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# Contents

<b>Guidelines of publication in the Al-Esraa University College Journal for Medical Sciences.</b> .....	5
<b>Detection of Van B gene in Staphylococcus spp. Isolated from Food in Baghdad\Iraq</b> Zina A.S Hadi and Mohamed F. Al-Marjani .....	15
<b>Prevalence of Syphilis Disease Throughout Some Expatriate Workers in Iraq</b> Dr. Israa Mamdooh Subhi and Abdul-Raheem Yahya Mahdi.....	27
<b>Exposed Root Coverage After Soft Tissue Tumor Removal</b> <b>Using Two-Step Surgery Technique (Case Report)</b> Dr. Nafhat Almisk Amer Saleh and Dr. Yousif Laith Mahmood.....	37
<b>Nefopam Versus Ketorolac for Post-operative Pain Control in Cesarean Section</b> Shireen KH Almuradi, Ali H Mosleh, Ghison IK Al-Adal .....	55
<b>Betamethasone Gel Compared with Lidocaine Gel</b> <b>to Reduce Tracheal Tube Related Post-operative Airway Symptoms</b> Mustafa BS Atatfah, Ali H Mosleh, Ghisan IK Al-Adal.....	73



# Detection of Van B gene in Staphylococcus spp. Isolated from Food in Baghdad/Iraq

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**الكشف عن جين مقاومة الفانكومايسين في المكورات  
العنقودية المعزولة من الاغذية في بغداد - العراق**

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## Abstract

Seventy three *Staphylococcus* spp. isolates were recovered from bacterial sample included: poultry , foods , sewage and soil .The antibiotic susceptibility test to all environment isolate to Methicillin and Vancomycin were prepared , and the result showed that 39 *Staphylococcus* spp. isolates (53.42%) were resistant to Methicillin while 26 isolates (35.61%) were resistant to Vancomycin. The range of the minimum inhibitory concentration of Vancomycin were (2-512  $\mu\text{g/ml}$ ). Results of plasmid DNA extraction from Methicillin and Vancomycin resistant isolates showed that some isolates have one plasmid band. The results of the detection of Vancomycin resistance genes (van A and van B) showed the presence of van B gene in isolate No. ESf44 with MIC  $\geq 64 \mu\text{g/ml}$  that isolated from raw milk , while didn't notice the presence of van A gene in other isolates were resistant to Vancomycin that have been studied . This study was conducted to investigate the van B gene within the isolated MRSA strains from food, sewage water and soil in Baghdad.

**Keywords:** *Staphylococcus* spp. , Vancomycin resistance genes and Bacterial isolates .



## المستخلص

حصل على 73 عزلة تعود لجنس *Staphylococcus spp.* من عينات بيئية مختلفة شملت الدواجن والأغذية ومياه المجاري والتربة . اختبرت حساسية جميع العزلات البيئية لمضادى الميثيسيلين و الفانكوميسين و أظهرت النتائج أن 39 عزلة كانت مقاومة لمضاد الميثيسيلين و بنسبة % 53.42 في حين كانت 26 عزلة مقاومة لمضاد الفانكوميسين و بنسبة % 35.61 . حدد التركيز المثبط الأدنى (MIC) لمضاد الفانكوميسين للعزلات قيد الدراسة التي اظهرت مقاومة تجاه هذا المضاد في فحص الحساسية بطريقة انتشار الاقراص وقد بينت النتائج قيمة الـ MIC تراوحت ما بين 2-512 مايكرو غرام /مل. أظهرت نتائج ترحيل الدنا البلازميدي المستخلص من العزلات المقاومة لمضادى الميثيسيلين و الفانكوميسين احتواء بعض العزلات على حزمة بلازميدية واحدة . بينما العزلات الاخرى بينت نتائج التحري عن جينات مقاومة الفانكوميسين (van B و van A) وجود جين van B في العزلة رقم ESf44 المعزولة من الحليب الخام والتي كانت ذات MIC 64 مايكرو غرام /مل ولم يلحظ وجود van A في جميع العزلات المقاومة للفانكوميسين التي درست. هذه الدراسة ركزت على البحث عن جين المقاومة المعزولة من سلالات المقاومة للميثيسيلين من الاغذية ومياه المجاري والتربة في مدينة بغداد .

