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Medicare Beneficiaries Utilize

Clinical Review of the Management

} Highlights }

Chemical Inhibition of JAK2 Mimics

Discovering Thoughts, Inventing Future

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A Clinical Review of the Management of Deep Vein Thrombosis

By Niketh Desouza & Mishal De Souza

University Private Practitioner, India

Abstract- Background: Deep vein thrombosis or DVT is a blood clot that forms within a deep vein typically in the lower leg or thigh, although they can also occur in other parts of the body. This thrombus/clot prevents the flow of blood in that vein leading to swelling and pain. When a part of the clot breaks off from the main thrombus it is known as an embolus. The most feared complication of DVT is pulmonary embolism, which is potentially life-threatening, in which the embolus travels to the lungs. Pulmonary embolism is thought to be one of the most common causes of preventable deaths in hospitals in the U.S. Other complications include post thrombotic syndrome which can affect up to 50% of patients who develop DVT. DVT is estimated to occur at an incidence of 1 per 1000 adults annually with an increased risk in males versus females and is most common in adults over the age of 60. Venous thromboembolism (VTE) is the term given to include both deep vein thrombosis as well as pulmonary embolism.

Aim: Provide an update on the proper management of DVT to reduce morbidity and mortality.

Methods: A review of online publications and medical journals.

Keywords: deep vein thrombosis, pulmonary embolism, venous thromboembolism.

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Niketh Desouza ^α & Mishal De Souza ^ο

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Aim: Provide an update on the proper management of DVT to reduce morbidity and mortality.

Methods: A review of online publications and medical journals.

Conclusion: The primary goal of treatment is to prevent the clot from enlarging, breaking off and causing a pulmonary embolism, preventing new clot formation and to prevent long-term complications such as post thrombotic syndrome. The mainstay of treatment is anticoagulation². Compression stockings should be worn to prevent the development of post thrombotic syndrome. Inferior vena cava filters can be used in patient where anticoagulation therapy is contraindicated. Other rarer forms of treatment include thrombolysis and thrombectomy.

Keywords: deep vein thrombosis, pulmonary embolism, venous thromboembolism.

I. INTRODUCTION

Deep vein thrombosis is an underdiagnosed, serious but preventable medical condition. It can happen to anybody which is why it is important to know about. Risk factors for developing DVT are inherited blood clotting disorders such as Factor V Leiden thrombophilia, prolonged bed rest, immobility, injury, surgery, hormone replacement therapy, birth control pills, cancer, heart failure, inflammatory bowel disease, prior history of DVT/PE, family history of DVT and age over 60³. The classical symptoms of DVT are warmth, pain, redness and swelling of the affected limb. A clinical diagnosis of DVT can be done using Well's score which indicates the clinical probability of having a DVT. However radiologic studies should be done to

confirm or rule out the diagnosis such as lower extremity Doppler studies, contrast venography and MRI/CT scanning. D-Dimer testing can be done to rule out DVT if the clinical probability for having one is low⁴. Once the diagnosis is made treatment can be initiated via the following techniques which we will discuss in detail below.

II. ANTICOAGULATION

The most common treatment of DVT is by using anticoagulants. This is due to the fact that they are non-invasive, treats up to 90% of patients, has a low risk of complications and is shown to reduce morbidity and mortality. Initial anticoagulation (i.e. 5-10 days) can be done with the following medications⁵:

- Low molecular weight heparin (subcutaneous): enoxaparin, dalteparin and tinzaparin.
- Factor Xa inhibitor (subcutaneous): fondaparinux.
- Unfractionated heparin (intravenous).
- Direct factor Xa inhibitors (oral pill): rivaroxaban and apixaban.

All patients should be assessed before and during anticoagulation therapy for their bleeding risk. Certain factors such as weight loss, renal failure and pregnancy may affect the half-life of the anticoagulant. The appropriate agent can be selected based on clinician's experience, patient's risk of bleeding, cost, patient's comorbidities and preference. Certain patients can be treated on an outpatient basis based on their preference and clinical condition. They should be hemodynamically stable, have a low risk of bleeding, normal kidney functions and have a system in place for the surveillance and administrations of the therapy⁶. After the initial therapy, long term anticoagulation should be initiated for a finite period of usually three to six months and may also extend up to twelve months in certain scenarios. Usually direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) are preferred because they can be taken orally and do not require monitoring. Warfarin can be used but required periodic checking of the patient's International normalised Ratio (INR). Long-term anticoagulation can be either subcutaneous or oral. Patient's preferences are particularly important in selecting a long term agent for anticoagulation. Full anticoagulation should be maintained during the transition period as this period has the highest risk of recurrent thrombosis. Once

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anticoagulation has been initiated and the patient's acute symptoms have resolved the patient should be encouraged to ambulate as tolerated.

III. TREATMENT RECOMMENDATIONS

1. Distal leg DVT:
 - Severe symptoms: Anticoagulation therapy for 3 months regardless of whether DVT was caused by a risk factor (surgery, hospitalization etc.) or was unprovoked.
 - Asymptomatic or mildly symptomatic: If no risk factors for clot extension (cancer, positive D-dimer, inpatient status) are present anticoagulation is not needed. Serial Doppler ultrasound examinations should be done over the next two weeks. If clot extension is noted anticoagulation therapy is begun for 3 months duration. If no extension is noted anticoagulation therapy is not required and no further testing is warranted.
2. Proximal leg DVT:
 - Should be treated with anticoagulation as outpatient if possible.
 - If DVT caused by surgery or mild risk factors (immobility, hospitalization or estrogen therapy) anticoagulation should be continued for 3 months.
 - If DVT was unprovoked, long term anticoagulation can be initiated if bleeding risk is not very high with physician reevaluating the patient every year or so.
3. Asymptomatic or incidentally found DVT:
 - Leg or pelvic DVT: anticoagulation therapy for same duration as discussed above.
 - Abdominal DVT (portal, splenic or mesenteric vein): anticoagulation therapy not required.
4. Cancer associated DVT:
 - Long term treatment with anticoagulation preferred unless bleeding risk very high. If bleeding risk is high then treatment for 3 months should be done. Low molecular weight heparin is preferred over warfarin.
5. Arm DVT (Axillary or proximal veins)
 - Upper extremity DVT not associated with central venous catheter: 3 months of anticoagulation is recommended.
 - Upper extremity DVT associated with a central venous catheter: Catheter should be left in place if functional and anticoagulation therapy continued as long as catheter is in place. Once catheter is removed anticoagulation should be continued for 3 more months⁷.
6. If a permanent risk factor is present such as thrombophilia is present or the patient has had two

or more episodes of DVT some experts recommend continuing anticoagulation therapy indefinitely.

IV. COMPLICATIONS OF ANTICOAGULATION

1. *Bleeding*: Patients can bleed more easily when taking anticoagulants such as heparin or warfarin. Patients should be counselled on medication dosing, strict compliance and methods to reduce the risk of bleeding such as avoiding contact sports and taking care while using sharp objects. Bleeding may develop in areas such as the nose or gums, excessive menstrual bleeding and bleeding in the urine/stool. Patients should also be told to avoid NSAID's and aspirin as these can increase their risk of bleeding. For cases of clinically significant bleeding reversal agents exist primarily for warfarin and heparin.
2. *Heparin induced thrombocytopenia (HIT)*: This occurs in patients receiving various forms of heparin. The platelet count begins to decrease 5-14 days after the initiation of heparin therapy. The patient can be clinically asymptomatic. There can be an extension of the previous clot or the formation of a new clot somewhere else in the body. Patients receiving heparin intravenously may have systemic reaction with fevers, chills, tachycardia and chest pain. Diagnosis involves the findings of thrombocytopenia, platelet 4 antibodies and heparin induced antiplatelet antibodies. The treatment of HIT consists of stopping all heparin products and using a direct thrombin inhibitor such as argatroban or lepirudin.
3. *Warfarin induced skin necrosis*: This occurs due to acquired/innate protein C deficiency in patients taking warfarin. It occurs between the third and tenth day of warfarin therapy. Symptoms range from pain and redness in the affected area initially to the formation of large bullae with eventual necrosis and eschar formation. It occurs in areas with subcutaneous fat such as breast, buttocks and thighs. Treatment includes discontinuing warfarin while initiating heparin, fresh frozen plasma and subcutaneous vitamin K. Care of the necrotic wound should be done with appropriate antibiotics, wound care and surgical interventions where necessary.

