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Study on Impact of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on Renal Function in Postpartum Period

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Abstract

A prospective, observational study was conducted in the Department of Obstetrics & Gynaecology of Combined Military Hospital (CMH), Dhaka, Bangladesh, to assess pre-delivery and post-delivery (5 days after administration of NSAID) change in renal function by determining the serum creatinine levels in pregnant women. The study was conducted on 120 purposively selected patients attending for their delivery purpose in the selected hospital from January to June of 2022. Following the delivery, tablet Paracetamol 500 mg thrice a day for 5 days have been prescribed to all the respondents. Diclofenac Sodium 100 mg suppository twice a day up to for 3 days had been prescribed with dosage adjusted as required. Serum creatinine levels were evaluated on two time points: the day before delivery and 5 days after delivery. Compared to the day before delivery, 53.3% of the respondents showed increased level of serum creatinine 5 days after delivery. Acute kidney injury (AKI) was identified in 9.17% patients with a change more than 0.3 mg/dL from the pre-delivery report. The change in the serum creatinine level pre-delivery to post delivery was statistically significant, which was also dependent on the NSAIDs dose with a positive linear association. Though NSAIDs regarded as a safe choice for postpartum pain management, yet apparently healthy mothers showed fluctuations in serum creatinine level in association to dosage of NSAIDs use.

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Introduction

During the postpartum period women often entails a range of discomforts and pains, reported by 75% of the women on average, management of which is an essential component of postnatal care.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are regularly given medications to alleviate these postpartum discomforts. Hence, it's crucial to understand the potential risks associated with postpartum NSAID use, especially concerning kidney health. Pregnancy-related AKI (PR-AKI) occurs in 1.5% of the deliveries.[2]

NSAIDs work by inhibiting enzymes involved in the production of prostaglandins, which are chemical messengers that play a pivotal role in various physiological processes, including the regulation of blood flow to the kidneys.[3] By reducing prostaglandin synthesis, NSAIDs can decrease blood flow to the kidneys, potentially affecting their function.[4] Increasingly, pregnant women are at risk for PR-AKI due to advanced

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maternal age, hypertension, preeclampsia, diabetes, hemorrhage and obesity.[5] However, studies also have reported AKI followed by initiation of NSAID in apparently healthy individuals.[6,7] In AKI attributed by NSAIDs, the clinical manifestations usually are oliguria and an raised levels of serum creatinine, which occur 3-7 days following administration of NSAIDs.[8] There is little research on the consequence of using NSAIDs to treat postpartum pain particularly in relation to renal function in a Bangladeshi cohort. Therefore, the present observed the change in creatinine level following postpartum administration of NSAIDs in an apparently healthy cohort from a tertiary care center in Dhaka, Bangladesh.

Methods

This prospective, observational study was conducted on 120 purposively selected patients attending for their delivery purpose in the Department of Obstetrics & Gynaecology, Combined Military Hospital (CMH), Dhaka, Bangladesh, from January to June of 2022. Normotensive pregnant mothers with no significant comorbidities, having non-complicated singleton pregnancies, who delivered their babies on term, have been included in the study. Pregnant mothers with volume depletion, electrolyte imbalance, or any other significant co-morbidities (oliguria, arterial hypertension, congestive heart failure, pregnancy induced hypertension, liver cirrhosis, chronic kidney disease, diabetes mellitus, gestational diabetes) and patients who were unwilling to participate remained excluded from the study.

Complete clinical evaluation of the patients including history, physical examination, relevant medical history had been checked. Following the delivery (childbirth), Tablet Paracetamol 500 mg thrice a day for 5 days have been prescribed to all the respondents. Diclofenac Sodium 100 mg suppository twice a day up to for 3 days had been prescribed (as required). Serum creatinine level had been evaluated on two time points: the day before delivery and 5 days after delivery.

The demographic information, relevant clinical history and, investigation report, were recorded in a standard data collection sheet. Statistical analysis of the results was done by using IBM-SPSS software version 25.0 (SPSS Inc, Chicago, IL, USA). Comparison between two creatinine level tests was done by paired sample t test. Other statistical Pearson correlation was applied to evaluate association of NSAID dosage and difference in serum creatinine. A probability ‘p’ value of 0.05 or less was considered as significant.

This research was approved by the institutional review committee of the Combined Military Hospital (CMH), Dhaka, Bangladesh.