كلمات مفتاحية: *Staphylococcus spp.* , جينات مقاومة الفانكوميسين وعزلات

بكتيرية .



## Introduction

The *Staphylococcus* genus belongs to the family Staphylococcaceae, a common species of Commensal, which is present naturally in the nose and pharynx of the human. It may be pathogenic due to its rapid adaptations to the selective pressures of the host and the length of their survival on the surfaces, even if they are not alive (Al-camo,2001 ; Malachowa and Delo ,2010).

*Staphylococcus aureus* is one of the causes of food-borne diseases, which are usually associated with unprocessed raw milk produced from cows infected with *Staphylococcal mastitis* (Morgan,2008) and have an important role in the formation of taste and odor in some foods such as cheese and sausages (Pietti and Verschaegen, 2009).

Infectious bacteria may cause serious infections to newborns, children, elderly people, diabetic patients or persons suffer from cancer. These bacteria will cause dangerous injuries such as a deep skin injury or they may be carried out to the blood and other organs causing septicemia, failure for heart valves and other diseases (Benson, 2002).

The first strain of methicillin resistant *Staphylococcus aureus* was isolated in 1961, but it did not become a major problem until late 1970 and early 1980 and is believed to have an animal origin, i.e. it can be transmitted from animals to humans and vice versa (Yamamoto, *et al.*, 2010).

The risk of infection of these bacterial strains is their resistance to multiple antibiotics. Vancomycin is considered to be the best treatment to Methicillin-resistant *Staphylococcus aureus* (MRSA) strains, but due to the selection pressure, many strains of *Staphylococcus aureus* showed resistant to Vancomycin and Teicoplanin specifically in the MRSA strains, which



reduces the possible treatment options and increases the risk of bacterial infection (Hawkey, 2009)

The emergence of strains resistant to Vancomycin Resistant *Staphylococcus aureus* (VRSA) has become one of the major medical problems.

The first recorded appearance of these strains was in Michigan 2002, after which there were infections in many hospitals in the United States of America (Cui, *et al.*, 2003).

Several types of Vancomycin resistance have been described which were distinguished from each other, depending on the sequence of the synthetic gene of the Vancomycin-resistant Ligase (van A, van B, van C, van E and van G). These types were investigated by PCR technique.

PCR technique can identify between each of these genes and will thus determine the genotype as well as the phenotype of each gene, especially types van A and van B, which is known for their high levels of resistance to Vancomycin as well as their transmission between different bacterial species, making them dangerous sources for the spread of resistance between these species (Kolar, *et al.*, 2006).

This study aim to detection on methicillin and vancomycin resistance isolates from clinical samples (Al-Kindy hospital and Baghdad teaching hospital) and environmental samples (poultry, food, sewage and soil) increase vancomycin resistance isolate is alarm because this drug of choice for patient that suffered from multi-resistance of antibiotic and this alarm threat on community in Baghdad and this case must be need production new generation of antibiotic that treat VRSA and MRSA.

Therefore, this study was conducted to investigate the van B gene within the isolated MRSA strains from food sewage water and soil in Baghdad.



## Materials and Methods

### Bacterial Isolates

Various environmental samples, including poultry, food, sewage and soil, were collected to investigate the presence of *Staphylococcus* spp. in them.

The samples were cultured on blood-agar medium and then transferred to selective cultures. The isolates were identified on the basis of their microscopic and cultural characteristics on the Mannitol salty medium.

A number of biochemical tests were performed, also, including Coagulase, Urease and Catalase according to (Brooks, *et al.*, 2007).

### Sensitivity testing of Methicillin and Vancomycin

The sensitivity of isolates under study was tested for Methicillin (10 µg / ml) and Vancomycin (30 µg / ml) according to the method of the spread of tablets on Muler-Hinton solid culture, while resistance and sensitivity were determined based on the standard diameters method according to (CLSI,2011).