V. THROMBOLYTICS

Thrombolytic agents such as streptokinase and urokinase contain an enzyme which helps in the lysis of the already formed clot which will lead to normalised blood flow through the previously obstructed vein. They are usually administered directly to the clot through a catheter directly into the affected vein under imaging guidance. Systemic administration can also be done but this is not preferred as it has more bleeding complications and is a less targeted approach.

Thrombolytics help lower the incidence of post thrombotic syndrome and pulmonary embolism. Thrombolytics are administered in patients who present with an acute proximal DVT, having symptoms of less than 14 days duration, have a low risk of bleeding, good functional status and a life expectancy of more than 1 year⁸. Anticoagulation is preferred however due to the lower incidence of bleeding complications. The only real indication for thrombolytics are patients with an acute PE who are unstable (hypotension [systolic BP <90]) or have right ventricular dysfunction.

VI. IVC FILTER

These are used to decrease the risk of pulmonary embolism in a patient with contraindications to anticoagulation therapy. They prevent blood clots from travelling to the heart and lungs. Some of the contraindications to anticoagulation therapy include intracranial bleeding within 3 months, active bleeding, coagulation defects, severe thrombocytopenia and malignant hypertension⁹. Some of the risk factors for anticoagulation associated haemorrhage are increasing age, alcoholism, liver disease and chronic corticosteroid use. IVC filter may also be placed if there are recurrent pulmonary embolisms despite the use of anticoagulation, prophylaxis before surgery in patients with DVT, poor compliance with anticoagulants and right ventricular dysfunction with and enlarged right ventricle on echocardiography. In the last indication the disease is so severe that an IVC is placed because the next PE, however small it maybe, could be fatal. IVC filters are either permanent or non-permanent. Non-permanent filters can be retrieved or repositioned up to a certain amount of time. The procedure is done under local anaesthesia and the filters are introduced through the jugular or femoral vein via fluoroscopy guided or ultrasound guided techniques. In the long term however IVC filters can increase the risk of thrombus formation.

VII. THROBECTOMY

Before the introduction of intravenous heparin, open surgical thrombectomy was the only means to effectively treat an acute symptomatic DVT. However there were many disadvantages of this approach. During the procedure there can be significant blood loss. Retrombosis also occurs in many patients due to the damage to the venous endothelium by the previous clot itself or mechanically during the surgery. Postoperatively the patient would also be at risk for various wound complications¹⁰. Hence thrombectomy has a very limited role in the present day treatment of DVT.

VIII. PREVENTION OF DVT

Inpatients: High risk patients undergoing certain surgeries such as bone or cancer surgeries can be

prescribed anticoagulants to reduce the risk of DVT. Patients should be encouraged to ambulate as tolerated when they can. Compression stockings are recommended for immobilised patients or those who have a contraindication to anticoagulation. Patients should be counselled and thought leg exercises to prevent DVT.

Prolonged travel: There is a two to fourfold increased risk of developing DVT during prolonged travel (longer than 6-8 hours). Patients should be explained methods to decrease DVT formation such as leg exercises, wearing loose fitting clothing, moving around every hour or so and avoidance of sedatives and alcohol which can impair the patient's ability to move around.

Pregnancy: Pregnancy induces a hypercoagulable state which increases the risk of VTE by about five times. Pregnant women with homozygous factor V leiden and a family history of VTE were advised to begin therapy with low molecular weight heparin and either continue with LMWH or a vitamin K antagonist for 6 weeks after delivery. Warfarin is not used in pregnant women as it is a known teratogen.

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Do Medicare Beneficiaries Utilize Different Reports when Selecting a Health Care Plan

By Michael Castro, D.B.A.

Abstract- Medicare beneficiaries may encounter several limitations when trying to select a health care plan. These limitations may vary depending on the geographic location and other factors. Medicare beneficiaries may have a difficult experience when selecting a health care plan due to their level of education, income, age, sex, low rates of literacy, and the type of insurance (Greenwald et al., 2006). Medicare beneficiaries possess the ability to obtain data comparing the different health plans via booklets, the World Wide Web, and toll-free hotlines. The HFCA operates a website (<http://www.medicare.gov>) that includes a database that allows individuals to compare different plans on cost, benefits and quality.

The purpose of this paper was to determine whether Medicare recipients utilize different comparative reports before they select a health care plan. The two participating counties within this researcher consisted of Miami-Dade and Broward County's populations. The researcher utilized one research question in order to fulfill the objective of the paper. A total of 16 Medicare beneficiaries from both counties were interviewed.

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I. UTILIZATION OF REPORTS BY BROWARD COUNTY MEDICARE BENEFICIARIES

After interviewing participants from Miami-Dade County and Broward County, the researcher drew conclusions about whether they utilize different reports to compare the different health care plans. Five of the eight Broward County beneficiaries (3 females and 2 males) indicated that they did compare the health care plans available to them. However, only one participant actually utilized a quality report to compare the health care plans that were available. Age played a role. Older participants indicated that they compared the health care plans available to them. These results indicated that the female sample from Broward was more concerned with comparing the different health care plans available to them, in contrast to the male participants.

II. UTILIZATION OF REPORTS BY MIAMI-DADE COUNTY MEDICARE BENEFICIARIES

Five of the eight Miami-Dade County participants (3 females and 2 males) also compared the health care plans available to them or utilized quality reports. Age again also played a role. Older participants indicated that they compared the health care plans available to them. Two of the 5 participants who

compared reports stated that they did both (compared the health care plans available to them and utilized quality reports). Overall, these results demonstrate that females in Miami-Dade County were more prone to compare the health care plans available to them compared to male Medicare beneficiaries.

III. COMPARISON OF UTILIZATION OF REPORTS BY BROWARD COUNTY AND MIAMI-DADE COUNTY MEDICARE BENEFICIARIES

The researcher concluded that Broward County participants and Miami-Dade County participants were similar with respect to comparing health care plans and quality reports. For both Broward County and Miami-Dade County participants, age played a key role. These results indicated that the younger participants from both counties typically utilize comparative reports to compare the different health care plans available to them. Both counties had five participants who either compared the plans, utilized quality reports, or did both. Both counties had a total of three female participants and two male participants that compared the health care plans available to them. Such results indicated that the female populations from both counties had more of a concern regarding the plan into which they planned to enroll. The female samples from both counties usually compared and utilized quality reports at a higher probability in contrast to the male participants.

The only substantial difference on the question of utilizing reports pertained to the total number of participants who utilize quality reports. Only one Broward County beneficiary utilized quality reports when selecting a health care plan. This participant was a female. In contrast, two Miami-Dade County beneficiaries utilized quality reports, one female and one male. The researcher concluded that the samples from both counties used a similar approach when trying to select a health care plan.

IV. SUMMARY OF UTILIZING REPORTS WHEN SELECTING A MEDICARE PLAN AMONG BROWARD COUNTY AND MIAMI-DADE COUNTY SAMPLES

Results indicated that both of the samples had similar responses with respect to comparing health care plans and utilizing quality reports to make decisions

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about a Medicare plan. In both samples, five beneficiaries compared plans, utilized quality reports, or did both. In both samples of beneficiaries who compare reports, three were female and two were male. These results suggested that the female from both counties are more prone to compare the different health care plans available to them compared to males.

