

Correlation of metformin with intravenous iodinated contrast media and precautions

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Abstract: To discuss metformin and iv-contrast induced acute renal failure with its reported cases worldwide, associated risk factors and precautions that can be taken to reduce this tragedy & to address this sensitive issue to my technologist family working in clinical situations. As these studies were observational studies and just report contrast induced nephrotoxicity in different countries by analyzing patients data; By Personal experience or by analyzing data available on PACS (Picture archiving and communication system) most commonly available in Hospitals now a days, that is why these studies did not use any scientific procedure. In our study, we collected opinions of Senior Doctors about use of Metformin before and after contrast study. All Doctors were agreed upon investigation of serum creatinine before contrast study. Doctors were not agreed on single opinion but surely they agreed on stop of Metformin before and after procedure. They said its responsibility of imaging technologist or Radiologist to guide patient about this problem. Diabetic patients using Metformin are at high risk of acute renal acidosis if they are undergoing for iodinated contrast study.

Keywords: Intravenous contrast media, metformin.

INTRODUCTION

Metformin is most usually used in diabetic patient as an antidiabetic drug which decreases blood glucose level. It belongs to a group of drugs called "biguanides." It lowers the amount of glucose prepared by our liver, lowers the quantity of glucose by absorbing in body and rises the result of insulin in our body. Insulin helps our body to remove extra sugar from blood. This drops blood sugar level. Some extra actions are also shown by this medication, it stop the formation of glucose and also decreases glucose absorption in intestine (Lalau *et al.*, 2018).

Most common adverse consequence that happen with metformin are nausea, diarrhea, heartburn sensations, abdominal pain, & gas. There may be some serious adverse effect that are lactic acidosis & sudden Hypoglycemia (Godoy *et al.*, 2018).

Contrast agents are mostly used to highlight the anatomical boundaries and to differentiate normal and abnormal findings. Nowadays most commonly used contrast media is iodinated contrast agent (ICAs), first time was used in 1950s in clinical practice. Seventy five

million doses approximately are given in all over the world each year (Christiansen, 2005). The iodine contrast media is divided into 4 major classes, each class have their own different physical, chemical and biological properties (McCartney *et al.*, 1999). They are eliminated by glomerular filtration and exert stress on kidney function that is why concern has been expressed in different published paper regarding patients who undergo intravascular contrast studies (Bjarnason and Elung-Jensen, 2006). All iodinated contrast media have low ability to bind with protein (<10%) distribution from intravascular compartments towards highly perfused organ like liver, kidneys and brain is so fast (Hornsby, 1996). Administration of contrast media is according to body weight by volume about 1ml/kg (For Adult) of body weight. It is directly excreted through renal system mostly from glomerular filtration. With normal renal functions mostly about 90% eliminated in first 24 hours but sometime its elimination period can be prolonged in child or elder patients (Thomsen, 2003).

According to one research done in four province of Pakistan in urban areas, prevalence of diabetes was found in women is 6.8% and in men is 5.1%, and in rural areas in women is 4.8% and in men is 5%. This number raises every year as effect of a poor intake, obesity, and weighty. As most of these patients are likely to need a huge number of diagnostic tests with intravenous (IV)

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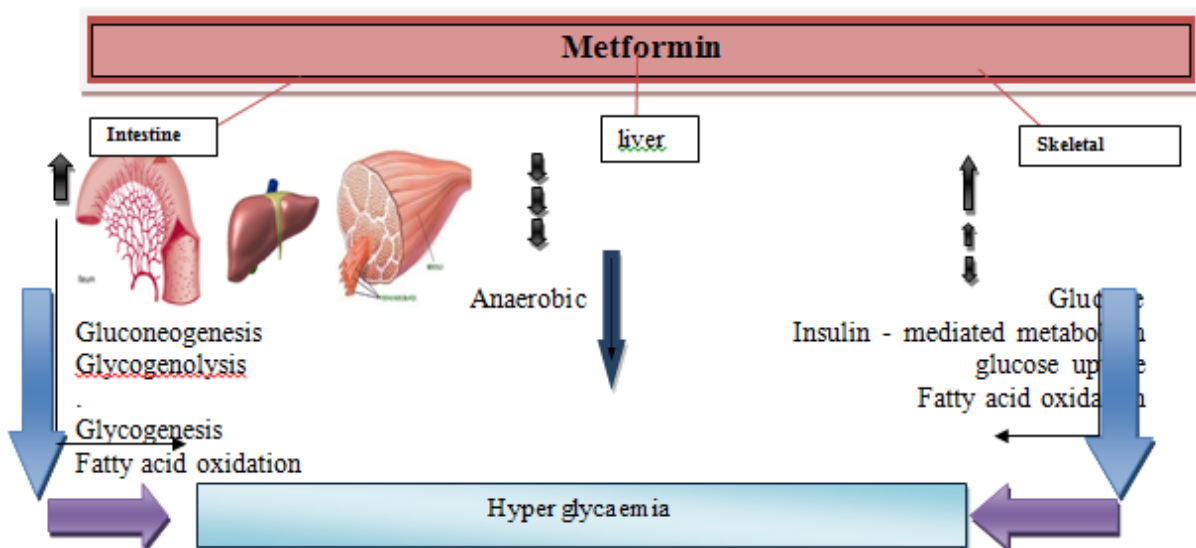


