

Prospective single blind placebo-controlled randomized clinical trial to assess the efficacy and safety of metformin in promoting wound healing and weight reduction in non-diabetic overweight post-operative female patients

C. Meenal^{1,2}, Revathy Saravanan^{3*}

¹Department of Obstetrics and Gynecology,

Sri Venkateshwaraa Medical College Hospital and Research Center, Ariyur, Pondicherry, India,

²Department of Obstetrics and Gynecology, Manipal Medical College, Maleka, Malaysia, ³Department of Pharmacology, Sri Venkateshwaraa Medical College and Research Center, Ariyur, Pondicherry, India

Received: 26 February 2015

Accepted: 07 March 2015

***Correspondence to:**

Dr. Revathy Saravanan,

Email: dr_rsmail@yahoo.co.in

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Obesity is an important preventable risk factor that can affect wound healing. Oral hypoglycemic drug metformin apart from its antihyperglycemic and not hypoglycemic property has been reported to promote wound healing in non-diabetic animal studies and weight reduction in non-diabetic individuals. Hence, this: prospective randomized study single-blind placebo-controlled study was designed with the aim to assess the efficacy and safety of metformin in wound healing and weight reduction in a tertiary care hospital in Pondicherry during the period between December 2012 and January 2014.

Methods: 215 non-diabetic post-operative patients with body mass index (BMI) of 25-29.9 kg/m² from the Department of Obstetrics and Gynecology included after obtaining informed consent received tablet metformin 500 mg or placebo B.D from 2nd post-operative day up-to 30 days. Fasting blood sugar, postprandial blood sugar, BMI were recorded initially, and at the end. Clinical evaluation of wound was done on 8th, 15th and 30th post-operative days. Unpaired t-test was applied to compare the two groups for quantitative analysis and Chi-square test to analyze the qualitative outcome by using GraphPad prism - 6 software. p<0.05 was considered to be statistically significant.

Results: Surgical site infection of 13.3% and 3.3% was observed in control and metformin groups respectively. Wound healing promoting effect of metformin was evidenced by p=0.0087 and 0.01 on 8th and on 15th day. Weight reducing effect was evidenced by p=0.0001 on comparing BMI. No significant hypoglycemia was observed. No adverse drug reaction was reported.

Conclusions: Our study has shown metformin having best wound healing and weight reducing effect without producing hypoglycemia. Long-term studies on all types of surgeries in both males and females including emergencies are suggested.

Keywords: Metformin, Wound healing, Weight reduction, Non-diabetic overweight post-operative female patients

INTRODUCTION

Obesity being an one of the well-known preventable factors that can affect wound healing in many ways, can increase the incidence of other systemic risk factors like diabetes mellitus, hypertension for wound healing.¹⁻³ WHO and National Family Health Survey (NFHS) studies have reported steady increase in obesity more in females than

in males.^{4,6} Undernutrition will be an added risk even with the low prevalence of obesity (2.1%) in India.^{5,6} Resistance lowering effect of obesity on the aponeurotic scars has been demonstrated by a study on abdominal wound in obesity-induced Wistar rats.⁴ Wound infection rate has been reported as 29% and 24% in gynecology abdominal hysterectomies in obese patients by Krebs and Helmkamp,⁷ respectively, whereas it was only 4% in non-obese patients.⁷

High incidence surgical site infection (SSI) of 26.7% with body mass index (BMI) of 60 kg/m² and low 6.4% with BMI 30-40 kg/m². have been observed.⁸ It has been concluded that in India where health care expenses had to be met with, out of pocket, increase in hospital stay due to SSI will have additional financial burden to an already resource constrained set by EMBASE and Medline data analysis.⁹ Even though many new expensive therapies are suggested, hypoglycemic drugs have been demonstrated to promote wound healing in diabetic ulcers except glibenclamide causing gastric ulceration instead.¹⁰ This has been demonstrated in three wound models in euglycemic Wistar rats without causing hypoglycemia.¹⁰

Evidence on weight reducing effect of metformin is not well-defined in few studies done already.^{11,12} As not much trials on the effect of metformin on wound healing and weight reduction could be traced in India, this study has been undertaken to assess the efficacy and safety of metformin in promoting wound healing and weight reduction in overweight female post-operative female patients.

METHODS

A randomized single-blind placebo controlled comparative study was done on overweight female post-operative female patients from the Department of Obstetrics and Gynecology in a tertiary care teaching hospital in Pondicherry from December 2012 to January 2014. Approval of Institutional Research and Ethics Committees were obtained before the commencement of the study.

Inclusion criteria

1. Female patients in the age group of 30-60 years
2. Female patients with BMI of more than 25-29.9 kg/m²
3. Patients who have undergone major abdominal gynae surgery after obtaining fitness
4. Patients with fasting blood sugar (FBS) of <100 mg/dl and postprandial blood sugar of <140 mg/dl.