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Interventional Study to Find Out Effect of Yoga on Anxiety and Stress among MBBS Students

By Dr. Padmaja Kanchi

Terna Medical College & TSHRC, India

Abstract- Background: MBBS students are always under stress. Extremes of stress results in stress induced disorders and deteriorating performance. The present interventional study is conducted in III/I MBBS students to determine benefits of yoga on anxiety & stress. Such study among MBBS students of Terna Medical College was never done before.

Objectives: 1.To find out number of students suffering from Anxiety 2.To find out number of students suffering from Stress 3.To find out effect of Yoga on Anxiety & Stress.

Methodology: Questionnaire DASS21 for anxiety, stress in form of a Pre-test was administered to the students. Out of 102,96 students responded. It was considered as a pre-test. Accordingly, students were divided into anxious and non-anxious groups. 40% students came positive & were included in the study group. To the study group, intervention with 4 types of Pranayam namely, Bhastrika, Kapalabhati, Anulom- Vilom and Bhramari were given. Post- test was applied on the same group at the end of 8 weeks. Results were compared.

Keywords: pranayam, anxiety & stress, medical students.

GJMR-K Classification: NLMC Code: QT 104



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Interventional Study to Find Out Effect of Yoga on Anxiety and Stress among MBBS Students

Effect of Yoga on Anxiety & Stress

Dr. Padmaja Kanchi

Abstract- Background: MBBS students are always under stress. Extremes of stress results in stress induced disorders and deteriorating performance. The present interventional study is conducted in III/I MBBS students to determine benefits of yoga on anxiety & stress. Such study among MBBS students of Terna Medical College was never done before.

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Results: 71.1% students were suffering from mild level of anxiety, 26.3% had moderate and 2.6% students had severe type of anxiety. Post-test results show none of the student was suffering from anxiety after intervention. 73.7% students were suffering from mild level and 26.3% students were suffering from moderate level of stress. During post-test, all the students found to be within normal range of stress.

Conclusion: Yoga decreased stress & anxiety among study group. It is advised to continue to practice yoga regularly in future. Performing yogic exercises should be included as a part of a curriculum.

Keywords: pranayam, anxiety & stress, medical students.

I. INTRODUCTION

MBBS students are always under stress. A student under optimal stress does bring out his or her best, however extremes of stress can result in stress induced disorders and deteriorating performance.^[1] Can yoga be of benefit in stress induced effects in medical students? The present interventional study is conducted in III/I MBBS students to determine the benefits of yogic practices on anxiety & stress levels during their day to day life.

Such study of Yoga as an interventional measure to decrease stress and anxiety among IIIrd year MBBS students of Terna Medical College was never

done before. Hence the present study is conducted to find out the effect of Yogic practices on anxiety and stress.

a) **Aim:** To find out the effects of Yoga on Anxiety & Stress on IIIrd year MBBS students.

b) **Objective:**

1. To find out number of students suffering from Anxiety
2. To find out number of students suffering from Stress.

II. METHODOLOGY

a) **Study group:** Students of III/I batch **Inclusion criteria:** all Students of III/I batch

b) **Exclusion criteria:** Students who are not willing to participate

c) **Duration of the study:** 3 months

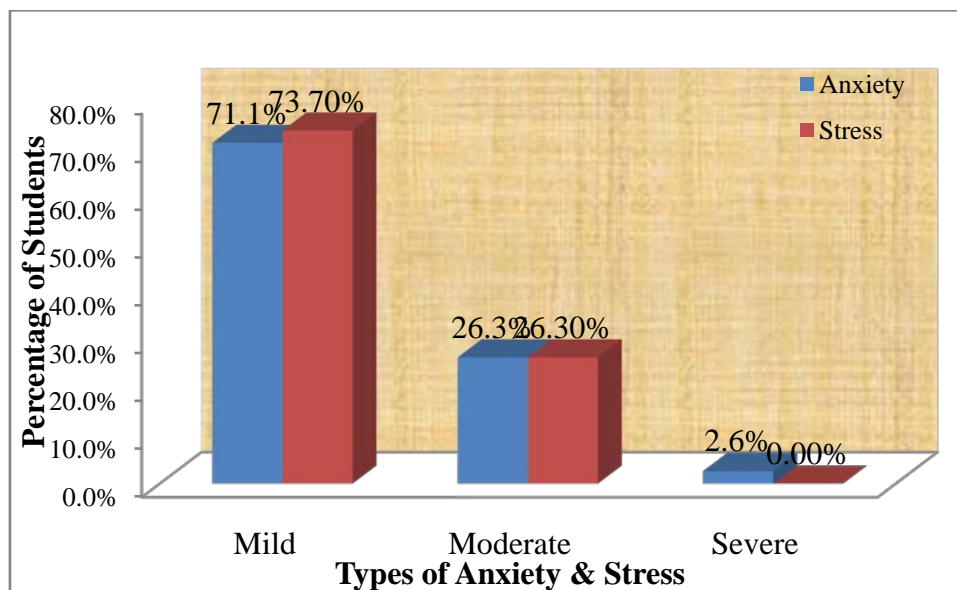
d) **Methodology:** A predesigned validated questionnaire [DASS 21-Depression Anxiety Stress Scale 21^[2]] was used to collect the information on, Anxiety, stress experienced by students of III/I batch. Identification data was collected separately.

- Scientific Research Society Approval & Ethics Committee Approval was taken.
- A pretested validated questionnaire DASS by Lovibond, S.H. & Lovibond P.F^[2] containing the questions on anxiety, stress in form of a Pre- test was administered to the batch of IIIrd year MBBS students. There were 102 students in the III/I MBBS batch. There were 7 questions each on depression, anxiety & stress. Total 21 questions hence DASS 21 is the name of the scale. Questions on anxiety & stress were analysed.
- As per the scoring on the scale, students were divided into anxious and non- anxious groups.
- To the anxious group, intervention with 4 types of Pranayam namely, Bhastrika, Kapalbhathi, Anulom-Vilom and Bhramari was given by trained teacher.^[3] 6 avaratans of each were conducted in each session. It took around 30 minutes to conduct a session. 3 such sessions per week were conducted and continued for 8 weeks. Students were asked to practice them regularly at home.

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- Post- test was applied on the same group at the end of the session.
- Results of Pre-test & post-test were compared.

III. RESULTS



Graph 3.1 : Students with Anxiety & Stress

Graph 3.1 shows that 71.1% students chosen from pre-test had mild anxiety, 26.3% students had moderate anxiety & 2.6% students had severe anxiety.

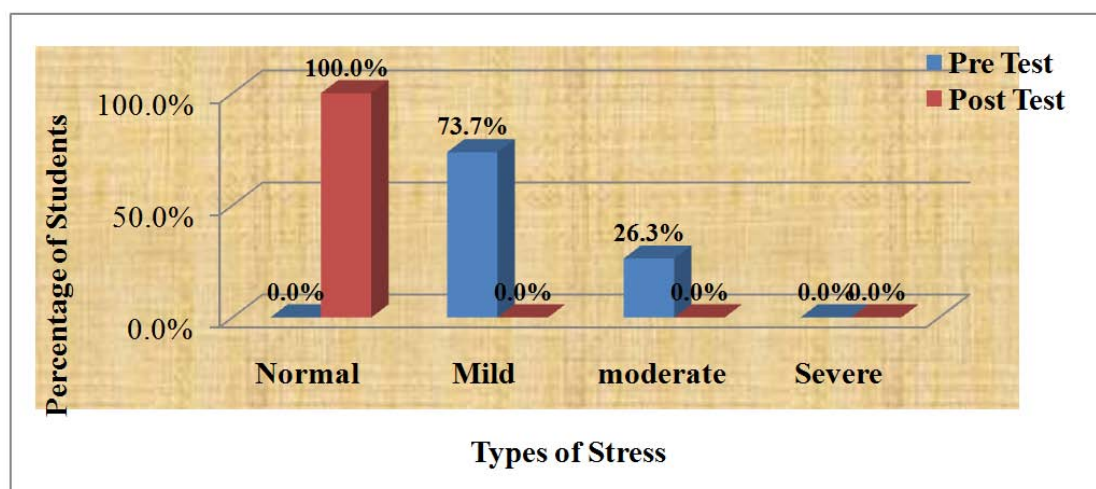
Also 73.7% students had mild stress, 26.3% students had moderate stress & none of them had severe level of stress.