Fig. 1: Metformin Mechanism of Action. (Image reproduced from Medscape)

Table 1: Suggestions summary of Senior Doctors

If Serum Creatinine is Normal i.e. < 1.5ml/dl	If Serum Creatinine is Elevated i.e. >1.5ml/dl
Suggestion# 1: At least 5 hr before and 12 hr after Procedure.	If Patient stable: Suggestion: (All Doctors agree) Advice Increase Water intake and Delay Procedure.
Suggestions #2: 12 hr before and 12 hr after Procedure.	In Emergency situations: Suggestion: (All Doctors agree) Follow the advice of Senior Doctors, if procedure has to perform then Metformin should be stopped 48 hr after that and follow up Screening for elevated creatinine should be done to take necessary steps.
Suggestion #3: 12 hr before and 48 hr after Procedure.	

iodinated contrast media (MRI, urography, cholecystography, angiography, CT Scan) to diagnose atherosclerosis, kidney disease and ischemic heart disease etc. (Zalazar, Tobia et al.).

Creatinine clearance is gold standard before intravenous contrast media injection. Following are ESUR and American guidelines for iodine administration. Serum creatinine level should be measured in all diabetic patients that are treated with metformin former to administration of intravascular contrast media. Low-osmolar non-ionic contrast is preferred in these patients (Cohan *et al.*, 2013). In current study, we analyzed the implementation of these instructions in major Government and Private hospitals of Faisalabad.

MATERIAL AND METHODS

Available research articles were carefully analyzed in which studies are conducted on kidney lactic acidosis in diabetic patients who undergo an IV-contrast study. There are many death cases seen in patient which are using metformin and goes under iodinated contrast media

diagnostic test due to lactic acidosis (Bjarnason and Elung-Jensen, 2006, Parra *et al.*, 2004).

As these studies were observational studies and just report contrast induced nephrotoxicity in different countries by analyzing patients data; By Personal experience or by analyzing data available on PACS (Picture archiving & communication system) most commonly available in Hospitals nowadays, that is why these studies did not use any scientific procedure. Standard way that they used for separating cases of contrast induced nephrotoxicity was two definition of it for example 0.5ml /dl increase or 25% increase in creatinine level after 48 hr injection of contrast. When contrast volume is <100 ml then stop of Metformin at least 5hr before and 12 hr after procedure or 12 hr before and 12hr after procedure.

The risk factor of contrast related nephropathy is more if renal function is already disturbed. The chances are only 5% to have normal renal function, but 50% more in those patients which have already renal dysfunction (Thomsen, 2003).

Table 2: Summary of Instructions in Faisalabad Hospitals

Hospital name	Instructions about Metformin use
Mujahid Hospital	Just Preprocedural Serum Creatinine and no instructions about use of Metformin
National Hospital	Just Preprocedural Serum Creatinine and no instructions about use of Metformin
DHQ Hospital	Just Preprocedural Serum Creatinine and no instructions about use of Metformin
Allied Hospital	Just Preprocedural Serum Creatinine and no instructions about use of Metformin
FIC Hospital	Preprocedural Serum Creatinine and stop of any medicine used for Diabetes. (No specific name of Metformin)

Patient with normal serum creatinine level of 1.2 to 1.9 mg/dl, 2.0 to 2.9 mg/dl and 3 mg/dl or more, have more chances like 2.4%, 7.4% and 12.8% of contrast related nephropathy after the use of iodinated contrast media (Rihal, Textor *et al.*, 2002).

According to one report contrast induced nephropathy chances are rare if pre-procedural serum creatinine level is normal about 1.2 mg /dl or less than 1.3 the chances of nephropathy is 2%, and if preprocedural creatinine level is 1.3 to 1.9mg/dl than the chances of nephropathy is more about 10.4%. If the preprocedural creatinine level is more than 2.0 then chances also increase almost 62% (Hall *et al.*, 1992).