Exclusion criteria

1. Known diabetic patients/with family history of diabetes
2. Patients with BMI of 18.5-24.9 kg/m²
3. Minor postoperative cases
4. Patients with other co-morbid conditions
5. Patients with previous abdominal surgery
6. Pregnant and lactating mothers
7. Polycystic ovarian disease patients.

Patients who were admitted and have fulfilled the above criteria for surgeries in the Department of Obstetrics and Gynaecology were included in this study after obtaining informed consent. They were allotted to one of the following groups by simple randomization method to Group-A or Group-B. Study subjects were blinded.

Study subjects in Group A were started on tablet metformin 500 mg twice a day from 2nd post-operative day. Group B was treated as control and received only tablet calcium 500 mg twice a day as placebo. Both the groups received other drugs as prescribed by the operating surgeon. After suture removal on the 8th post-operative day, healing of the wound was clinically evaluated as per the criteria given in Table 1. The participants in A and B groups were asked to continue tablet metformin 500 mg or tablet calcium 500 mg twice a day for 30 days after starting the drug. Patients of both the groups were reviewed on 8th (day of suture removal), 15th, and 30th post-operative days to evaluate the wound healing. BMI, FBS, and postprandial blood sugar were repeated on the 30th day, for both the groups to compare the effect of metformin on blood glucose and body weight. Patients whose wound has not healed completely on the day of suture removal were kept in the hospital till the healing was complete. Based on this, hospital stay period was calculated.

Statistical analysis

BMI and blood glucose level between groups were compared by unpaired t-test. Wound healing grading and hospital stay period were compared using Chi-square test for statistical significance. Analysis was done by using Graph pad prism-6 software. p<0.05 was considered to be significant.

RESULTS

Of 228 recruited subjects, after screening, 100 persons were allotted to control the group of which there was 6 drop outs and 94 completed the study. Of the 128 patients allotted to test drug group 121 patients completed the study and 7 persons who could not be followed up (Figure 1).

Table 1: Criteria for grading of wound healing.

Grading of wound	Criteria
Grade I	Completely healed dry wound
Grade II	Healed wound with slight serous discharge
Grade III	Partially healed with some spots of wound dehiscence
Grade IV	Not healed wound with complete wound dehiscence

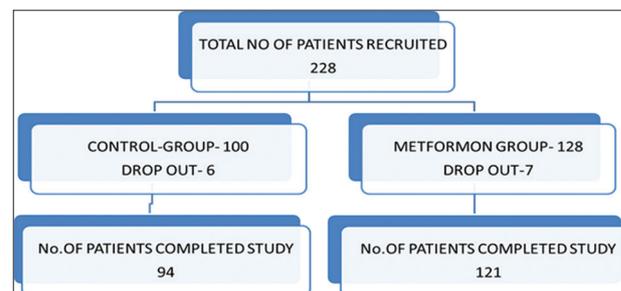


Figure 1: Recruitment and allocation of study subjects.

There was equal number of patients in both the A and B Groups in the age group of 41-50 and 51-60 with 37 patients in each and it was 50 in the metformin group versus 23 in control group in the 30-40 years age group (Figure 2).

Average BMI belonging to different age groups among control and test groups has been shown in Figure 3, which is almost homogenous. Among different types of gynae surgery that was carried out, total abdominal hysterectomy was the most common one followed by laparotomy, sling surgery, myomectomy, and ovariectomy and ectopic (Figure 4). Average BMI of the control group was 27.3±0.99 and that of test group was 27.5±0.99 before starting the study at the basal level with no statistically significant difference

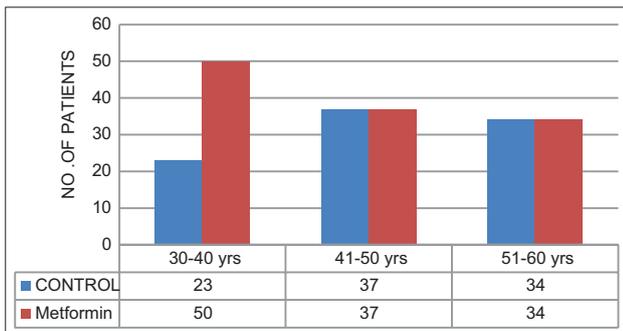


Figure 2: Number of patients from different age groups in control and test groups.

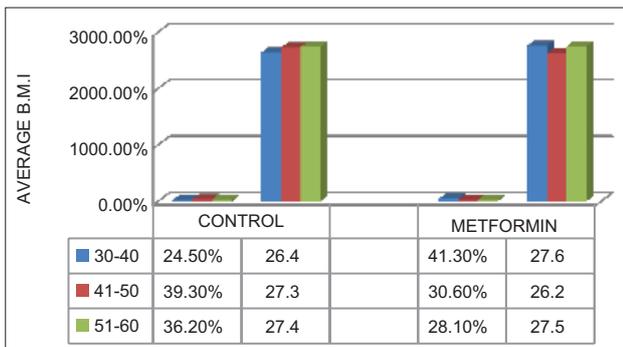


Figure 3: Average body mass index age wise from both control and test groups.