Table 3.2 : Effect of Yoga on Anxiety

Types of Anxiety	Pre-Test		Post-Test	
	No.	%	No.	%
Normal	00	0.0	38	100
Mild	27	71.1	00	00
Moderate	10	26.3	00	00
Severe	01	2.6	00	00
Toal	38	100	38	100

$Z = -5.383$, $P = 0.000$ highly significant at 1% level as per Wilcoxon Signed Rank Test

Table 3.2 shows the results of pre-test which suggests that 71.1% (27) students who were suffering from mild level of anxiety, 26.3% (10) had moderate and 2.6% (1) students had severe type of anxiety as per the calculations of the scores. Post –test results show none of the student was suffering from any form of anxiety after yogic intervention. Since stress, anxiety cannot be measured the scale is non parametric. For non-parametric values, Wilcoxon Signed Rank Test is used. Windows Excel 2010 and SPSS version 21 is used for statistical analysis. It proved that Yoga played a significant role in decreasing anxiety. The results are statistically significant.



Graph 3.3 : Effect of Yoga on Stress

$Z = -5.280$, $P = 0.000$ highly significant at 1% level as per Wilcoxon Signed Rank Test

Graph 3.3 shows that 73.7% (28) students were suffering from mild level of stress and 26.3% (10) students had moderate level of stress. None of the student had severe form of stress during pre –test. During post-test, all the students found to be within normal range of stress showing the role of daily practice of Yoga in decreasing the stress among students. The results are highly significant as per the Wilcoxon Signed Rank Test.

IV. DISCUSSION

1. IIIrd MBBS students are under mental stress pertaining to their study and examinations.
2. Out of 96 students of IIIrd year MBBS, 39.58% (38) came to be positive for anxiety and stress as per DASS21. It was considered as a pre-test.
3. Yogic practices in form of Pranayama/ breathing exercises namely, Bhastrika, Kapalbhathi, Anulom-Vilom and Bhramari were given to the study group for 8 weeks.
4. At the end of the study, post –test was performed on the study group. The results of pre-test and post-test were compared.
5. results of pre-test suggests that 71.1% (27) students who were suffering from mild level of anxiety, 26.3% (10) had moderate and 2.6% (1) students had severe type of anxiety as per the calculations of the scores. Post–test results show none of the student was suffering from any form of anxiety after yogic intervention. Atezaz et al^[7] also found positive effect of pranayam on anxiety among medical students.
6. 73.7% (28) students were suffering from mild level of stress and 26.3% (10) students had moderate level of stress. None of the student had severe form of stress during pre –test. During post-test, all the students found to be within normal range of stress showing the role of daily practice of Yoga in

decreasing the stress among students. Jadhav et al^[4], Sharma et al^[5] & Li et al^[6] also found decrease of stress among medical students after yogic interventions in their respective studies. Malathi et al^[1] found the positive effects of Yoga in relieving the stress among medical students. Arvind et al^[9] also found significant difference after yogic practices in his study group of 1st year medical students. Chandla et al^[10] & Pal et al^[11] also found similar positive effects of Yoga in relieving stress among the participants.

V. CONCLUSION

III/I MBBS students were under stress & anxiety. Yoga in form of Pranayama or breathing exercises decreased stress & anxiety among them. It is advised to continue to practice the yoga regularly in future.

VI. RECOMMENDATIONS

- To implement it on all the batches of MBBS
- To make it a regular activity for all the batches every year.

VII. LIMITATIONS

1. Less time was available for the study.
2. Sample size was small.
3. Since students knew that the investigator is a faculty member & examiner, and the study was not anonymous, it may have created a bias.

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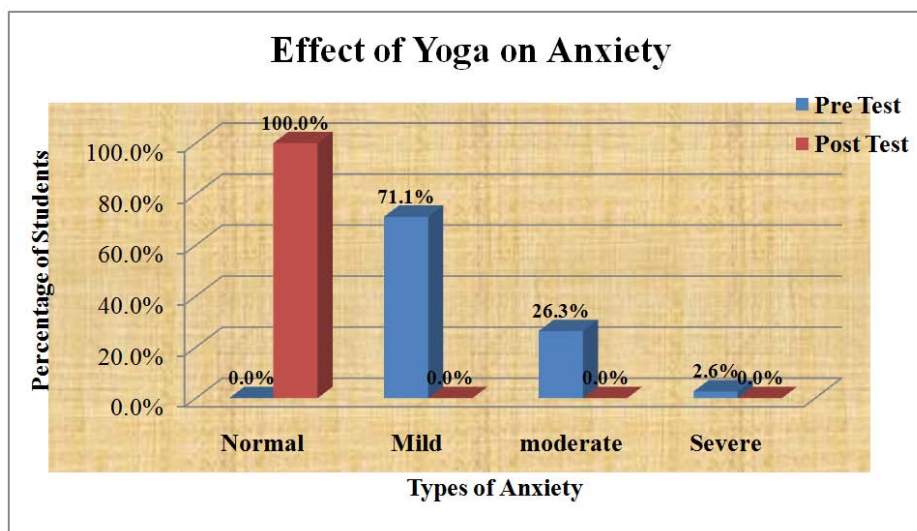
EXTRA

Table 3.1 : Students with Anxiety & Stress

No. of Students	Anxiety		Stress	
	No	Percentage	No	Percentage
Mild	27	71.1	28	73.7
Moderate	10	26.3	10	26.3
Severe	01	02.6	00	00.0
Total	38	100	38	100

III/1st MBBS students are under mental stress pertaining to their study and examinations.

Table 3.1 shows that out of 96 students of 3rd year MBBS, 39.58% (38) came to be positive for anxiety and stress as per DASS21. It was considered as a pre-test.



Graph 3.4

Same set of questions were used for pre-test and post-test. Post test was given to the 38 students who were found to be anxious and under stress as per the DASS scale. According to the scoring of the scale²

the students were divided into mild, moderate & Severe state of Anxiety.

Table 3.3 shows that results of pre-test suggests that 71.1% (27) students who were suffering from mild level of anxiety, 26.3% (10) had moderate and 2.6% (1) students had severe type of anxiety as per the calculations of the scores. Post –test results show none of the student was suffering from any form of anxiety after yogic intervention. Since stress, anxiety cannot be measured the scale is non parametric. For non – parametric values, Wilcoxon Signed Rank Test is used. Windows Excel 2010 and SPSS version 21 is used for

statistical analysis. It proved that Yoga played a significant role in decreasing anxiety. It is also statistically significant.

Jadhav et al^[4], Vivek Sharma et al^[5] also found subjective wellbeing & decrease of stress among medical students after yogic interventions. Li et al^[6] also found similar result in his review on stress & yoga. S.Y.Atezaz et al^[7] also found that for anxiety disorders, exercise and yoga have shown positive effects.

However Bhupendra Singh et al^[8] did not find significant reduction in anxiety level of his study group of high school students.

Table 3.5 : Effect of Yoga on Stress

Types of Stress	Pre Test		Post Test	
	No.	%	No.	%
Normal	00	00.00	38	100
Mild	28	73.70	00	00
moderate	10	26.30	00	00
Severe	00	00.00	00	00
Total	38	100.00	38	100



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Chemical Inhibition of JAK2 Mimics Genetic Ablation of Uterine Function of Leukemia Inhibitory Factor

By JrGang Cheng & Colin L. Stewart

National Cancer Institute at Frederick, United States

Abstract- Uterine receptivity needs to be synchronized with embryonic development, so the blastocyst stage of the embryo can implant. Leukemia Inhibitory Factor (LIF) is an essential factor for implantation, which is involved in the initiation of the window of implantation. However, the process by which the LIF signal pathway is transduced in the uterine luminal epithelium (LE) that leads to uterine receptivity is not completely elucidated. We tested the ability of cellular signaling inhibitors to disrupt uterine support of the embryo. Only Tyrphostin-AG490, an inhibitor of Jak2, can interfere with LIF signaling. Not only can AG490 reduce phosphorylated STAT3 levels in isolated LE, but it also ablated implantation when injected into uterine lumen. Furthermore, AG490 treatment in wild-type animals mimics the consequences of genetic ablation of LIF that results in free floating hatched embryos, which are unable to implant. Our results support the notion that Jak2 is the sole Janus kinase to mediate LIF activation in LE, and the signaling pathways of cytokines can serve as contraception targets.

