# Comparison Between Two NSAIDs (Non selective & selective COX-2 Inhibitor) According to their Renal Toxicity on Elderly People

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**االخلاصة:**

**تستعمل مضادات الالتهابات الاستيرويدية كثيراً في كل انحاء العالم لمختلف انواع مشاكل المفاصل والعضلات. وحالها حال كل المركبات الكيميائية فان لها تاثيرات جانبية مثل تاثيرها وسميتها لوظيفة الكلى خاصة اذا استعملت لفترات طويلة من كبار السن والذين يعانون اصلاً من انخفاض وظيفة الكلى لديهم او لديهم مشاكل قلبية او كلوية مرضية. هذه الدراسة تركز على هذه النقطة، وذلك بمقارنة نوعين من هذه المركبات احدهما لا انتقائي باتجاه انزيم (COX) وهو الاندوميثاسين والاخر ذو انتقائية باتجاه انزيم (COX-2) وهو الميلوكسيكام، وحسب تاثيرهم وسميتهم على الكلى وذلك باخذ مقدار تغير قيم (BUN), (S. Cr) و (S. K+) كدلائل على مثل هذه السمية على كبار السن للمقارنة بينهما. وفي اتجاه اخر، نحاول ان نبين هل ان وجود مشاكل قلبية او كلوية عند هؤلاء المرضى تساعد في زيادة هذه السمية او لا.**

**شملت هذه الدراسة 80 مريضاً كبيراً بالسن، بعضهم اصحاء والبعض الآخر يعاني من مشاكل قلبية او كلوية، واختيروا من عيادة خارجية خاصة للمفاصل والرماتيزم حيث اعطوا احد المركبين كدواء اساسي لعلاج المشكلة التي جاءوا من اجلها ولمدة 15 يوماً.**

**ظهر واضحاً من نتائج الدراسة بان كلا المركبين (الانتقائي وغير الانتقائي للـ COX) يسببان نفس التاثيرات الجانبية على وظيفة الكلى لهؤلاء المرضى الكبار بالسن كما ان وجود مشكلة قلبية او كلوية قد يساعدان في زيادة هذه الاعراض او سمية هذه المركبات على وظيفة الكلى وخاصة الامراض مثل ارتفاع ضغط الدم ذو الاسباب الكلوية او نقصان فعالية الكلى المرضي.**

## Abstract :

**The nonsteroidal anti-inflammatory drugs (NSAIDs) are widly used all over the world for different rheumatic musculoskeletal disorders. Like any other chemical compounds, they have different side effects like renal toxicity that becomes very serious when used for long time especially from elderly people whose already have a reduced renal function or those This with renal or cardiac problems that may increase the incidence of such toxicity.**

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**study focusing on this point, by comparing between 2 NSAIDs, a non selective-COX inhibitor (Indomethacin) and selective COX-2 inhibitor (Meloxicam) according to their renal toxicity on elderly patients, depending on changes in values of blood urea nitrogen (BUN), serum creatinine (S. Cr.) & serum potassium (S. $K^+$) concentrations as parameters of such toxicity. In another way we investigate whether the renal or cardiac problems will increase such toxicity of NSAIDs on elderly patients or not.**

**The study involved 80 elderly patients, healthy and with renal or cardiac problems, selected from rheumatologic outpatient clinic and given one of the 2 NSAIDs as adrug of choice for their present complaints for a period of 15 days.**
**It was clearly appeared from results, that both NSAIDs couse similar extent of renal side effects and the presence of renal and/or cardiac problems could increase the susceptibility of such toxicity especially renal impairment & renal hypertension.**

## Introduction:

**All NSAIDs can inhibit the prostaglandin (PG) mediated renal function due to inhibition of kidney PG synthesis [(1)]. This effect increase in patients with PG depending renal problems to oppose the increased vasoconstrictive influence of norepinephrine and angiotensin [(2)], in addition to the activity of PG in increasing glomerular filtration rate (GFR) and blood flow[(3)], Those PG dependent disease states include volume depletion, cirrhosis, congestive heart failure, nephrosis & chronic renal failure [(4)]. The manifestations of NSAIDs associated renal toxicity include hyperkalemia, tubulointerstitial nephritis and acute renal failaure [(5)]. In the past, the COX-1 enzyme isoform was believed to be the important enzyme involved in renal prostaglandin synthesis. However, the COX-2 enzyme was recently noted to have an important role in prostaglandin production during inflammatory process [(6)]. As a result, this isoform was considered to be constitutive and integral to the maintenance of organs (such as kidney & GI tract) integrity [(6), (7)]. Although the effect of selective COX-2 inhibition on renal function was essentially not known, the recent studies suggest a role of this enzyme in the regulation of rennin release [(8),(9)]. A study of isolated human kidney (nephrotomy specimen) showed constitutive expression of COX-2 in location, it is localized in endothelial and smooth muscle cells of arteries, arteriols, veins & vasa recta of the medulla [(9)].**
**The ubnormal laboratory findings may include increasing in BUN, increasing S. Cr, protineurea, heamaturea & albuminurea. In case of Indomethacin, serum potassium concentration increase by 0.5 mEq/L within 12-36 hours after the administration in normal renal function but in renal impairment, S.$K^+$ increase by more than 1 mEq/L and reach more than 5 mEq/L and this mainly happen in an elderly, renal dysfunction & hypertensive patient (10).**