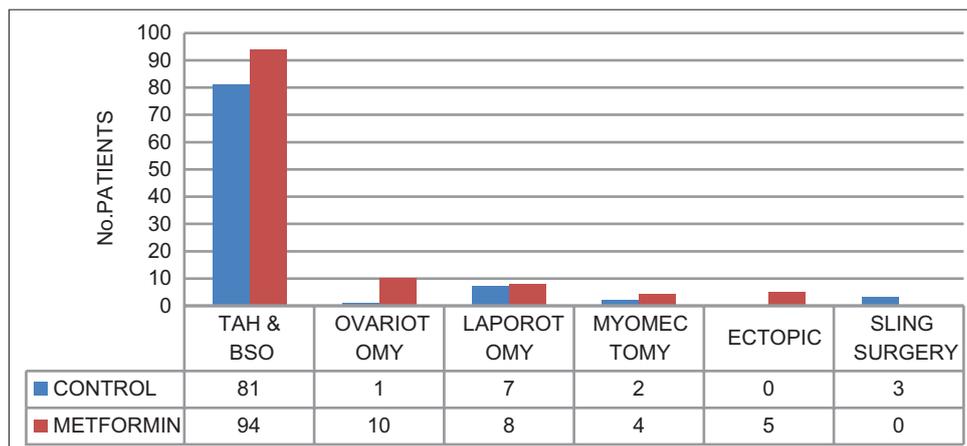


Figure 4: Types of surgeries underwent by persons from both the study groups.

(p=0.06) (Figure 5 and Table 2). However, at the end of 30 days, average BMI of control and metformin group were 26.88±0.33 and 25.7±1.1 respectively with the statistical difference of 0.0001 (Figure 6 and Table 2). There was no statistically significant difference in the postprandial blood sugar level between the placebo and metformin groups before starting and after therapy with the p=0.06 and 0.16, respectively (Figures 7 and 8, Table 3). Statistical analysis of wound healing grading has shown significant difference with metformin on the day of suture removal and on the 15th post-operative day with p=0.0087 and 0.01 respectively, on comparing with that of control (Figures 9-12, Table 4). But no significant difference was obtained on the 30th post-operative day regarding wound healing between the groups showing a p=0.10 (Figures 13 and 14). Overall wound infection rate observed in our study was 7.4%. Higher incidence of wound infection with 13.3% was noted in the control group of whom two patients had to stay for more than 4 weeks and had to undergo wound resuturing. Among the patients who received tablet metformin, wound infection was observed in 3.3% of patients and complete wound healing was obtained by 30th day with no extension of hospital stay.

Similar statistical difference was observed with metformin group regarding hospital stay with p=0.04 (Figures 15 and 16, Table 4). No adverse effects were reported or observed among study population during the study period.

DISCUSSION

Wound healing is still one of the clinical challenges met with even after technical improvements in the past two decades in many surgical procedures with minimal exposure like laparoscopic surgeries and use of intermittent pneumatic compression, hyperbaric O₂ to overcome the ill effect of hypoxia and availability of many antimicrobials to control infections.¹ A completely healed wound can be defined as the one that has returned to its normal anatomic structure, function and appearance within a reasonable period of time which is normally in 4-6 weeks.¹ Wound healing is achieved by four precisely programmed phases namely hemostasis, inflammation by means of neutrophil and monocyte

Table 2: Statistical analysis of BMI (control vs. metformin group).

Groups	Before and after medication			
	Average BMI standard deviation before	p value	Average BMI-standard deviation after	p value
Control	27.3±0.99		26.8±0.99	
Metformin	27.5±0.99	0.06	25.7±1.1	0.0001

BMI: Body mass index

Table 3: Blood sugar: Values and statistical analysis of PPBS (control vs. metformin group).

Groups	Average FBS standard deviation before	Average FBS standard deviation after	Average PPBS standard deviation before	p value	Average PPBS standard deviation after	p value
	Control	76.3±6.5	82.4±6.1	115.2±6.5	0.06	112.4±4.6
Metformin	83.52±10.6	87.0±8.1	116.8±59		111.4±5.2	

FBS: Fasting blood sugar, PPBS: Postprandial blood sugar

Table 4: Statistical analysis of wound healing and hospital stay (control vs. metformin).