Keywords: leukemia inhibitory factor (LIF), implantation, janus kinase 2 (Jak2), tyrphostin, AG490, DMSO, signal transduction, contraception.

GJMR-K Classification: NLMC Code: WP 440



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Chemical Inhibition of JAK2 Mimics Genetic Ablation of Uterine Function of Leukemia Inhibitory Factor

JrGang Cheng ^α & Colin L. Stewart ^σ

Abstract- Uterine receptivity needs to be synchronized with embryonic development, so the blastocyst stage of the embryo can implant. Leukemia Inhibitory Factor (LIF) is an essential factor for implantation, which is involved in the initiation of the window of implantation. However, the process by which the LIF signal pathway is transduced in the uterine luminal epithelium (LE) that leads to uterine receptivity is not completely elucidated. We tested the ability of cellular signaling inhibitors to disrupt uterine support of the embryo. Only Tyrphostin-AG490, an inhibitor of Jak2, can interfere with LIF signaling. Not only can AG490 reduce phosphorylated STAT3 levels in isolated LE, but it also ablated implantation when injected into uterine lumen. Furthermore, AG490 treatment in wild-type animals mimics the consequences of genetic ablation of LIF that results in free floating hatched embryos, which are unable to implant. Our results support the notion that Jak2 is the sole Janus kinase to mediate LIF activation in LE, and the signaling pathways of cytokines can serve as contraception targets.

Keywords: leukemia inhibitory factor (LIF), implantation, janus kinase 2 (Jak2), tyrphostin, AG490, DMSO, signal transduction, contraception.

I. INTRODUCTION

Embryonic implantation is a complex and dynamic physiological interaction between embryo and uterine tissues¹. Prior to implantation, the uterus shifts from a “refractory” phase to a “receptive” phase during which the embryos can attach and survive. This “window of implantation” can be characterized both hormonally and morphologically in the uterus², which is primarily regulated by the ovarian steroid hormones estrogen (E2) and progesterone (P4)³. In rodents, a rise in E2 levels on the 4th day of pregnancy (called nidatory estrogen) initiates the window of implantation and the onset of the receptive state⁴.

The effect of nidatory E2 is in fact mediated by LIF, as not only does E2 up-regulate LIF expression in the endometrial glands, but a single injection of LIF into

hormone-primed and ovariectomized mice can replace nidatory E2 efficiently, resulting in implantation⁵. Genetic ablation of LIF in the mice results in female infertility. Without LIF, female mice have normal mating and ovulation yet avoid both embryonic attachment and the initiation of decidualization resulting in implantation failure^{6,7}.

LIF binds to the heterodimeric LIF receptor/gp130 complex, which is expressed in the LE and to a lesser extent the glandular epithelium, but not in the stroma in the uterus⁸. LIF receptors recruit Janus kinase, Jak1, Jak2, Jak3 and TYK2, to initialize the signaling cascade. LIF's action in the uterus and activation of STAT3 is primarily centered on the LE, which in turn plays an obligatory role in interacting with the embryonic trophoblast in attachment and in controlling decidualization. Two major pathways, the Jak/STAT and ras/MAP kinase, have been identified as being activated by LIF binding to the LIFR/gp130 receptor complex in the uterine LE, embryonic stem cells, and neurons^{9,10,11}.

To understand the signaling pathways employed by LIF that are necessary for uterine receptivity, different inhibitors were tested to block LIF function. Only AG490, a Jak2 kinase inhibitor, is capable of blocking the formation of implantation nodules and yielding similar phenotypes as that of LIF null females⁶. To initialize the window of implantation in mice, LIF binds to LIFR/gp130, activates Jak2, which in turn phosphorylates STAT3. These results also suggest JAK/STAT signaling pathways may serve as potential contraceptive targets.

II. MATERIAL AND METHODS

Mice. LIF-deficient mice were maintained in an existing colony. Six to eight week female mice (B6C3F1) were purchased from Charles River Laboratories. Animal care was provided in accordance with the procedures outlined in the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 86-23, 1985). Surgical procedures were performed under tribromoethanol (Avertin) anesthesia according to institutional guidelines (NCI-Frederick ACUC Guidelines and Policies). All mice were naturally mated with the assumption that mating occurred around midnight, with day 1 of pregnancy being equivalent to the day with plug after mating (Day1

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p.c.) and the evening of Day4 being the time of implantation.

AG490 inhibition of LIF induced STAT3 phosphorylation. To confirm the inhibitory effect of AG490 on the Jak2/STAT3 pathway, levels of tyrosine phosphorylation of STAT3 were monitored. LE from late Day3 p.c. mice was purified and incubated with the indicated concentration of AG490 overnight at 37°C in serum-free Opti-MEM (Gibco-BRL/Invitrogen)¹². LIF (100ng/mL, Chemicon) was then added to activate the Jak2/STAT3 pathway with or without AG490 treatment for 30 min. LE was also purified from LIF null females, due to its lower p-Ty-STAT3 background, was treated with 1mM AG490 for 3 hours before LIF treatment. Treated LEs were collected by centrifugation, solubilized in SDS PAGE protein lysis buffer, with trituration using a 1 ml syringe with a 27-gauge needle. Protein extracts were collected, aliquoted and stored at -80°C. Control samples were handled in parallel with those of the treated group. Duplicated samples were prepared, run on the gel, and proteins transferred to a PVDF membrane for immunoblotting. Protein blotting was performed using standard procedures.

The primary antibodies were either polyclonal antibodies to P-Ty-STAT3, STAT3 (Cell Signaling Technology) or a monoclonal antibody to STAT3 (BD - Transduction Labs). Peroxidase conjugated anti-rabbit or anti-mouse IgG antibodies were used to detect binding. Specific bands were visualized with chemiluminescence (ECL plus, Amersham) by using a DCC camera (Stratagene) and exposure to film (Kodak). Signal quantification was performed by NIH-Image (v1.62). The responsiveness of LE to LIF was determined by the ratio between tyrosine phosphorylated STAT3 and total STAT3 signal, with respective antibodies on the same protein blot.

Inhibitors of signaling pathways. Inhibitors used to block signaling as follow: A. EGF signaling inhibitor Tyrphostin, AG 1478 (4-(3-Chlotoanilino)-6,7-dimethoxyquinazoline; (IC₅₀= 3 nM - EGFR). B. Jak2 kinase and EGF inhibitors, AG490 (Tyrphostin B42; α -Cyano-(3,4-dihydroxy)-N-Benzylcinamide; (IC₅₀=100 nM - EGFR; 10 μ M -Jak2)), and AG43 (Tyrphostin A64; α -Cyano-(4 - hydroxy) dihydropyrimidinone; as a negative control). C. Inhibitor of MEK1/2 U0126 (1,4-Diamino-2, 3-dicyano-1,4-bis(2-aminophenylthio) butadiene (IC₅₀= ~65 nM)). MEK inhibitor PD98059 (2'-Amino-3'-methoxyflavone (IC₅₀= 2 μ M-MEK1)), and as a negative control U0124 (1,4-Diamino-2,3-dicyano-1,4-bis (methylthio)butadiene; negative control). D. Inhibitor of p38 kinase, SB 203580 (4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl) 1H-imidazole (IC₅₀=~ 0.4 μ M-p38 MAPK; 4 μ M-PKB) and as a negative control SB202474 (4-Ethyl-2-(p-ethoxyphenyl)-5-(4'-pyridyl)-1H-imidazole). All reagents were from Calbiochem or Sigma. Reagents were dissolved in DMSO at a concentration of 20mg/mL

shortly before injection. With M.W. around 300 ~ 400 per mole, the molarity of each chemicals is between 50 ~ 67 mM.