## Method and patients:

**80 elderly male & female patients aged between 57 & 73 years, were involved in this study & selected from rheumatologic out patient clinic. They were suffering from deferent rheumatic & musculoskeletal disorders in which the NSAIDs are the 1st choice treatment prescribed by the physician.**
**The patients were divided into 4groups, 20 healthy patients taking indomethacine capsules 25 mg 3 times daily in group-1, another 20 patients with renal and/or cardiac**

**problems taking also indomethacine capsules 25 mg 3 times daily in group-2, group-3 involved 20 healthy patients taking meloxicam 7.5mg once daily & finally group –4 involved 20 patients with renal and/or cardiac problems taking meloxicam 7.5mg once daily. The treatment period is 15 days.**

**Age, sex, systolic & diastolic blood pressure, s.cr., BUN & s.k+ for all the patients were reported at baseline using Jaff's method , enzymatic method, and the Flame Emission Spectrophotemetry method( FES )for estimation of those parameters respectively , taking into account the normal value for each parameter according to the method used as follow ( male s.cr. 0.9-1.3 mg/dl , female s.cr. 0.6-1.1 mg/dl ),( over 60 year BUN 6-20 mg/dl ) and finally ( s.k 3.5-501 mmol/L) .**

**Treatment discontinuation was required for all patients with a history of peptic ulcer, known sensitivity to NSAIDs and used NSAIDs within 2 weeks prior to start of this treatment. In addition, treatment discontinued if s.cr, BUN & s.k+ increased above prespecified safety values or even in any abnormal physical examination.**

**All patients informed and educated to come to the clinic for checking and for taking blood sample to measure BUN,s.cr & sk+ after 4 days, 8 days , 12 days & after 15 days . 10 mls of venous blood was taken before starting the treatment (baseline) and at the design days for measuring the laboratory parameters (BUN,S.cr & s.k+) in which abnormal changes of those parameters used as a detector for renal toxicity for the compared 2 NSAIDs , indomethacine & meloxicam.**

**All results are expressed as mean ± SD, T-test for unpaired data was employed & P-value of less than 0.05 was considered significant**.

## Results:

**All treatment were well tolerated & the patients completed the treatment period with the exception of 2 patients in group-2 in which the measurements of laboratory parameters after 12 days of treatment show a high increase that the physician preferred to discontinue the treatment, also 3 patients from gronp-4 were excluded due to the same reason in which high values of the laboratory parameters after the same period (12 days) necessate the discontinuation of treatment.**

**Figure-1 shows that there is significant differences ($p<0.05$) in BUN concentration after treatment with indomethacin in both grup-1 & group-2 patients when compared with control (baseline) of the same group.**

**In figure-2, Also there is a significant difference ($p<0.05$) in BUN concentration with meloxicam in both group-3 & group-4.**

**There is a significant difference in S. Cr. Concentration after treatment with indonethacin in both group-1 & group-2 in comparison with the contral of each group as shown in figure-3.**

**The same result can be shown in figure-4 in which there is a significant difference ($p<0.05$) in S. Cr. Concentration after treatment with meloxicam in both group-3 & group-4 patients in comparison with their control.**

**Figure-5 & figure-6 show the same significant difference ($p<0.05$) in S. K+ concentration after treatment with indomethacine & meloxicam respectively in comparison with the control of each group.**

**The figures from 7 to 12 show the comparison between the 2 compounds according to their extent of changes on the laboratory parameters. So, in figure-7, there is no significant difference ($p>0.05$) in BUN level between the healthy patients treated with Indomethacine & those treated with meloxicam (group 1&3).**

**The comparison between the effect of treatment with Indomethacine & meloxicam on patients with cardiac and/or renal problems (grup-2 & 4) show only a significant difference in BUN concentration after 4 & 8 days of treatment as shown in figure-8.**

**Figure-9 shows that there is only a significant difference in S. Cr. concentration after 12 days of treatment, between group-1 patients & group-3.**
**Figure-10 shows that there is a significant difference in S. Cr. concentration after 4 &8 days of treatment between the patients of group-2 & group-4.**
**Figure-11 shows that there is a significant difference in S. K+ concentration between the patients of group-1 & group-3 while in figure-12 there is only a significant difference in S. K+ concentration after 4 & days of treatment between group-2 & 4 patients.**

