomic impacts. The present study was conducted in postgraduate department of Anatomy, Government Medical College Srinagar. After randomization, 36 male albino rats were divided into two groups. 12 rats in Group 1 and 24 rats in Group 2, which were further divided into two groups - Group 2A and Group 2B. Group 1 served as control group while as Group 2 served as study group. The Study Group received graded doses of nicotine. Group 2A and Group 2B received 5mg and 7.5mg of nicotine in 10ml of water respectively. The objective was to study the effects of graded doses of oral nicotine on kidney. In kidney, no apparent macroscopic or microscopic changes were seen in Group 1(control). In case of study groups, no gross changes were seen at any stage of our study however microscopic changes in the form of cellular inflammatory infiltration, tubular dilatation, tubular casts were seen. Cellular inflammatory infiltrate appeared in renal parenchyma at week 8 and was mild, which later became moderate at week 12 in 2A (low dose) group while as in 2B (high dose) group, it appeared at week 8 and was mild which later became severe at week 12. Once drug was stopped, there was partial recovery in both 2A and 2B groups. Tubular casts were mild at week 8 and moderate at week 12 in both 2A and 2B groups. Tubular dilatation appeared at 12th week and was mild in 2A (low dose) group while as in case of 2B (high dose) group, it was mild at 8th week and moderate at 12th week. There was

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complete recovery of tubular dilatation in both 2B (high dose) and 2A (low dose) groups during recovery period once drug was stopped for 4 weeks. There was partial recovery once drug was stopped for 4 weeks in both study groups. These findings were more marked in 2B group as compared to 2A group and were in conformity with Menshawy MM et al (2019) 94 while working on effects of nicotine on kidney of male albino rats. Their results were almost similar to our study, however the changes were more prominent in their study possibly because of route of drug administration. Goksel S et al (2004)72 while working on nicotine induced oxidative damage of rat urinary bladder and kidney found similar result, although of greater intensity possibly because of parentral mode of drug administration.

Conclusion

The present study was undertaken in the post graduate department of Anatomy Government Medical College Srinagar. The objective of this study was to evaluate changes in micro-anatomy of kidney of adult male albino rats treated with oral nicotine. Total of 36 male albino rats were taken and were divided into two groups. Control group containing 12 rats, Study group containing 24 rats. The study group was further divided into two groups, 2B (High dose) group and 2A (Low dose) group containing 12 rats each. 3 rats from each group were sacrificed at 4th, 8th, 12th and 16th week at a regular interval of 4 weeks. The kidneys of rats treated with nicotine were normal on gross examination, however microscopy showed inflammation, tubular casts, tubular degeneration and tubular dilatation. These changes started at 4th week and were progressive with time. These changes were more in high dose group as compared to low dose group and were absent in control group. At week 16, once the drug was stopped for 4 weeks, there were partial or complete recovery of these changes. As already discussed the findings were less in intensity as compared to the other studies possibly because of the dosage, duration and the way of administration of the nicotine.

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Our study revealed a multitude of effects on kidney of adult male albino rats.Nicotine may have similar effects on human kidneys, considering the marked anatomical similarity between human and rat anatomy. Thus the present study conclude that besides shutting doors of all ways of abusing nicotine, one must be extra careful while prescribing nicotine as a drug in modern medicine.

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