Many other factors are also included such as age systemic disease that lead the patient to renal dysfunction (DM and HTN), and also the factors which reduce cardiac output such as MI, dehydration, CHF within 24 hours after iodinated contrast media. Recent use of aminoglycosides, drugs that change hemodynamic level (NSAIDs and ACE inhibitors) also refer the patients towards contrast related nephropathy (Goldenberg and Matetzky, 2005).

The chances of nephropathy is more after the administration of high osmolar contrast especially in those patient which already have impaired renal functions (Auti *et al.*, 2019). If injected amount of iodinated contrast media increases the risk of contrast related nephropathy also increased. If 100 ml iodinated contrast media increase 12% risk also increase (Rihal *et al.*, 2002).

The rate of side effect is most common when we use high osmolarity agents almost 15% vs just 3% due to low osmolarity iodinated contrast media. So the use of high osmolarity contrast agents has reduced day by day (Lalau and Race, 2001).

The routes of contrast administration also affect the risk factors of nephropathy. Recent studies of nephropathy choose to intra-arterial contrast while corresponding study of nephropathy after I.V contrast are somewhat missing but some scholars had quizzed the frequency of nephropathy after the injection of intravenous contrast (Rao and Newhouse, 2006).

So Iodinated contrast media is not only the risk factor for lactic acidosis in diabetic patient but it is associated with

poor renal function, hypertension, route of choice and volume of contrast used (Goldenberg and Matetzky, 2005).

No specific precautions are used in main Government and private Hospitals of Faisalabad for Metformin use, before and after iodinated contrast study. When contrast volume >100ml 48 hr stop of Metformin should strictly follow Standard operating Protocols (SOP) of American and European Union (EU) are discussed in current paper. Common practice in Faisalabad city is discussed in comparison of those standards in 'Discussion chapter'.

Suggestions about use of Metformin before and after Iodinated contrast study were collected by a questionnaire filled by urologist, Radiologist, cardiologist and Results are given in table and chart form.

RESULTS

In our study we collected opinions of Senior Doctors about use of Metformin before and after contrast study. All Doctors were agreed upon investigation of serum creatinine before contrast study. Creatinine clearance is gold standard before IV contrast media injection. Following are ESUR (European Society of urogenital Radiology) and American guidelines for iodine administration. Serum creatinine level should be measured in all diabetic patients treated with metformin former to intravascular injection of contrast. Low-osmolar nonionic contrast media should be used in these patients. If the serum creatinine is normal, the imaging inspection should be done and metformin should be withdrawn before the study and metformin should not be restarted for 48 hours. If kidney function is not normal, the metformin should be withdrawn for 48 hours prior to the contrast media study. Metformin should not be resumed 48 hours after study (Cohan *et al.*, 2013). In current study, we analyzed the implementation of these instructions in major Government and Private Hospitals of Faisalabad. There suggestions when creatinine level is normal and elevated, are summarized in table 1. As for normal creatinine there are different suggestions so vote for each suggestion is expressed in chart 1.

The difference of opinion is discussed in the end of this chapter. Along with collection of suggestions we collected information about implementation of these kinds of

advices in different hospitals of Faisalabad and then we found that tertiary care Hospitals (DHQ, Allied Hospital) and many Private Hospitals (like National Hospital and Mujahid Hospital) did not include any specific instruction about use of Metformin in Leaflet, given to patients before the Procedure.

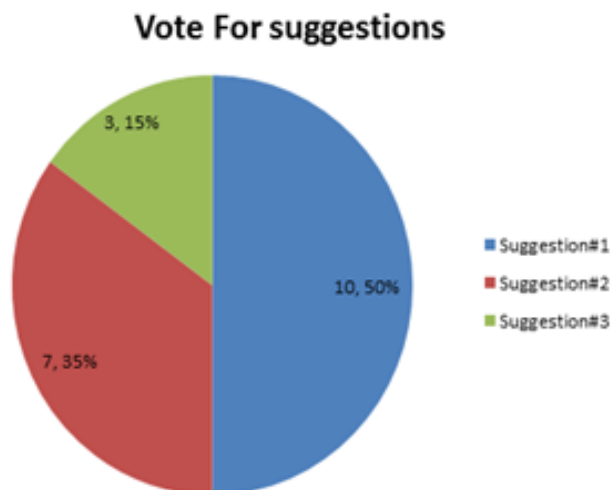
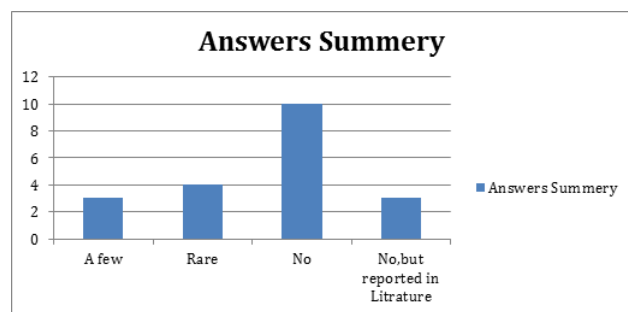


Chart 1: Frequencies of Suggestions in co-relation with above table

Only FIC (Faisalabad institute of Cardiology) had included instruction about use of diabetic's medicine before the procedure of Angiography and Angioplasty that is "On the day of procedure do not intake Medicine for Diabetes." Although they did not specifically indicate metformin name. Result of survey is summarized in table.