Uterine injection. Mice were anaesthetized with 0.45mL of 1.2% Avertin. A surgical incision was made through the midline of the back, between the two ovaries with the mouse lying ventrally, and the right uterine horn was pulled from the peritoneal cavity via the fat-pad attached to the ovary. A solution of 20 μ L (0.4 mg) was injected into the uterine horn by either mouth pipette or capillary syringe near the oviduct on the morning of Day3 pc (or the time indicated). To reduce any "stress" the injection might cause, a limited amount of solution and only one uterine horn was injected; a procedure similar to embryo transfer. Even with the injection of 1 horn, solutions can have effect on the other horn by diffusion or circulation. After three days (or Day6 pc), the mouse was sacrificed and its uterus examined. The ovary from the unmanipulated uterine horn was removed to mark the injected side, and the uterus was isolated and stuck onto to a strip of 3mm filter paper (Whatman) to prevent it from contracting and curling. The straightened uterus was then measured with a ruler to determine the implantation sites distances from the cervix. If a uterus showed no signs of implantation, flushing was performed to confirm the presence or absence of hatched blastocysts. When blastocysts are present, animals were marked as blocking. Without a viable embryo mice are considered non-pregnant.

III. RESULTS

a) *Interfering Implantation*

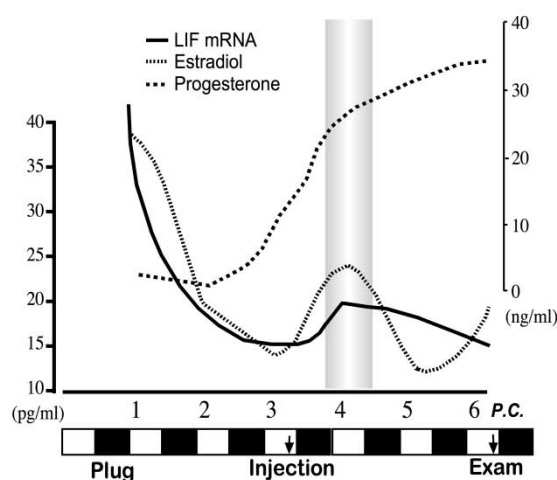
To address which signal transduction pathway (Jak/STAT or MAP kinase) is necessary for LIF function, selected blocking chemicals were injected into the mouse uterus and then verified as lacking of implantation nodules, which is a sure sign of implantation failure. These blockers fall into one of the four different signal pathway categories: JAK2, EGF, MAP kinase (Mek1/2), and p38 MAP kinase. All chemicals are prepared in the same manner, with 20 mg/ml in DMSO and 20 μ L solution was applied (0.5 mg/per animal). Based on the peak of LIF mRNA expression around Day4 pc (Shade area), injection was performed on Day3 (Figure 1A). For an easy and unambiguous way to determine whether embryos have implanted or not, Day6 uteri were examined instead of using Skyblue to mark sites of early decidualization. Uteri showing no sign of implantation were double-checked with flushing to verify the existence of embryos and rule out those animals without an embryo. Unmanipulated horns served as controls.

During the pilot experiment, it was noticed that the injected horn was more prone to be devoid of implantation than the control side without injection. As the common denominator is the physical injection and

the use of DMSO as the solvent, it was decided to check whether the injection itself or the solvent played any role in blocking embryo implantation. The same volume of 20 μ l common solvents, DMSO, DMF, Isopropanol and ethanol, was injected into one of the uterine horns of Day3 pc animals, and three days later, both horns were examined. All injected solvents had no effect on the unmanipulated (non-injected) horn (Figure 1B, shaded table), meaning that all the animals listed were pregnant and implantations occurred on that side. Thus, the results of various treatments are centered on the injected uterine horn. DMSO completely nullified the

sign of any implantation nodule in the injected horn. When the concentration of DMSO was diluted with PBS, its effect was reduced as well. DMF (dimethylformamide) exhibited no effect on implantation, thus the punch wound generated by the injection itself had no apparent effect. Injection with ethanol and isopropanol also did not block the formation of implantation nodules. However, the implantation nodules of the injected horn were reduced in size when compared with the unmanipulated side in the same animal, indicating a reduction or delaying decidualization response.

A



B

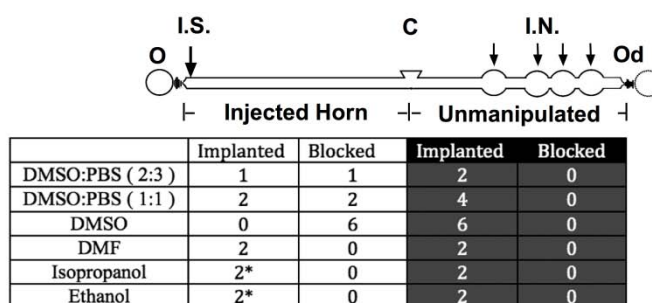


Figure 1 : Effects of various solvents on implantation nodules. A. Summary the change of ovarian hormones and LIF message RNA during early pregnancy. Shaded area marked naditory estrogen. Injection protocol of chemicals with day (white) and night (black) indicated (based on reference 3 & 5). B. Diagram and table show both horns (injected horn and unmanipulated side (Shade) with different solvents. Number in unmanipulated horns shown pregnant mouse (Shade area) that are the sum of implanted and blocked (Non-shade area). *Smaller implantation nodules found in the injected horn than in the unmanipulated horn of the same animal. I.S.: Injection site; O: Ovary; Od: Oviduct; C: Cervix, I.N.: Implantation Nodule. P.C.: post coitus

In order to distinguish the DMSO effect from the chemicals' blocking effect, the assumption was relied upon that DMSO effects are very local, affecting only the injected horn. Also, DMSO inhibition is very reproducible. From all the animals (86) injected with DMSO with or without inhibitors, there were only 8

DMSO-treated mice having implantation nodules in the injected horns, which coincided with the DMSO solution leaking during the injections. When DMSO was diluted with PBS, the blocking effect became inconsistent. In addition, most of the chemical inhibitors used are soluble in DMSO. Furthermore, compared the IC₅₀

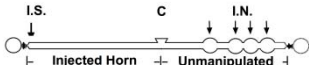
among chosen inhibitors, Jak2 inhibition by AG490 required higher concentration (10 μ M). For the above reasons, the blocking chemicals were dissolved in DMSO, injected into one horn, and the unmanipulated horn of the same animal was subsequently examined for either pregnancy or implantation failure. The injected horn was used as a successful injection control, in that a sufficient volume of chemicals was delivered.

The numbers of mice with various outcomes after being injected with different chemicals on the Day3 pc are shown (Figure 2A). Of the chemicals injected into the uterus, only tyrphostin AG490 achieved a blocking rate of nearly 50%. Both Mek1/2 blockers (U0126 and PB98059) showed no effects. Particularly, U0124, a negative control for U0126, showed a rare blocking effect as well as aberrant uterine morphology. Despite the small sample size (3), SB233580, a p38 MAP kinase blocker, also had no effect on forming implantation nodules. Tyrphostin AG490 inhibits both Jak2 (IC_{50} = 10 μ M; also Jak3, which is not expressed in LE) and EGF pathways (IC_{50} =100 nM). However, another tyrphostin AG1478 (IC_{50} =3 nM), which has a higher affinity and better specificity than AG490 with regard to the inhibition of EGF pathways, showed no effects on blocking implantation.