Groups	P value			
	WH-SR	WH-15 th day	WH-30 th day	Hospital stay
Control				
Metformin	0.0087	0.01	0.10	0.04

WH: Wound healing; SR: On suture removal

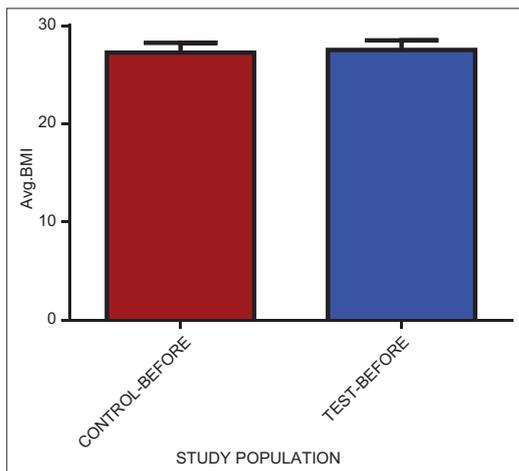


Figure 5: Comparison of body mass index between control versus metformin group before starting. Study showing homogeneity (p=0.06).

infiltration, proliferation by re-epithelization, angiogenesis, collagen synthesis, and extracellular matrix formation and finally by collagen remodeling, vascular maturation, and regression.² If any one of them is affected it can lead to impaired wound healing.

Many local and systemic factors have been identified to result in impaired healing of which obesity being one important well known deciding factor which can affect in many ways. Decreased vascularity of adipose tissues can cause hypoperfusion resulting in ischemia and decreased delivery of antibodies. Increase in wound

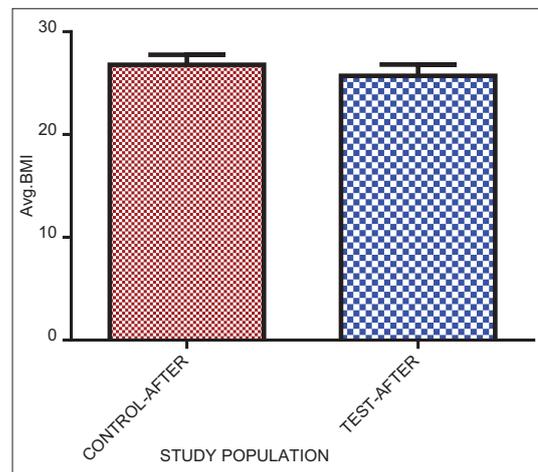
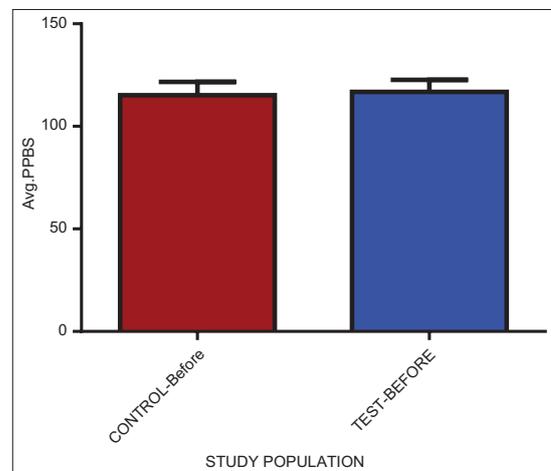


Figure 6: Body mass index control versus metformin after treatment p=0.0001.



Figures 7: Post prandial blood sugar control versus metformin before treatment p=0.06.

tension at the edges will cause hypoxia. Increase in tissue pressure resulting in hematoma and seroma formation will delay healing and can result in infections which will be encouraged by accumulation of microorganisms in between the skin folds.²

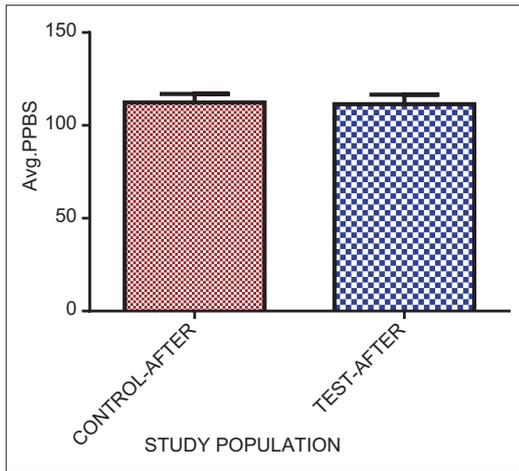


Figure 8: Postprandial blood sugar control versus metformin after treatment $p=0.16$.

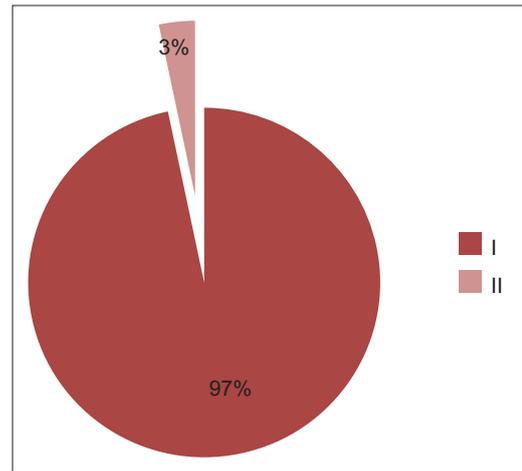


Figure 11: Grading of wound healing on S.R day-test group ($p=0.0087$).