## Discussion:

**An important factor that affects the renal function is the age in which this function in elderly people undergoes a remarkable decline with age. This effect could be worsen more in presence of NSAIDs therapy and may lead to serious conditions if accompanied by one or more of renal or cardiac problems which include electrolyte disturbances, edema, hypertension, acute & chronic nephritis & acute renal failure.**
**Impaired synthesis of renal prostaglandins produced locally in the kidney by NSAIDs underlies the pathological process in most cases (11).**
**In this study, it was clearly shown that both selective COX-2 inhibitor (meloxicam) & the nonselective COX-inhibitor (Indomethacin) cause a significant increase in the laboratory parameters of kidney function (BUN, S. Cr. & S. K+) in comparison with the control value as shown in the figures 1 to 6. This significant increase occurs in both healthy elderly patients & in orderly patients suffering from cardiac or renal problems. Although, the higher degree of changes in laboratory parameters occur in group-2 & group-4 patients, whose with such problems, which may indicate the probable risk factors that lead to increase renal toxicity of NSAIDs. The degree of increase of the laboratory parameters in those patients excluded from the study may support this result, those 5 patients (2 patients from grup-2 & 3 patients from group-4) already suffer from mild to moderate renal impairment with hypertension and/or with congestive heart failure. The BUN, S. Cr & S.K+ increase after the treatment to values that make the physician to discontinue the treatment after 12 days of treatment, the values of these parameters for after 12 the 5 patients were found as follow: (BUN control: 47, 45, 45, 47 & 48 mg /dl days: 64, 63, 63, 68, 69 mg/dl), (S. Cr control: 1.6, 1.8, 1.7, 1.6 & 1.6 mg/dl after 12 days: 2.6, 2.5, 2.5, 2.7 & 2.8 mg/dl) & finally (S. K+ control: 5.2, 5.0, 4.9, 5.2 & 5.0 mEq/l after 12 days: 6.4, 6.3, 6.3, 6.2 & 6.4 mEq/l). The another point that support our finding is that such higher values of the laboratory parameters began to decrease after discontination of the treatment and reach to levels near control with the use of Bumetanide tab, a loop diuretic, preseribed by the physician.**
**These results were in agreement with other study when rofecoxib was compared with Indomethacine in 60 healthy subjects whose ages ranged from 65 to 80 years and whose baseline creatinine clearance ranged from 30 to 80 ml/min, both rofecoxib and Indomethacine significantly reduced GFR equivalently 10% to 12% than control value(12).**
**Another study that support our results was the report by Perzella and Eras(11), & Whelton(13) et al who studied the effect of NSAIDs on both elderly with renal problems and healthy elderely patients.**
**In such cases, cardiac and/or renal problems (ex: congestive heart failure & myocardial failure) in which these is low renal volume perfusion, act as risk factors to increase NSAIDs renal toxicity because those drugs act as renal afferent arteriole vasoconstrictors, and in the presence of other medications used for such problems like vasodilators (ex: angiotensin converting enzyme inhibitors) which act as efferent arteriole vasodilators, this lead to alter renal homodynamic. In addition to such mechanism, NSAIDs have direct effect on glomeruli leading to nephropathic condition (14).**

**On another way in our study, the figures from 7-12 show the comparison between the 2 types of NSAIDs, the selective COX-2 inhibitor (Meloxican) and the non selective- COX inhibitor (Indomethacin) according to their extent of changing effect on laboratory parameters on elderley patients. It was clearly shown that in spite of the significant differences in the effect of 2 compounds on laboratory parameters in different period of treatment, there is no significant changes between the 2 compounds in affecting the renal function of elderly patients, this mean that the 2 compounds cause similar extent of renal toxicity on those patients. Those results are in agreement with other studies, in 29 healthy elderly subjects without renal insufficiency, treatment with celecoxib for 10 days was compared with nonselective COX-inhibitor naproxen, in a prospective cross over trial, the GFR declined at the 6th day of treatment and the urinary excretion of prostaglandins was significantly reduced with both drugs, but no significant differences in urinary levels was noted between the 2 medications (15).**

## Conclusions:

**Both healthy elderly patients & elderely with renal and/or cardiac problems might be at risk when using the NSAIDs due to their renal toxicity, with increasing the risk probability in those that suffer from impaired renal function, uncontrolled renal hypertension and congestive heart failure in which the prostaglandin play important role in kidney function. So, those drugs should be avoided or at least used cautionusly for short periods of time in those patients due to increasing the risk of developing acute renal failure because the over all toxic effect of those compounds increase parallel to the period of using them. In addition, both selective-COX and nonselective COX-inhibitor can cause the same renal side effects**.