### Determination of the minimal inhibitory concentration (MIC) of

#### Vancomycin

The minimum inhibitory concentration (MIC) of Vancomycin was determined by the method of double-stranded dilution in the solid-root culture as indicated by (Merello, *et al.*, 2003).



## Plasmid DNA Isolation

Plasmid DNA was isolated from bacterial isolates resistant to methicillin and vancomycin by using several ready-made kits and according to the instructions of the Geneaid company. The results of the extraction were carried out using agarose gel (0.8%).

## Detection of van A and van B genes using PCR technique

The primers of gene van A and gene van B in the study isolates according to Table (1).

The solution was prepared according to the instructions of Certificate of Analysis (USA) Company with the use of sterile distilled water to obtain a concentration of 100 picomole /microliter.

**Table 1. The primers used in the study**

No.	Primer	Sequence of the primer			No. of bases bp	Conc. Pmol	Size $\mu$ D.w1	Size of the product Bp	Reference
		5'	→	3'					
1	vanA-F	GGGAAAACGACAATTGC			17	229900	2299	732	Dutka malen et al.(1995)
	R	GTACAATGCGGCCGTTA			17	252800	2528		
2	vanB-F	AAGCTATGCAAGAAGCCATG			20	63300	653	536	Elsayed et al. (2001); Jackson et al.(2004)
	R	CCGACAATCAAATCATCCTC			20	216200	21628		

Electrophoresis was carried out in the agarose gel. The gel was examined after the end of the run by exposure it to a source of ultraviolet radiation. The molecular size of the multiplied piece was determined by comparison with the location of the used run volumetric guide with the conjugated products.



## Results and Discussion

Out of 73 isolates of *Staphylococcus* spp. were obtained from various environmental samples including poultry, food, sewage and soil, these isolates were: 43 isolates from poultry, 15 isolates from sewage, 9 isolates from food and 6 isolates from soil.

The bacterial isolates were identified initially as *Staphylococcus* spp. according to their phenotype properties after were cultured on blood-agar at aerobic conditions, at 37 °C for 24 h. The size of the colonies were medium to large with a diameter of 1-3mm, regular smooth, convex, shiny dark with buttery edges.

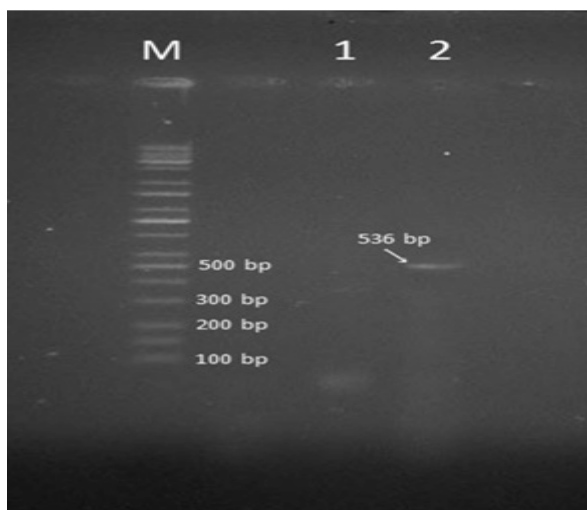
These colonies were surrounded by a narrow decomposition zone which corresponds with what mentioned by (Merello, *et al.*, 2006).

The sensitivity of all isolates was tested for Methicillin and Vancomycin, and the results showed that 39 isolates were resistant to Methicillin (53.42%), while 26 isolates were resistant to Vancomycin (35.61%).

The minimal inhibitory concentration (MIC) of Vancomycin was determined for the isolates as above with the value of MIC ranged 2-512 µg /ml.

*Staphylococcus* bacteria have the ability to acquire the van operon genes, and these acquired genes have the ability to migrate to other species such as *Enterococcus* spp., *Streptococcus* spp. and anaerobic bacilli (Guardabassi, *et al.*, 2005).

The results of the investigation of the van B gene showed that the isolate ESf44 from food has van B gene after running the replication product through agarose gel and compared it with the size of the evidence of approximately 536 base pairs (Fig. 1).