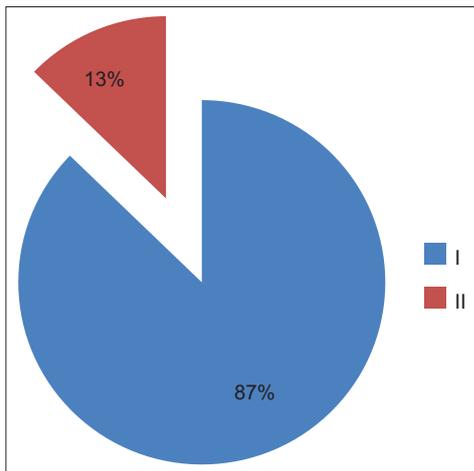


Figure 9: Grading of wound healing among the control group on 8th postoperative day.

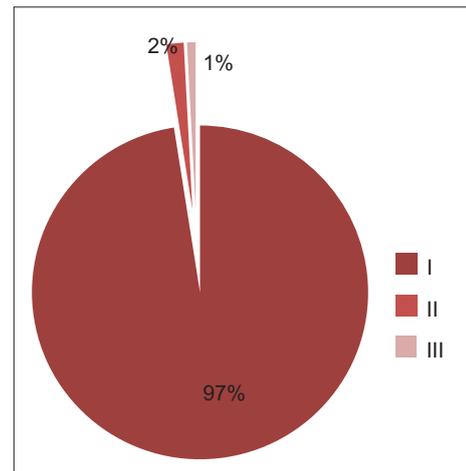


Figure 12: Grading of wound healing on 15th postoperative day in the study group (metformin) ($p=0.01$).

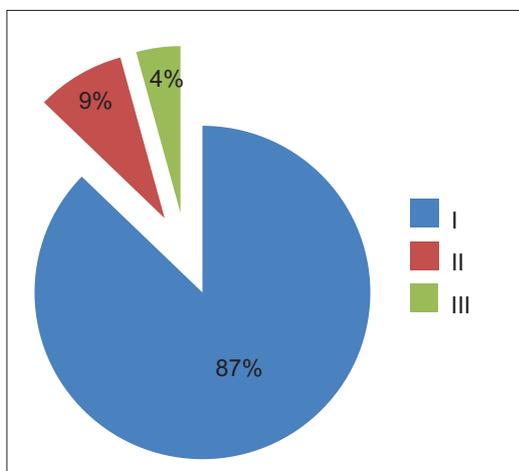


Figure 10: Grading of wound healing among the control group on 15th postoperative day.

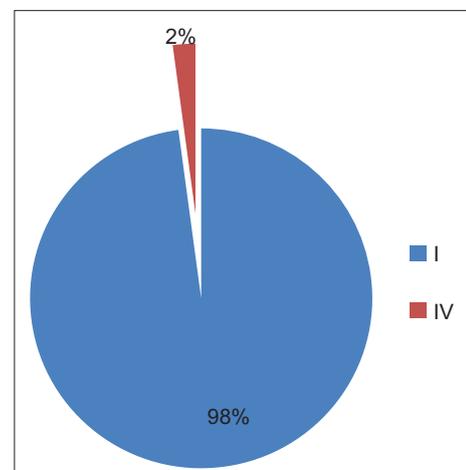


Figure 13: Grading of wound on the 30th post-operative day control.

Increased incidence of systemic diseases like diabetes mellitus, hypertension with obesity will be the added risk factors for wound healing.^{2,3} Obesity can also decrease inflammatory and immune response needed for good wound

healing. Adipokines secreted by adipose tissues can have a negative influence on the immune system even though direct evidence is lacking.²

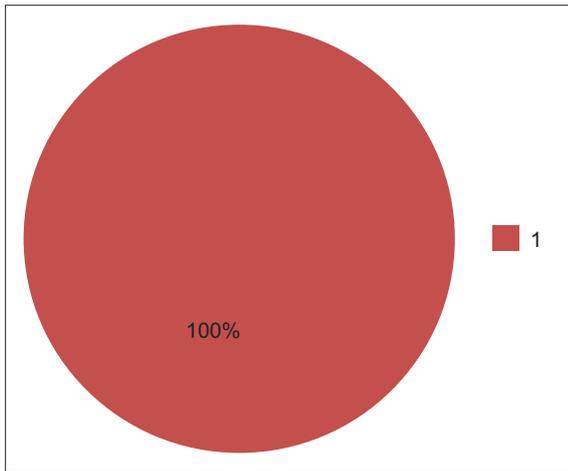


Figure 14: Grading of wound on the 30th post-operative day - study group (p=0.10).