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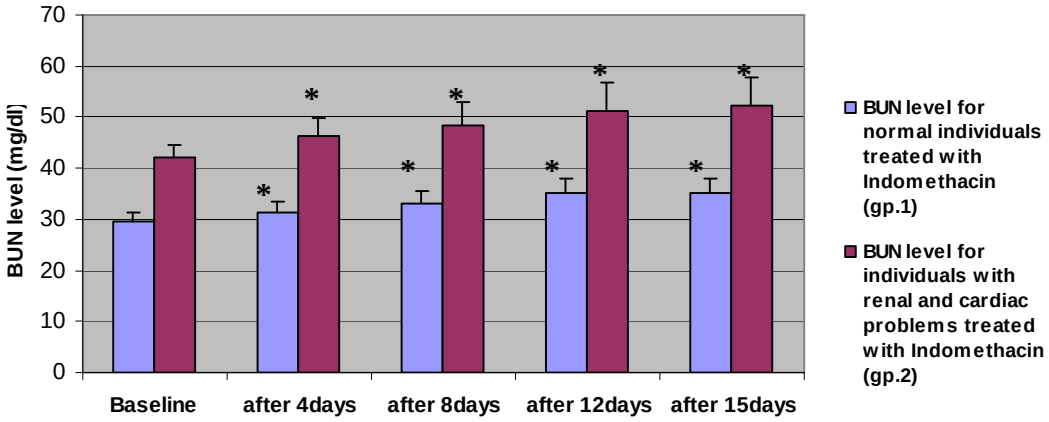


**Figure-1: Comparison between control and the effect of treatment with Indomethacin on BUN for group-1 & group-2 patients. (*: significant difference in comparison with control of the same group).**

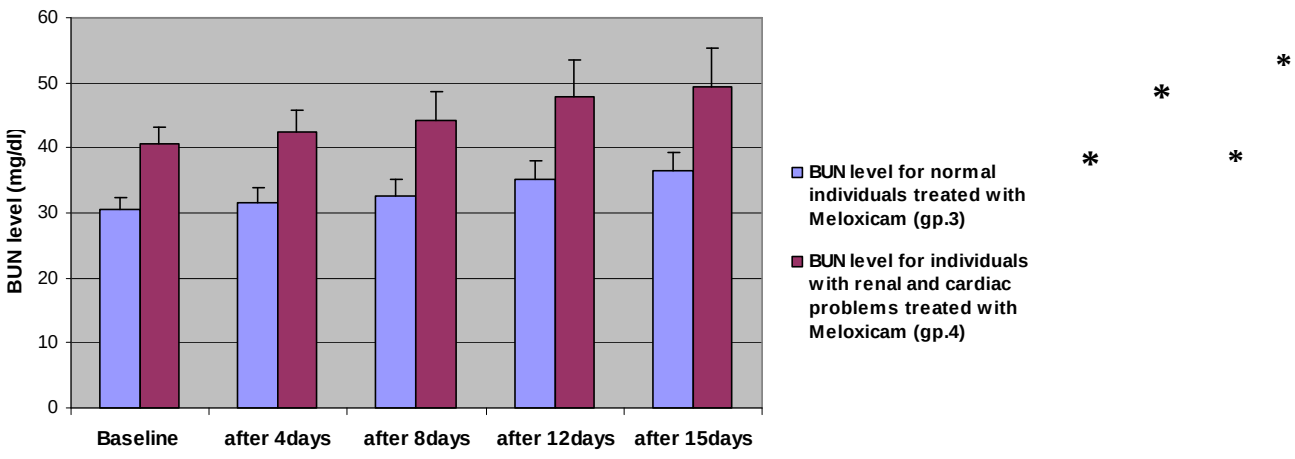

**Figure-2: Comparison between control and the effect of treatment with Meloxicam on BUN for group-3 & group-4 patients. (*: significant difference in comparison with control of the same group).**