**Figure 1:** Electrical run of the PCR reaction product of *Staphylococcus* spp using the primaries of van B gene when dyed with Ethidium bromide and exposed to ultraviolet radiation. Gel concentration, voltages (75) volts for 45 minutes Path (M), Volumetric guide Path (1): isolate (ESF47) Path (2): Isolate (ESF44)

This study (Figure 1) is important because van B gene located on the plasmid and to improve that this gene located on it.

When compared with the results of (Elsayed, *et al.*, 2001), this isolate has the genotype and the phenotype of the gene van B, which means it resist Vancomycin and is sensitive to teicoplanin. A study conducted by (Guardabassi, *et al.*, 2005).

showed that the isolated strains are resist to Vancomycin and could contribute to the spread of this resistance to human-pathogenic bacteria isolates.

The presence of van A gene was not observed in all Vancomycin-resistant isolates that was studied.



Studies show that resistance genes can be rapidly transferred from one bacterial cell to another. Studies also show that MRSA and VRSA strains can be passed from field animals to humans. also transmitted through contaminated food and water, which shows the importance of surveys on the spread of resistance genes of methicillin and vancomycin in the environment

## Conclusion

Out of 73 *Staphylococcus* spp. isolates were recovered from environmental samples included: poultry , foods , sewage and soil .The antibiotic susceptibility test to all environment isolate to Methicillin and Vancomycin were done, one isolates that have MIC 64 mg/ml showed that Van B gene which isolated from raw milk. While Van A gene did not appear in any other isolates.

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# Prevalence of Syphilis Disease Throughout Some Expatriate Workers in Iraq

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بغداد \ العراق



## Abstract

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*. Syphilis has been a major infection in man throughout recorded history and has challenged clinicians with its many clinical manifestations. It can also spread to other people by kissing or close body contact. The disease begins with sores and then could spread to other parts of the body through its stages (primary, secondary, tertiary and latent stages) and can also reaches heart and nervous system and it may be fatal. The data on this disease in Iraq is limited and literatures are scanty. A total of 70 sera samples were collected from expatriates working in Iraq. Detection of syphilis antibodies were performed by non-treponemal tests and confirmed by treponemal tests (TPHA) using miniVIDAS device. Thirty percent of cases were positive for syphilis. We conclude that the syphilis cases are continuously increasing. A serious reaction must be taken immediately for assessing protective measures.

**Keywords: Syphilis, STIs, Migration, Expatriates, *Treponema pallidum***

## المستخلص

يعد مرض الزهري احد الإصابات المنقولة جنسياً والمسبب الرئيسي له البكتيريا اللولبية *Treponema pallidum*. هذا المرض من أهم الإصابات التي تحدث عند الإنسان وعلى مر التاريخ وقد تحدى الأطباء والعاملين في المجال الطبي بأعراضه السريرية العديدة. والزهري يمكن له الانتقال أيضاً من شخص إلى آخر عن طريق التقبيل أو الاحتكاك المباشر مع الشخص المصاب. ويبدأ هذا المرض بالظهور بشكل تقرحات والتي تنتشر إلى مناطق أخرى من الجسم حسب المراحل المختلفة (البدائية، الثانوية، الرباعية والكامنة) ويمكن أن تصل إلى القلب والجهاز العصبي المركزي وقد يكون قاتلاً. إن البيانات والمعلومات حول هذا المرض في العراق محدود والدراسات حوله غير كافية. في هذه الدراسة، تم جمع 70 عينة مصل الدم من العمالة الوافدين إلى العراق وتم تشخيص الاجسام المضادة للزهري باستخدام اختبارات غير مباشرة لل*Treponema* وتم تأكيدها باختبارات مباشرة (TPHA) باستخدام جهاز miniVIDAS. ثلاثون بالمائة منها كان ايجابيا لهذا المرض. نستنتج ان حالات مرض الزهري في تزايد مستمر. وبسبب هذه النسبة المرتفعة، يتوجب على السلطات المحلية التحرك بصورة جادة لتقييم وتحديد الطرق الوقائية للحد من انتشار هذا المرض.