Results

This study observed that, compared to the day before delivery, on the 5th day after delivery, the serum creatinine level increased in 53.3% of the respondents. Here, in case of 9.17% respondents, the increase was more than 0.3 mg/dL from the pre-delivery estimation. The serum creatinine decreased in 32.5% of the respondents and remained unchanged in 32.5% of the respondents (Table-I). When categorical changes in serum creatinine assessed against different age group, it has been observed that, among the adolescent mothers’ group (aged 19 years or less), distribution of respondents with

elevated and unchanged serum creatinine before and after delivery (5 days after administration of NSAID) was same (42.9%) and respondents with decreased serum creatinine was, 14.3% in this group. In the age group of 20 to 34 years, elevation of serum creatinine was observed in 51.9% respondents compared to 14.8% respondents with no change and 33.3% respondents with decrease in serum creatinine. In the age group of 35 years or more all the respondents showed elevated serum creatinine level. These difference in changes in serum creatinine level was not statistically significant among the different age groups ($p>0.05$) (Fig. 1). When categorical changes in serum creatinine assessed against respondents delivered their babies by NVD or LUCS, elevation of serum creatinine was noted in 46.8% of the NVD group compared to 57.5% of the LUCS group. Serum creatinine remained unchanged in 29.0% of the NVD group compared to 34.2% of the LUCS group. Decreased level of serum creatinine was observed among 23.4% of the NVD group compared to 8.2% of the LUCS group. These difference proportion of change in serum creatinine were not statistically significant ($p>0.05$) (Fig. 2). A chi-squared test showed that status of gravida or urine examination was not found to be associated with different categories of serum creatinine changes ($p>0.05$) (Table-II). However, an ANOVA test showed significant association of serum creatinine level and dose of NSAIDs ($p<0.05$) (Table-III).

Assessment of the linear relationship between dosage of NSAIDs the difference of serum creatinine level before delivery and after delivery (5 days after administration of NSAID) was done by Pearson correlation coefficient. There was a statistically significant positive correlation between the NSAIDs dosage and the difference of serum creatinine levels [$r(df) = 0.270$ (119), $p =0.003$] (Table-IV).

A paired sample t-test showed that the participant's serum creatinine level's mean has increased from pre-delivery (0.773 ± 0.12) to post-delivery (5 days after administration of NSAID) (0.843 ± 0.15) which was statistically significant ($t = 5.858$, $df=119$, $p<0.001$) (Table-V).

The difference of serum creatinine level between pre-delivery and post-delivery period (5 days after administration of NSAID) have been assessed with paired sample t-test in different groups of age, and maternal factors of the respondents. It was observed that, among different age groups, the creatinine level did not differ significantly in the adolescent age group of respondents ($p>0.05$).

However, significant difference was observed in the age groups of 20 to 34 years and 35 years or more ($p<0.05$). This difference of serum creatinine was also significant among different groups according to gravida and mode of delivery ($p<0.05$). On urine examination, respondents with pus cells detected in their urine did not show significant difference in pre- and post-delivery serum creatinine levels ($p>0.05$) (Table-VI).

Multiple linear regression was computed to predict independent predictor of changes in serum creatinine in this sample, and found out that when adjusted for age, delivery mode and gravida status, NSAIDs dose is an independent predictor of change in serum creatinine (Table-VII).

Table-I: Categorical presentation of changes in serum creatinine level between pre-delivery and post-delivery period (5 days after administration of NSAID) (N=120).

Serum Creatinine	Frequency	Percentage
Increased	64	53.3%
AKI (increased ≥0.3 mg/dL)	11	9.17%
Decreased	17	14.2%
No change	39	32.5%

Fig. 1: Changes in serum creatinine level between pre-delivery and post-delivery period (5 days after administration of NSAID) in different age groups (N=120)

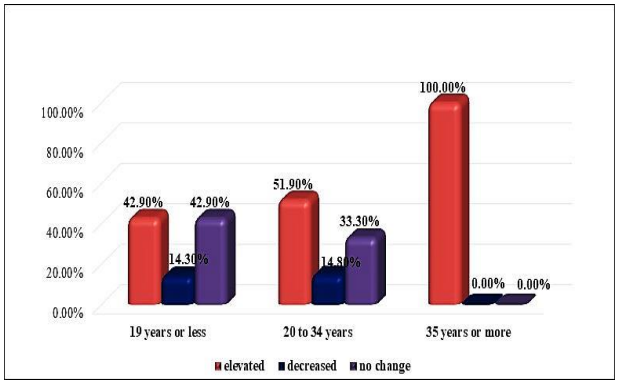

Fig. 2: Changes in serum creatinine level between pre-delivery and post-delivery period (5 days after administration of NSAID) in different groups according to mode of delivery (N=120)

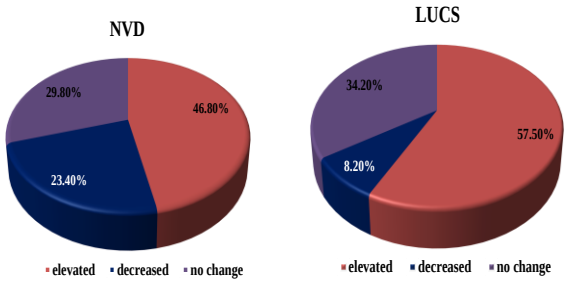

Table-II: Changes in serum creatinine level (categorical presentation) between pre-delivery and post-delivery period (5 days after administration of NSAID) according to gravida and urine examination (N=120).