Interestingly, some unmanipulated uteri had implantation nodules close to the oviduct, which is always spaced out evenly along a whole horn, indicating the effect of the chemicals declines along the uterine horn away from the injection site. In addition, a single

intraperitoneal injection with DMSO/AG490 showed no similar effect. The mouse uterus is a tube-like structure and solution can diffuse to another horn more easily than through circulation. Thus, the effectiveness of a specific chemical can be exhibited as the "range of action" with the injection site as the point of origin. Subtracting the effect of DMSO, the effective distance (E.D.) of chemicals can then be defined as the distance between the cervix (where DMSO lost its efficacy) to the first implantation site (designated as the center of the implantation nodule) divided by the length of the uterine horn (Fig. 2B). With such assumptions, and assigning a complete blockage of implantation with the score of 1, quantitative measurements for each chemical's effectiveness can be computed. The measurement results elucidate that AG490 not only yield better than 50% of complete blocking, but also showed longer range of efficiency than that of other chemicals (Fig. 2C). The wide range of E.D. from individual animals after treatments prohibits drawing a conclusive result with any other specific chemical. There is also no change of appearance or size of implantation nodules. Nevertheless, as the data indicates, the Jak2 pathway is necessary for the continuation of pregnancy. The general morphology of an AG490 treated uterus deprived of embryonic implantation shows a Day3-like appearance without any signs of edema (Fig. 2B). When performing uterine flushing at Day6 p.c., hatched embryos can be collected similar to those from LIF null females⁶ (Fig. 2D).

A



	Injected Horn		Unmanipulated		
	Implanted	Blocked	Implanted	Blocked	No Embryo
DMSO	0	7	6	0	1
AG43	0	20	19	0	1
AG490	0	23	9	10	4
AG1478	0	15	10	0	5
U0126	0	14	13	0	0
U0124	0	10	8	1	2
PB98059	0	5	3	0	2
SB233580	0	4	2	0	2
SB202474	0	5	1	0	4

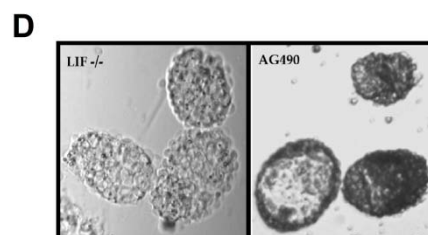
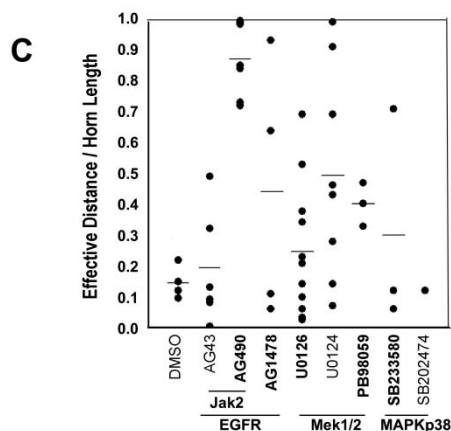
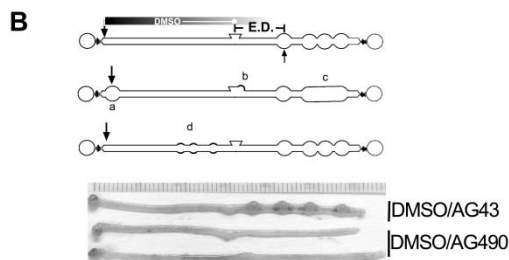


Figure 2 : Effects of chemical inhibitors in blocking of implantation. A. Diagram and table show both horns (injected home (Shade) and unmanipulated side with different chemicals. Number indicated all mouse, pregnant or non-

pregnant (No sign of implantation nodules, and blastocysts could not be recovered with flushing.) B. A diagram of experiment approaches to show the measure of Effective Distance (E.D. Cervix opening to the center of the first I.N), as well as the observed abnormality of swollen/implantation associated with certain injections, such as (a) injection site swollen, (b) epitopic nodules in cervix, (c) sausage-like swollen, and (d) various sizes of implantation nodules. Samples uteri show the disappearing of implantation nodules after injection with DMSO/AG490.C. The dot-plot of the relative location of the first implantation nodule away from injection site after injection. Animals without implantation nodules but with embryos are counted as 1. Chemicals in plain font are negative control for a respective signaling blocker. D. Hatched embryos collected from uterus treated with AG490 and from LIF null animal at Day6 p.c.

b) AG490 inhibits LIF Activation of STAT3

As chemicals delivered outside of the uterus showed neither DMSO nor AG490 effect, injection into the lumen of uterus is necessary for their actions. To confirm whether DMSO or AG490 can block the activation of LIF signaling pathways in the luminal epithelium, the purified LE was pre-treated with AG490, and then with LIF (100 ng/ml) for 30 min. Activation of p-STAT3 is normalized by the total STAT3 signals in the immunoblot (Fig. 3). Without AG490 (but with DMSO) pretreatment, LIF can increase the ratio between p-STAT3 / STAT3 around 3.7 fold, which is consistent with previous findings of using LE⁸. It also indicated that DMSO didn't seem to have any effect on LIF activation. With pretreatment of 0.1 mM AG490, the LIF effect was more than 50% reduced to 1.6 fold. With 1 mM AG490 pretreatment, the LIF activation of STAT3 was blocked completely in both WT and LIF null animals after incubation with AG490. Surprisingly, the basal level of p-STAT3 was reduced dramatically after AG490 treatments.

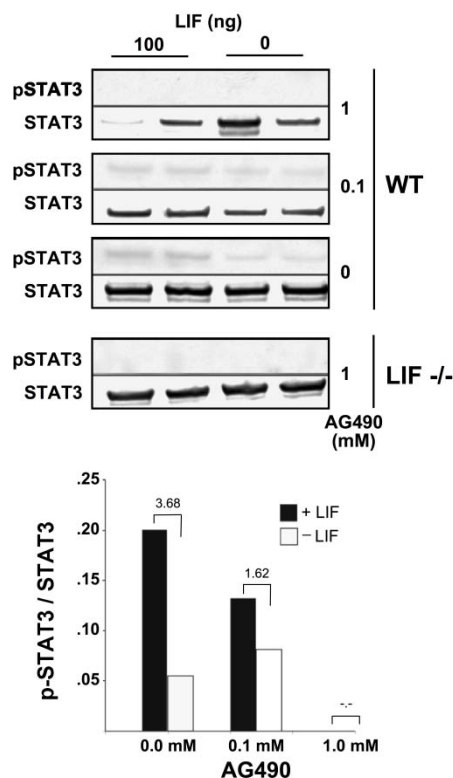


Figure 3 : AG490 can effectively block LIF induction of STAT3 tyrosine phosphorylation *in vitro*. The ratio of p-STAT3 / STAT3 was used to calculate the fold of

p-STAT3 induction after LIF treatment. Column shows that the higher the AG490 concentration, the lower the ability of LIF to induce p-tyr-STAT3 in LE.

c) Dose and Time Effects on AG490 Administration

Since AG490 can block pregnancy completely with only 50% efficiency as demonstrated in the previous injections (Figure 2), the subsequent question was whether or not injection of AG490 at different points in time during early pregnancy could alter its efficacy. Using similar approaches, AG490 was injected with two different concentrations into uterine horns at three different time points: the morning of Day2, the morning of Day3, and the morning of Day4. The results were summarized in Figure 4A. There are two major conclusions that can be drawn. First, injection on Day2 has better efficacy of stop pregnancy than injection on Day3, and there is no blocking effect when injection was done on Day4. Second, similar to the effect of AG490, which diminished abruptly on Day4, the effect of DMSO on the injected horn also disappeared on Day4. In fact, not only does Day4 injection of chemicals have no effect on inhibiting the formation of implantation nodules in the unmanipulated horns, but also only high concentrations of AG490 in DMSO can inhibit implantation in the injected horns, indicating a synergistic effect of both components. Using the values of Average Effective Distance (Fig. 2B), the change in AG490 effects on different days of injection can be more appreciated (Fig. 4B). The effects of DMSO are limited within injected horn. There is also a dramatic decrease in efficacy of low doses of AG490 (20 μ l of 2mg/ml) from Day2 to Day3 and again from Day3 to Day4. At high dosages of AG490 (20 μ l of 20 mg/ml), the change from Day2 to Day3 is not very significant. However, there is a dramatic reduction of efficacy when compared to AG490 effect on Day3 with Day4.