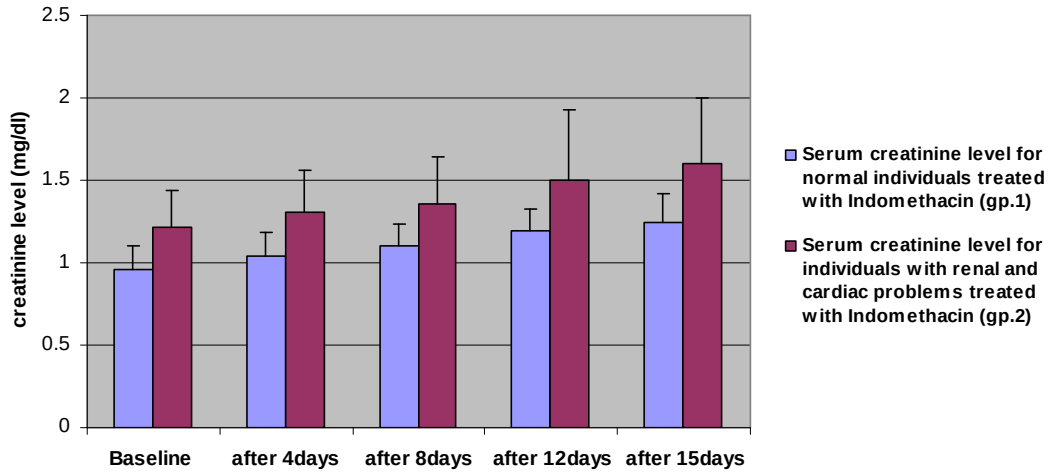


**Figure-3: Comparison between control and the effect of treatment with Indomethacin on S.Cr for group-1 & group-2 patients. (*: significant difference incomparison with control of the same group).**

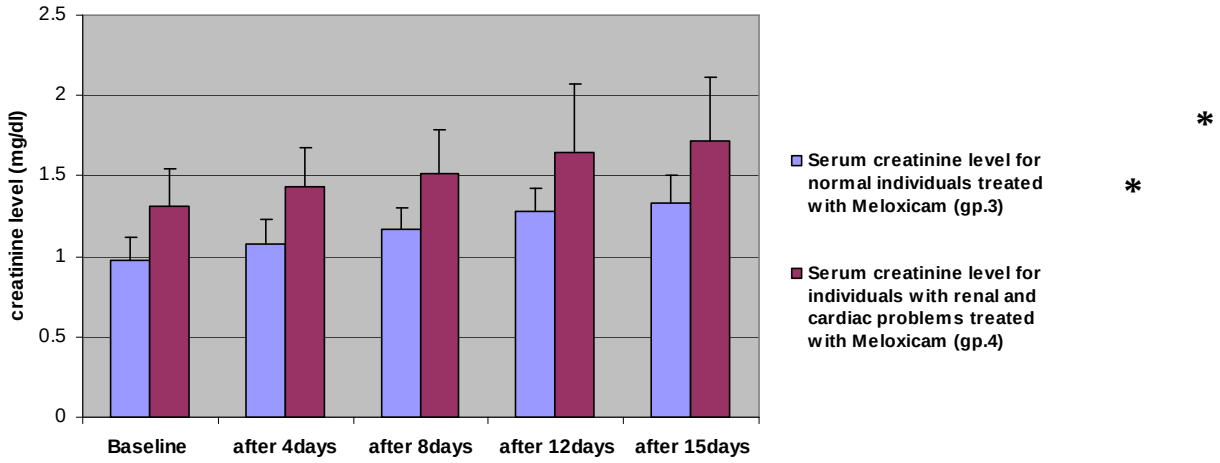


**Figure-4: Comparison between control and the effect of treatment with Meloxicam on S.Cr for group-3 & group-4 patients. (*: significant difference in comparison with control of the same group).**