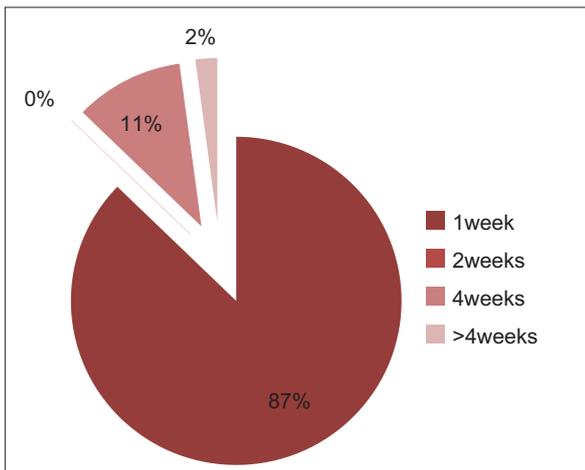


Figure 15: Duration of hospital stay by the control group subjects.

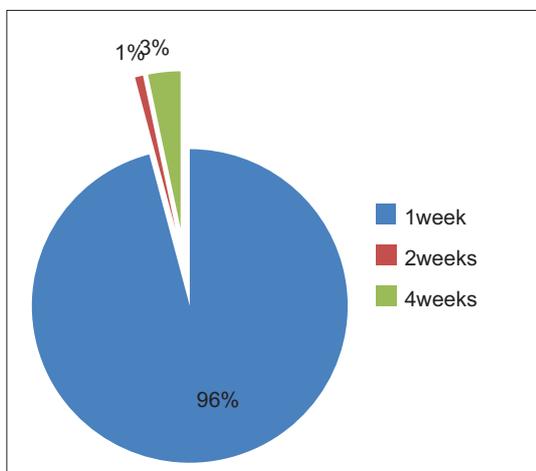


Figure 16: Percentage of patients from study group who stayed in the hospital for a period of 1, 2, and 4 weeks (p=0.04).

WHO has defined overweight as an abnormal accumulation of body fat with BMI >25 kg/m² and obesity as >30 kg/m.²⁻⁴ Steady increase in the percentage of obesity in adults and

children have been reported by WHO and NFHS studies. It is expected that by 2015 increase in the overweight population will be from 1.6 million to 2-3 billion and obesity from 400 million to 700 million.^{4,5} Prevalence of obesity is more in females than in males and is seen more in urban than in a rural population. In Indian scenario, even though the prevalence of obesity seems low with 2.1% (females 2.8% and males 1.3%) compared to international prevalence, 6 under nutrition will be an added risk.⁵

It has been demonstrated that obesity lower the resistance of aponeurotic scars by a study done to analyze the healing of abdominal wound in Wistar rats with induced obesity with high calorie diet.⁴ On analyzing 1112 potentially SSI and economic burden related Indian studies from EMBASE and Medline database, overall incidence of 10% wound infection has been noted. It also has been concluded that in India where health care expenses had to be met with, out of pocket, increase in hospital stay due to SSI will have additional financial burden to an already resource constrained set up. Reduction of SSI with proper interventional methods has been and has to be suggested to provide cash saving and improvement in health care efficiency.⁹

Many newer modalities are suggested to promote wound healing like gene therapy, use of specific growth factors, adhesion molecules, and inhibition of proteases.¹ Hypoglycemic drugs like insulin and oral hypoglycemic drugs are expected to promote wound healing as they have other properties like angiogenesis, increase in cellular proliferation, mineralization of tissue and decreased apoptosis in diabetic ulcers. Secretagogue like the glibenclamide, which was expected have this effect by stimulating insulin secretion has been reported to cause gastric ulceration instead.⁷ The wound promoting effect of metformin and acarbose on three models of wounds without causing hypoglycemia on euglycemic wistar rats have been demonstrated in a study.⁷

So far, drugs such as sibutramine and orlistat only have been suggested for weight loss in obesity. Evidence for weight reducing effect even in non-diabetic obese persons is inconclusive with insufficient evidence by the analysis of nine trials whereas evidenced effect has been reported by another 24 months placebo-controlled study done on non-diabetic African Americans with 1st degree diabetic relatives.^{8,9,12}

Not much trials on the effect of metformin on wound healing and weight reduction could be traced in India except for two ongoing trials in U.S.A, one to study the effect of insulin and metformin in wound healing and protein synthesis in burns patients (ClinicalTrials.gov identifier: NCT01666665) and another one to study the effect of metformin in non-diabetic obese pregnant women (ClinicalTrials.gov Identifier: NCT01273584).¹³ Metformin has got only anti-hyperglycemic property and not hypoglycemic property with other favorable effects like reduction of weight, promotion of wound healing by promoting angiogenesis, and decrease in total cholesterol and low density lipoproteins, and increase in

high-density lipoprotein. Commonly seen adverse effects are gastrointestinal tract disturbances. Very rarely lactic acidosis has been reported with the incidence of one in 100,000, that too not as definite isolated cause as they are seen also with concurrent sepsis, myocardial infarction, congestive cardiac failure and renal failure. Clearance is not altered up to the creatinine clearance of <50 ml/min. Low level of vitamin-B12 level is seen only on long-term therapy by inhibiting absorption.^{14,15}

As it is excreted as such and not protein bound, not much drug interactions are noticed except with cimetidine (not in use now) which competes with its renal excretion.