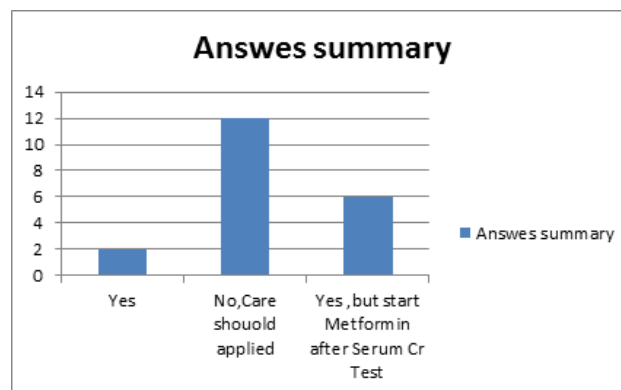
There were different questions asked from Senior Doctors in our Performa, answers are summarized below:

Do you face any incident in which patient have acute renal failure after IV-Contrast study?



Many Doctors were agreed that acute renal failure incidence have been reduced after screening test of serum Creatinine performed on every patient coming for contrast study. (Although it is not recommended for every patient in literature)

Do you think serum- creatinine test and wide practice of Ultravist and Urografin contrast media is enough strategy for metformin used patients?



Majority of Doctors were agreed that Metformin should be stopped but confusion present in implementation of "How to do it?" Confusion is mainly because of less patient encounter time to Urologist, Cardiologist and even to staff of diagnostic center, those going to perform contrast study.

DISCUSSION

Many Patients suffer from different types of diseases including atherosclerosis, ischemic heart disease and Urinary system problem etc. That is why large number of diagnostic test are required of these patients which mostly consist of iodinated contrast media such as angiography ,urography, cholecystography, CT-Scan with contrast, etc. from this percentage almost 90% patient have DM Type 2 and number of these patients (Zalazar, Tobia et al.). Diabetic patients using Metformin are at high risk of acute renal acidosis if they are undergoing for iodinated contrast study. Association factors for renal lactic acidosis along with Metformin are, Preprocedural renal function impairment (serum Cr >1.5mg/dl), intra-arterial route and >100 ml use of contrast volume (Katayama, Yamaguchi et al. 1990). The contrast media have very short half-life of 2 to 3 hours. They do not metabolize through hepatobiliary system. It directly excreted through renal system mostly from glomerular filtration. With normal renal functions mostly about 90% eliminated in first 24 hours but sometime its elimination period can be prolonged in child or elder patients even if creatinine level is normal due to many reasons like that reduced in muscle mass which reduced 50% glomerular filtration so that half-life of contrast media could be increased (Cochran, Bomyea et al. 2001). Majority of Doctors opinion is that, Metformin should be stopped for contrast study. But confusion among Doctors for timing is present. Maximum time used to prepare patients is hardly 8-12 hr. (overnight NPO). If serum creatinine is normal i.e. < 1.5ml/dl, At least 5hr before & 12hr after procedure. If serum creatinine is elevated i.e. > 1.5ml/dl, Doctors advice increase water intake & delay Procedure and if procedure has to perform then Metformin should stop 48hr after that & follow up Screening for elevated creatinine should be done to take necessary steps.

Literature advised 48 hour before and after stop of Metformin, that is practically not possible, even Doctors were not agreed on single opinion but surely they agreed on stop of Metformin before and after procedure. They said its responsibility of imaging technologist or Radiologist to guide patient about this problem.

CONCLUSION

No specific precautions are used in major Government and Private hospitals of Faisalabad for Metformin use, before and after iodinated contrast study. Despite 48 hr Pre & post procedural stop of Metformin is recommended in literature. Majority of Senior Doctors opinion is that, Metformin should be stopped along with normal screening test of serum Creatinine for contrast study. But confusion among Doctors for timing is present. When contrast volume is < 100ml then stop of Metformin at least 5 hr before and 12hr after procedure is most voted suggestion. Second most voted suggestion is 12 hr before and 12hr after procedure. When contrast volume >100ml 48 hr stop of Metformin should strictly follow.

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