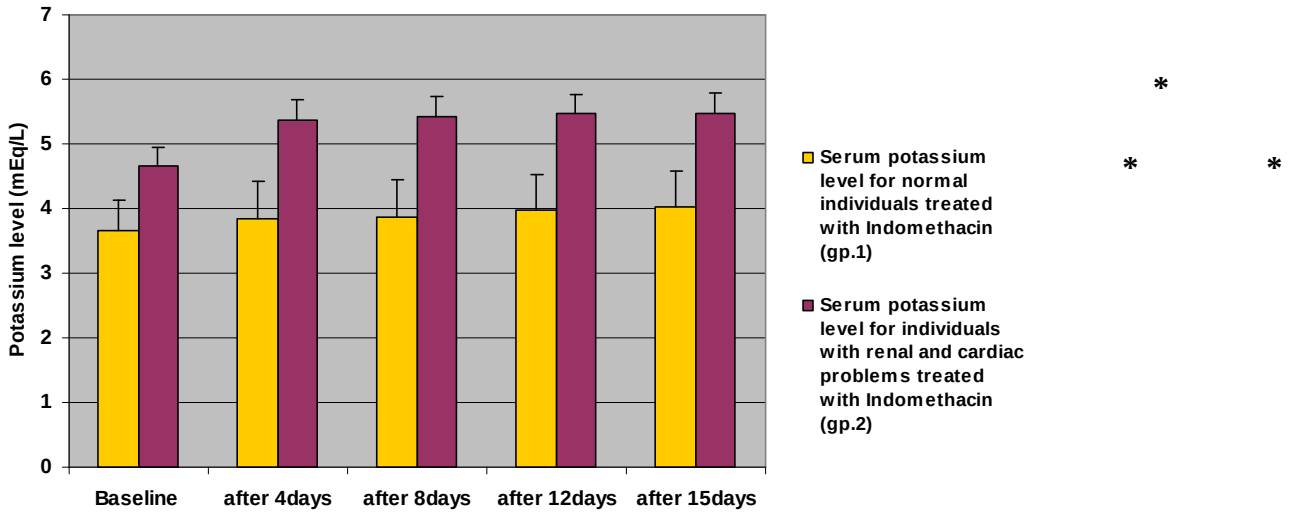


**Figure-5: Comparison between control and the effect of treatment with Indomethacin on S.K+ for group-1 & group-2 patients. (*: significant difference in comparison with control of the same group).**

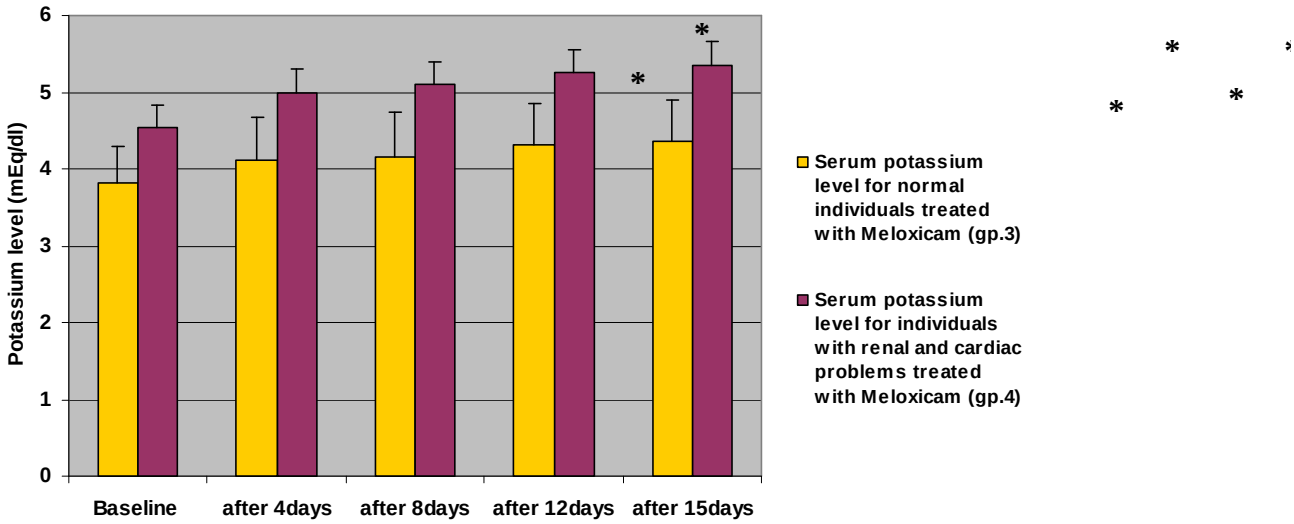


**Figure-6: Comparison between control and the effect of treatment with Meloxicam on S.K+ for group-3 & group-4 patients. (*: significant difference in comparison with control of the same group).**

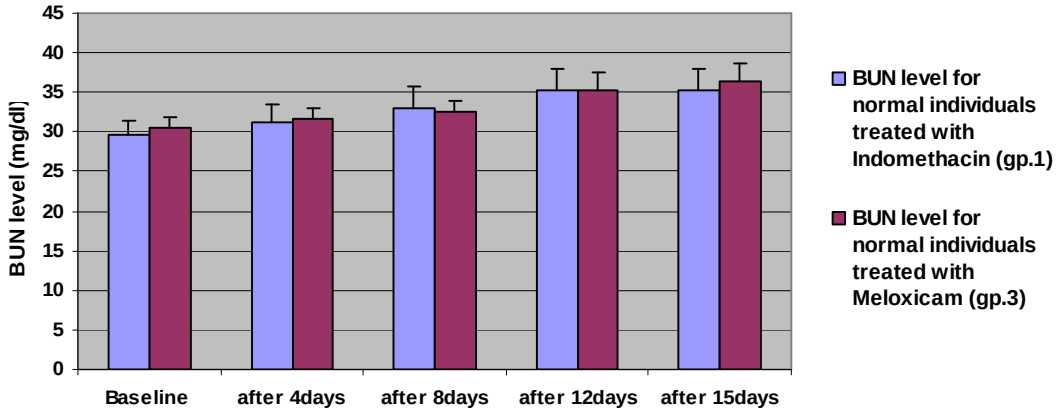


**Figure-7: Comparison between the effect of treatment with Indomethacin & Meloxicam on BUN for group-1 & group-3 patients. (*: significant difference between the 2 compounds at same time.)**