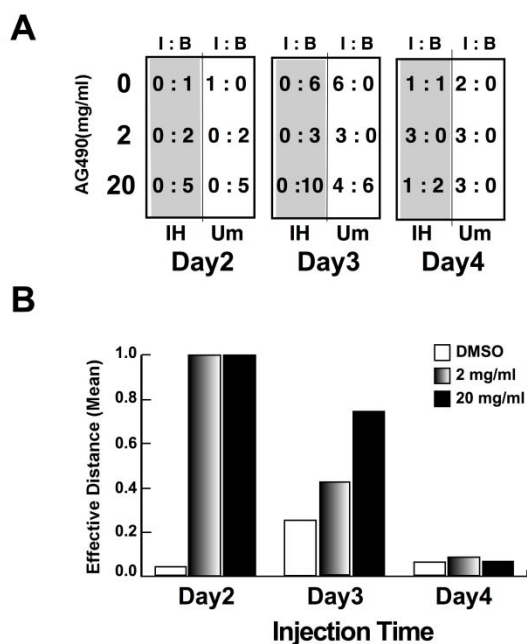


Figure 4 : Dose and temporal studies the effect of AG490 in blockage of embryo implantation. A. Number of uterine horns that are Implanted or Blocked (I:B) in either close to the injection site (IH = injected horn) or away from the injection site (Um, unmanipulated). The concentration of AG490 was from 0 (20 μ l DMSO only), 2 mg/ml (2 μ l stock solution with 18 μ l DMSO), and 20 mg/ml (20 μ l stock solution). B. Average effective range in the unmanipulated horns when AG490/DMSO was injected into Day2, Day3, and Day4 pc animals.

IV. DISCUSSION

Our results suggest that Jak2 has a unique and essential role in LIF signaling pathways during implantation, despite the fact that Jak1, and to a lesser extent Trk2, are also expressed in the LE (unpublished results)^{13,14}. It is surprising that blocking Jak2 with AG490 not only blocks STAT3 activation by LIF but also lowers the p-STAT3 basal levels. This indicates that not only Jak2 is the sole signal mediator of LIF in activating STAT3 but also suggests the presence of a strong counter-effect, likely from tyrosine phosphatases, against Jak2 by de-phosphorylating STAT3 in LE. A prior study has demonstrated that the nucleus translocation of STAT3 is associated with LIF null phenotype in the uterus⁹. When endogenous gp130 was replaced with mutated gp130 containing c-terminal truncation that had lost the STAT3 docking site, the homozygote female showed identical implantation deficiencies as that of a LIF null¹⁵. Using STAT3 membrane permeable oligo to sequester STAT3 binding in the uterus lumen may also lower implantation rates¹⁶. All of this data indicates the essential role of STAT3 in LIF signaling during implantation. Together with pharmacologic studies showing that Jak2 is necessary for STAT3 activation, indicating the uterine LIF binds to gp130 and LIFR,

utilizes Jak2, and activates STAT3 to initiate the uterine receptivity.

When evaluating the requirements of signal pathways in embryo implantation with specific blockers, no blocking effects are observed with MAP kinase P44/42, MAPK p38 and the EGFR. Since this experiment was designed to interfere with the function of LE during uterine preparation with specific timing and action sites (in lumen), it cannot be ruled out that the requirements of those pathways in earlier (proliferation) or later (LE apoptosis or decidualization) stages of implantation in LE are additionally contributory. Indeed, some aberrations have been observed after treatments, such as a sausage-like swelling that showed no spacing between implantation sites (DMF (1); U0124 (1); AG490 Day4-20 (2) animals). The implantation nodules also varied in size within the same horn (U0124 (3); PB98059 (1) animal). Furthermore, there was an implantation nodule-like swelling located in the cervix (U0126 (1) animal) (diagram shown in Fig. 2B). All these interesting observations indicate that those chemicals might interfere with different aspects of uterine-embryo interaction, such as implantation sites spacing, the progress of decidualization or embryo viabilities. However, as there is no consistent correlation between phenotype and a specific chemical but AG490, no further assay were employed to understand the mechanism of those abnormalities.

When injected earlier, even the lower concentrations of AG490 showed implantation blocking (2 mg/ml in Fig. 4), which is prior to naditory estrogen, likely indicating that AG490 has different yet unknown targets during Day2, there is an early requirement of Jak2, the effect of AG490 last, or has better efficacy before signal was activated. Based on the Day4 injection result that AG490 has no effect in blocking implantation, which is supposed to take place on Day4 evening, this finding supports that once LIF pathway is activated, it could not be reversed. Alternatively, a recent study linked Jak2 with Angiotension II-induced smooth muscle construct, thus changing blood pressure¹⁷. The uterus does experience edema and becomes rich in blood circulation prior to the implantation. However, the direct correlation between the blood flow and the implantation is not well established. It would be of interest to elucidate the unknown target of AG490 or Jak2 activator(s).

While using chemical blockers to dissect the essential signaling pathways for implantation, a surprising finding was that DMSO exhibited a reproducible effect in the inhibition of implantation despite a limited effective range. Time course studies indicated a narrower effective period than that of AG490. The gross feature of the uterine horn with injection is similar to that of Day2/3 pc uteri. However, unlike uterine horns treated with AG490, uterine flushing yielded zero or rarely hatched embryos. It is possible that DMSO is

toxic to the embryo, but its effect was attenuated along the uterus with dilution from the uterine fluid or infused into uterine tissue as implantation can occur in unmanipulated horn¹⁸. However on Day3 embryos still resided in the oviduct, so the DMSO did not have direct contact with the embryo. In addition, such explanation contradicts the observation that the blastocytes were spared, since similar to AG490, the effect of DMSO was completely gone on Day4 p.c. If DMSO is toxic to the embryo, it is likely before the forming of blastocysts. It is also possible that the effect of DMSO in reducing inflammation may also be a reason for blocking implantation, as the implantation process mimics an inflammation response¹⁹. However, the exact mechanism of interfering with either inflammation or implantation by DMSO is still unknown.

Jak2 is a prominent cancer target for leukemia treatment. Consequently, new generations of Jak2 inhibitors with better specificity and efficiency than AG490 will likely become readily available²⁰. Although the effect of AG490 blocking implantation was performed with the mouse, it may have general application for contraception in other animals. The surge of LIF around the implantation period has been seen in many other mammalian species, including humans^{9,21}. Thus, LIF signaling components can serve as good targets to block or enhance uterine receptivity for embryo implantation. Compared with inhibitory peptide and antibody blocking approaches^{17,22}, small chemicals can also provide advantages of both affordability and efficacy. In addition, both AG490 and DMSO treatments are reversible, as mice that went through the experiment without being sacrificed can have a normal pregnancy. With low toxicity (Acute oral toxicity (LD 50) = 14500mg/kg) and acute dermal toxicity (LD50) = 40000 mg/kg (Calbiochem Safety Data sheet), inexpensive cost, and a concentrated point of action (uterine lumen), DMSO, in conjunction with Jak2 inhibitors, which increase specificity and enhance range of action, could be a better alternative to hormone agonists and antagonists in achieving an effective and safe contraception.

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34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.



Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

- Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

- Use standard writing style including articles ("a", "the," etc.)
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- Align the primary line of each section
- Present your points in sound order
- Use present tense to report well accepted
- Use past tense to describe specific results
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- Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.



Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript-- must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

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The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
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- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.



- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
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Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently. You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.



Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
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- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.



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<i>Introduction</i>	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
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<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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