In this prospective placebo-controlled study done by us, overall SSI was noted in 7.4% of patients who underwent different elective clean gynecological (gynec) abdominal surgeries at the study site similar to a prospective observational study done in obstetrics and gynecology department between August-2011 and 2013 in Maharashtra, India, who has reported 6.1% of SSI as overall wound infection and higher 51.1% wound infection was noted only in emergency obstetric surgeries. Diabetes, anemia, and advanced age have been identified as added risk factors.¹⁶ Significant improvement in wound healing was observed in the group who received tablet metformin with SSI of 3.3% of patients compared to that of 3.3% in control group who received placebo, with significant $p=0.0087$ on the day of suture removal and 0.01 on the 15th post-operative day in our study (Figures 9-12 and Table 4). No significant difference could be identified on the 30th-day wound evaluation (Figures 13 and 14).

This shows that metformin is effective in early critical period of wound healing possibly by increasing angiogenesis through activation of AMPK in hepatocytes, cellular proliferation, and by its anti-oxidant property thereby preventing tissue damage and promote wound healing.¹⁰

SSI was reported to be of 14.33% incidence, which was seen to be increased with increase in pre-operative stay and in emergency surgeries in a 2-year prospective study done among 300 patients in surgical department of surgery at LN Medical College and JK Hospital, Bhopal. This has been postulated to be due to nosocomial infection by antibiotic-resistant organisms and contamination.¹⁷ in the same way prolongation of post-operative stay also may increase the chances of secondary infection by resistant organisms which can be more common in obese persons due to poor concentration of antibiotics at the site of infection due to many factors.

As improved wound healing has been obtained with metformin compared to the control group no prolonged hospital stay was necessary. However, in the control group two patients had to undergo resuturing and had to stay for more than 30 days for complete wound healing.

Meta-analysis of 57 potentially relevant studies done before to see the effect of metformin in weight reduction has

expressed insufficient non confirmatory reports in overweight non-diabetic persons giving an explanation that metformin might enhance effective weight loss with BMI >35 kg/m² as that is when insulin resistance, a potential mediator of weight gain and an inhibitor of weight loss becomes more prevalent and has suggested that observation for 1-year would provide more benefit.¹¹ On the comparison weight loss was obtained in overweight patients itself, that too in 30 days of drug administration in our study. This probably could be due to the inclusion of post-operative patients who might lose some weight due to many factors. However, significant $p=0.0001$ compared to that of 0.06 before metformin was seen on comparing with the control group on the analysis of BMI evidencing weight loss. It has also been reported that short-term modest weight loss is possible with metformin in patients on olanzapine (atypical antipsychotic) induced weight gain by a systematic review and Meta-analysis done on 12 randomized clinical trials.¹⁸ Metformin also has shown significant weight reduction by 7.5% in non-diabetic patients who gained more than 10% weight with atypical antipsychotic drugs comparable with sibutramin/ orlistat.¹⁹ Similarly, in our study significant weight reduction was noted in patients, who received metformin for a period of 30 days compared to control group (Figures 5 and 6, Table 2).

Further long-term study will be able to provide us definitive evidence of metformin's property of weight reduction which might be useful to prevent increased incidence of obesity-related medical disorders like diabetes, hypertension, hyperlipidemia, etc., this will open a new valuable benefit for metformin which has less side effects when specific and safe anti-obesity drug is still in search.

Not hypoglycemic effect of metformin also has been observed in our study. This is evidenced by observing non-statistical difference between metformin and placebo groups on analyzing postprandial blood sugar level before and after the trial (Figures 7 and 8, Table 3).

We consider the following factors as our limitations. We have included only planned well-prepared surgical patients in our study who did not had a much pre-operative stay. Hence, the evaluation of its effect in promoting wound healing in emergency, contaminated surgical procedures could not be done. Patients were followed up for 30 days only, so effect of metformin in promoting healing in deeper aponeurotic tissues, the resistance of which will be lowered in obesity with increased chance to develop incisional hernia in future could not be evaluated. The same restriction was felt in assessing the long-term effect of metformin in weight reduction.

CONCLUSION

Metformin a well-known oral anti-diabetic drug has been demonstrated to possess many other beneficial features like promotion of wound healing, weight reduction without causing hypoglycemia. Since this effect has been well-documented in diabetic patients with ulcers/in surgeries, it may be tried in non-

diabetic persons also having obesity as a risk factor. It could be a better option to reduce wound infection, prolonged post-operative stay which can lead to the acquisition of nosocomial infection by resistant organisms. Hence, unnecessary use of costlier antibiotics with more side effects could be avoided with reduction of the economical burden to the family and fear about the surgery and its complications. Development of organisms becoming resistant to available antibiotics also could be avoided. As metformin has shown weight reducing effect in our study, it can be thought of for reducing obesity and obesity related disorders like diabetes, hypertension etc., even in non-diabetic persons. As metformin was administered only for 30 days its long-term beneficial and adverse effects could not be evaluated even though no significant adverse drug reactions were noted in our study. Confirmation of these beneficial effects of metformin by further long-term studies including emergency surgeries for its wound healing effect and non-surgical persons to assess weight losing property among both males and females is suggested.