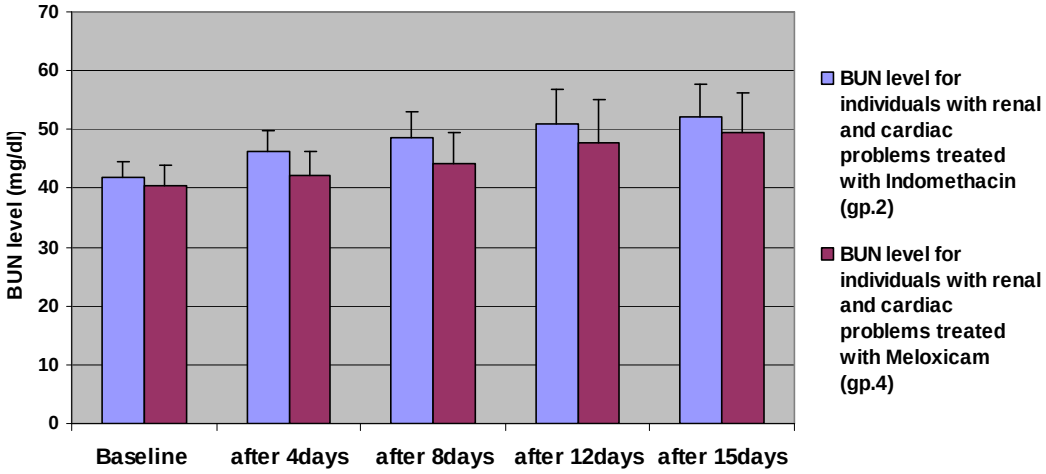


**Figure-8: Comparison between the effect of treatment with Indomethacin & Meloxicam on BUN for group-2 & group-4 patients. (*: significant difference between the 2 compounds at same time.)**

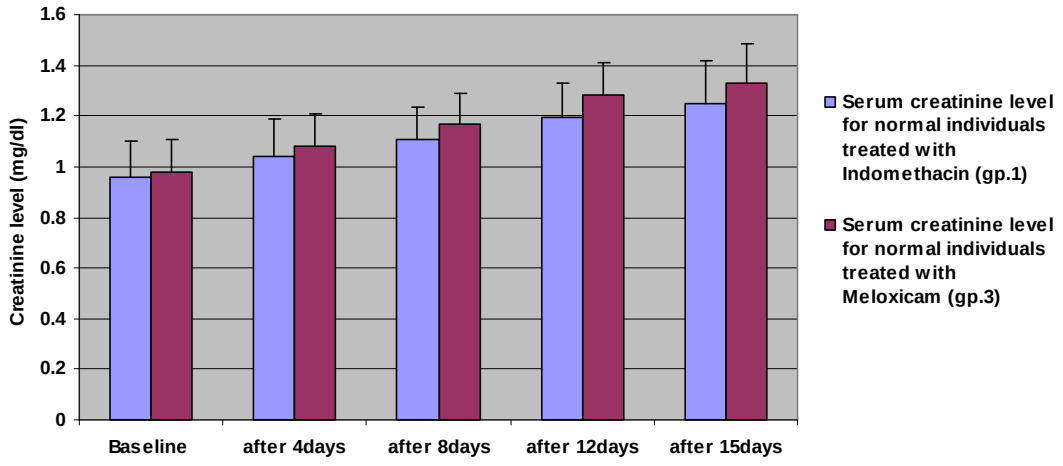


**Figure-9: Comparison between the effect of treatment with Indomethacin & Meloxicam on S.Cr. for group-1 & group-3 patients. (*: significant difference between the 2 compounds at same time.)**