		Elevated	Decreased	No change	p value
		Frequency (Percentage)	Frequency (Percentage)	Frequency (Percentage)	
Gravida	Primi gravid	15 (45.5%)	14 (42.4%)	4 (12.1%)	0.066
	Multi gravid	49 (56.3%)	25 (28.7%)	13 (14.9%)	
Urine exami-nation	Pus cell	7 (38.9%)	4 (22.4%)	7 (38.9%)	0.356
	Albumin	0 (0.0%)	0 (0.0%)	1 (100.0%)	0.351

Table-III: Changes in serum creatinine level (categorical presentation) between pre-delivery and post-delivery period (5 days after administration of NSAID) according to gravida and urine examination (N=120)

Serum Creatinine	Mean	SD	F value	p value
Elevated	64	3.72		
No Change	39	3.46	4.099	0.019
Decreased	17	2.76		

Table-IV: Pre-delivery and post-delivery (5 days after administration of NSAID) difference in means of serum creatinine level in association with the dosage of NSAIDs (N=120)

Difference in serum creatinine level	r	df	p value
Dosage of NSAIDs	0.270	119	0.003

Table-V: Changes in means of serum creatinine level between pre-delivery and post-delivery period (5 days after administration of NSAID) (N=120)

	Pre-delivery	Post-delivery (5 days after administration of NSAID)	r	t	df	p value
	Mean ± SD	**Mean ± SD**				
Serum creatinine	0.77 ± 0.12	0.84 ± 0.15	0.532	5.858	119	0.000

Table-VI: Pre-delivery and post-delivery (5 days after administration of NSAID) difference in means of serum creatinine level in association with background variables (N=120)

Background variables	Categories	Frequency (Percentage)	r	t	df	p value
Age	19 years or less	7 (5.8%)	0.821	1.000	6	0.356
	20 to 34 years	108 (90.0%)	0.527	5.369	107	0.000
	35 years or more	5 (4.2%)	0.250	3.500	4	0.025
Gravida	Primigravid	33 (27.5%)	0.789	2.775	32	0.009
	Multigravid	87 (72.5%)	0.426	5.197	86	0.000
Mode of delivery	NVD	47 (39.2%)	0.510	2.225	46	0.031
	LUCS	73 (60.8%)	0.539	6.003	72	0.000
Urine examination	Pus cell	18 (15.0%)	0.186	1.207	17	0.244
	Albumin	1 (0.8%)	- -	- -	- -	- -

Table-VII: Multiple linear regression to assess independent predictor of mean changes in serum creatinine level pre-delivery and post-delivery period (5 days after administration of NSAID) (N=120)

Variables				95.0% Confidence Interval for B	
	t	p value	B	Lower Bound	Upper Bound
Gravida	1.205	0.231	0.021	-.014	0.057
Delivery mode	-0.862	0.391	-0.029	-.094	0.037
Age	0.524	0.601	0.021	-.059	0.102
NSAIDs dose	2.726	0.007	0.035	0.010	0.060

Discussion

One of the most often used medications worldwide is an NSAID.[9] In the healthy population, NSAIDs are effective postpartum analgesics with a low rate of adverse consequences.[10] For postoperative pain and perineal discomfort in the postpartum phase, when paracetamol is unable to sufficiently relieve symptoms, NSAID usage is advised.[11] Rectal NSAIDs following an cesarean section and episiotomy are linked to reduced pain in the first 24 hours following birth.[12] In previously published literatures, NSAIDs have been shown to cause a brief, clinically inconsequential reduction in kidney function in those with normal renal function during the early post-operative period.[13,14] Serum creatinine tends to fall in normal pregnancy and comes back to normal after pregnancy.[15] This study observed that, in postpartum healthy respondents, Diclofenac dose dependent increase in serum creatinine in 53.3%

of the respondents, where, 9.17% respondents indicated onset of acute kidney injury with an increase in the serum creatinine more than 0.3 mg/dL from the pre-delivery observation. NSAIDs are showed to create dose-dependent adverse effects on the kidney and found to be an independent risk factor of increased serum creatinine level, which corresponds to the present study findings.[10,16,17] Research has shown that there is a twofold increase in the risk of acute renal failure in the general population during the first month of NSAIDs use.[18] This study observed that, all the respondents aged 35 year or above showed elevation of serum creatinine in the post-delivery period following NSAIDs consumption which supports the finding that advanced maternal age is a risk factor of pregnancy related acute kidney injury following NSAIDs use.[5] Previous studies also observed that, among the patients consuming NSAIDs, 1-5% of patients had significant adverse effects, with acute renal failure developing in 0.5–1.0% of patients taking.[17] This study is limited by its cross-sectional study design which is inherent with its weakness of analytical findings and generalizability. Being a single center study further diminishes its strength.

Conclusion

To conclude, since NSAIDs can be effective in managing postpartum pain and discomfort, their use in vulnerable situation like postpartum period requires careful consideration. Patients not having any significant co-morbidities also mandate routine evaluation of kidney functions when NSAIDs are being administered during post-partum period. It is important to note that while there are concerns about the potential risks of postpartum NSAID use on kidney health, these risks are generally considered to be relatively low when NSAIDs are used as directed and for a short duration. However, the risk is not negligible, and caution is paramount. Healthcare providers must engage in thorough risk-benefit assessments, considering the patient's overall health, the specific circumstances of the pregnancy and childbirth, and alternative pain management options.

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