ACKNOWLEDGMENTS

Authors would like to thank the management of Sri Venkateshwaraa Medical college Hospital and Research Institute, Ariyur, Pondicherry for granting permission to do this trial in their institute and other faculties from the Department of Obstetrics and Gynecology for their co-operation in the follow-up of subjects. Assistance given by Miss. U. Kavitha tutor in the Department of Physiology at Sri Venkateshwaraa Medical College Hospital and Research Centre in statistical analysis is thankfully acknowledged.

Funding: This study was supported by Sri Venkateshwaraa Medical College Hospital where it was carried out

Conflict of interest: None declared

Ethical approval: Approved by the ICMR registered Institutional Ethics Committee.

REFERENCES

- Rashid M, Wai-Ping LF, Guul S, Enoch S. How to undertake research in wound healing. *Wounds UK*. 2009;5(3):76-85.
- Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89(3):219-29.
- NIH. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda (MD): National Institutes of Health; 1998. Downloaded 16 September 2012.
- Biondo-Simões Mde L, Zammar GR, Fernandes Rdos S, Biondo-Simões R, Mello FS, Noronha Ld Obesity and abdominal wound healing in rats. *Acta Cir Bras*. 2010;25(1):86-92.
- Kalra S, Unnikrishnan AG. Obesity in India weight of the nation. *J Nutr Neuroceuticals*. 2012;1(1):36-41. Available at <http://www.jmn.org>. Downloaded 24 November 2012.
- OECD. Obesity Update – 2012. Available at www.oecd.org/health/fitnotfat. Accessed 25 November 2014.
- Rock JA, Jones HW. Incisions for gynaecological surgery. *Telinde's Operative Gynaecology*. 10th Edition. Philadelphia: Lippincott Williams & Williams; 2008: 246-79.
- Rao Bandaru N, Rangarao A, Vijayanadaprasad K, Ramamoorthy DVS. A prospective study of post-operative wound infections in a teaching hospital of rural setup. *J Clin Diagn Res*. 2012;6 Suppl 7:1266-71.
- Tan JT, Coleman K, Norris S, Mapari J, Shastri S, Metz L. Surgical site infection in India: a systematic review of the incidence and economic burden. *Jhonson and Johnson medical Asia pacific*. Available at <http://www.htanalyts.com>. Accessed 22 May 2014.
- Ambrish C, Torgal SS, Patil PA, Malur PR, Hiremath SV. Influence of oral anti-diabetic agents on wound healing in euglycemic male wistar rats. *Pharmacol Online*. 2009;1:476-83.
- Levri KM, Allen Last ES, Yeh J, Ference J, Amico FD, Wilson SA. Metformin as treatment for overweight and obese adults: a systematic review. *Ann Fam Med* 2005;3(5):457-61. Available at <http://www.annfam.org>.
- Schuster D, Gaillard T, Rhinesmith S, Habash D, Osei K. Impact of metformin on glucose metabolism in non-diabetic, obese African Americans: a placebo-controlled, 24-month randomized study. *Diabetes Care*. 2004;27(11):2768-9.
- Available at <http://www.ClinicalTrials.gov>. Downloaded 05 March 2013.
- Davis SN. Insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas. *Goodman & Gilman's: the Pharmacological Basis of Therapeutics*. 11th Edition. New York: McGraw-Hill; 2006.
- Harvey RA, Champe PC, Mycek MJ. Insulin and oral hypoglycaemic drugs. In: Harvey RA, Champe PC, Mycek MJ, editors. *Pharmacology*. Hagerstown, Maryland: Lippincott Williams & Wilkins; 1996. pp. 261.
- Bhadauria AR, Hariharan C. Clinical study of post-operative wound infections in obstetrics and gynaecological surgeries in a tertiary care set up. *Int J Reprod Contracept Obstetr Gynecol*. 2013;2(4):631-8.
- Saxena A, Singh MP, Brahmchari S, Banerjee M. Surgical site infection among postoperative patients of tertiary care centre in Central India-a prospective study. *Asian J Biomed Pharm Sci*. 2013;3(17):41-4.
- Praharaj SK, Jana AK, Goyal N, Sinha VK. Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2011;71(3):377-82.
- Björkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. *J Psychopharmacol*. 2011;25(3):299-305.

doi: 10.5455/2319-2003.ijbcp20150441

Cite this article as: Meenal C, Saravanan R. Prospective single blind placebo-controlled randomized clinical trial to assess the efficacy and safety of metformin in promoting wound healing and weight reduction in non-diabetic overweight post-operative female patients. *Int J Basic Clin Pharmacol* 2015;4:363-70.