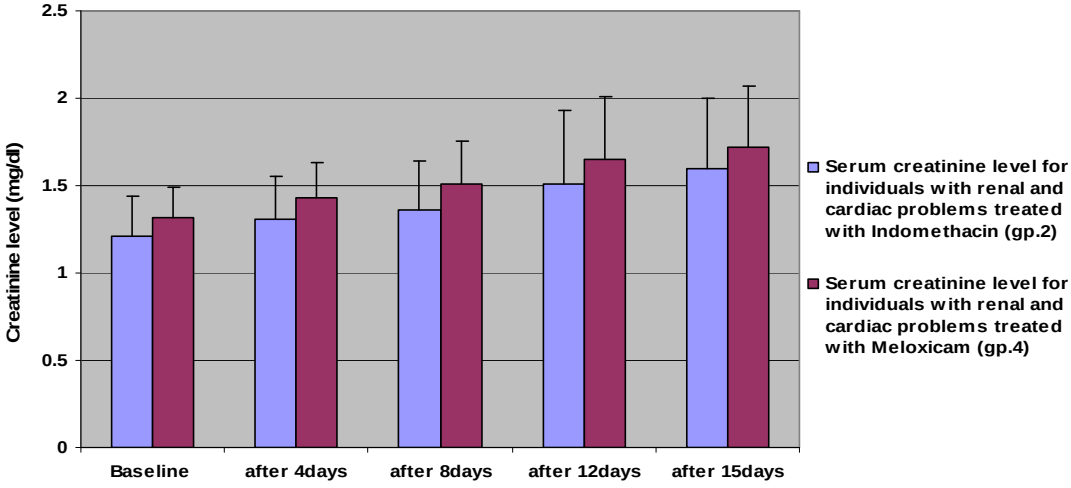


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**Figure-10: Comparison between the effect of treatment with Indomethacin & Meloxicam on S.Cr. for group-2 & group-4 patients. (*: significant difference between the 2 compounds at same time.)**

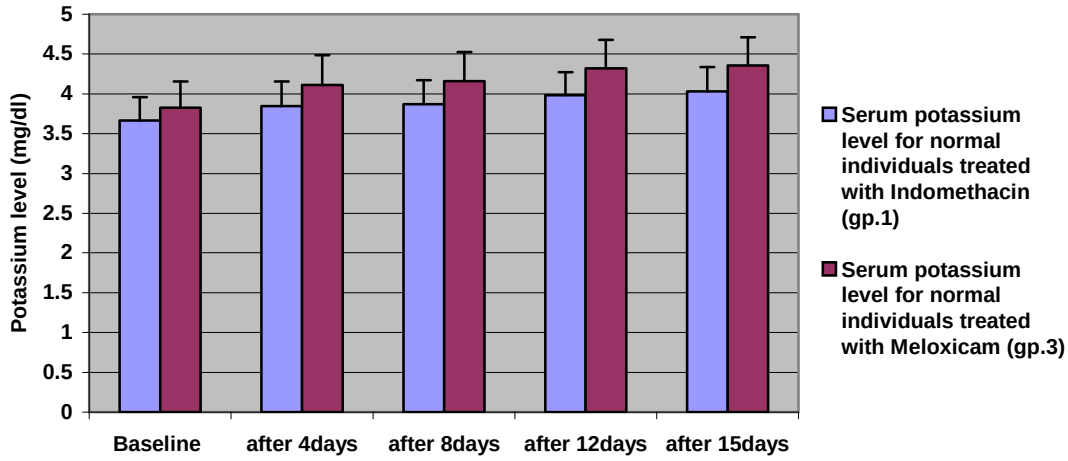


**Figure-11: Comparison between the effect of treatment with Indomethacin & Meloxicam on S.K+ for group-1 & group-3 patients. (*: significant difference between the 2 compounds at same time.)**

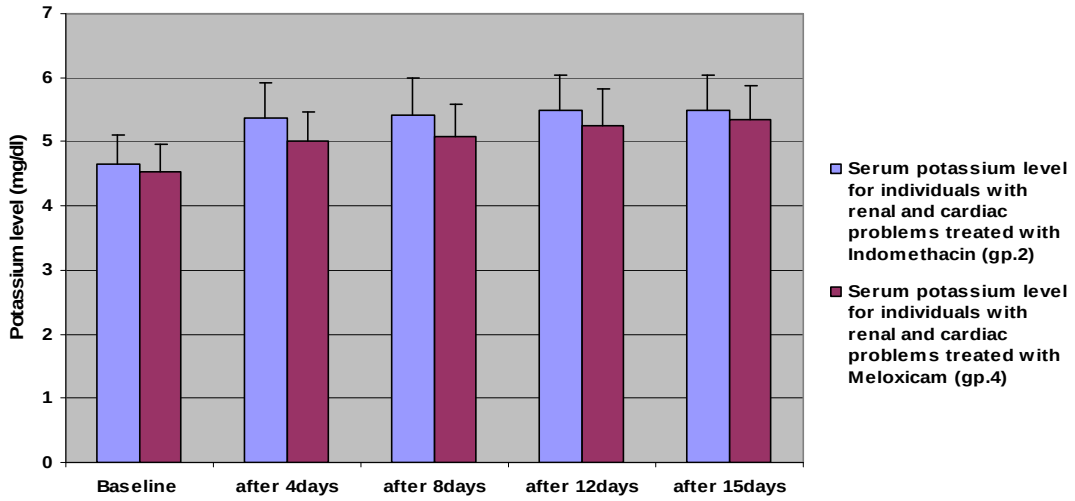


**Figure-12: Comparison between the effect of treatment with Indomethacin & Meloxicam on S.K+ for group-2 & group-4 patients. (*: significant difference between the 2 compounds at same time.)**