الكلمات المفتاحية : الزهري، الامراض المنقولة جنسياً، هجرة، العمالة الوافدة،

*Treponema pallidum*



## Introduction

Syphilis is a sexually transmitted infection (STI) usually caused by the bacterium *Treponema pallidum* subspecies *pallidum*. Sexually transmitted infections are transmitted through chains of multiple sexual partnerships, and hence the configuration of these chains will influence the instant spread of STIs (La Fond and Lukehart, 2006).

South Africa has been ranked with the most highest levels of STIs and that is considered a major public health concern for their government, in 2007 the South African government introduced its first national strategic plan (NSP) for human immunodeficiency virus (HIV) and STIs and its latest plan for 2017–2022 includes STI interventions and targets (South African National AIDS Council, 2017). Sexually transmitted infections have been controlled by using standardized syndrome management guidelines approved since the mid-1990s (National Department of Health—Republic of South Africa, 2015). Those guidelines included the increased knowledge and awareness of reproductive and sexual health facilities such as encouragement of condom use, applying preventive activities, screening for syphilis during pregnancy, and carrying out national behavioral and social strategies for communication (Kularatne *et al.*, 2018).

Risk factors such as migration and mobility could increase high-risk sexual activities. Migration involves family separation, adaptation and a sense of obscurity leading to unsafe behavioral changes including early sexual relationships (Hesketh *et al.*, 2006), (Wang *et al.*, 2007), (Pandey *et al.*, 2008), (Roy *et al.*, 2010) and (Saggurti *et al.*, 2012).

The unsafe behaviors such as early sex with multiple partners with/without condom use will increase the spread of STIs (Abraído-Lanza



*et al.*, 2005 : 55) and (Adam *et al.*, 2005 : 5). Few studies have outlined the risk of these behaviors and their prevalence among domestic workers and migrants, those workers who associate with migrants should be carefully viewed to clarify their susceptibility to unsafe behaviors (De *et al.*, 2007), (Latkin *et al.*, 2010) and Al Rifai *et al.*, 2015).

Other important routes of syphilis transmission involve vertical transmission (from mother to fetus), accidental inoculation and blood transfusion. Sero-prevalence in developing countries range from 0.5 to 94% according to data on various age and gender groups (Aziz *et al.*, 2016) and (Newman *et al.*, 2016).

Venereal syphilis is uncommon in Iraq and other countries in the region. Moreover, to our knowledge, little data is available on the prevalence of this infection in Iraq. At regular basis, testing of expatriates for transmittable diseases is required. This usually involves screening for infectious agents such as Hepatitis B, HIV, tuberculosis, and syphilis for all jobs and all age groups.

Syphilis diagnosis depends on the detection of specific antibodies to *Treponema pallidum*. The pathogenesis starts by inoculation of treponemes onto mucosa or skin during sexual contact. They either directly penetrate mucous membranes or enter through breaches in skin during sexual activity. Attachment onto host cells and extracellular matrix is an essential step of infection. Once below the epithelium, the spirochetes multiply locally and disseminate through the lymphatic's and the bloodstream. The flexible, flat-wave shape of *T. pallidum* facilitates its penetration into tissues and vascular barriers throughout the body, along with its periplasmic movement apparatus which propels it forward via front-to-back swing coordinated in response to poorly understood chemotactic signals. Reaching and living



in distal skin mucosal sites will allow for subsequent transmission though it is not identified how *T. pallidum* benefits by invading deep visceral and musculoskeletal tissues (Radolf *et al.*, 2016).

Expatriates identified as positive for syphilis are normally treated and are tested periodically for antibody presence (Aziz *et al.*, 2016). Iraq after 2003 witnessed a new era, and a radical political and economic shift aims to restore what was destroyed by successive wars, according to the mechanisms of transition to market system under the new constitution to opening the doors to foreign investment, and allowing investors in the use of non-Iraqi labor, as also allowed for expatriates to enter Iraq, and conduct business in economic activities in Iraq (Jamal and Hayder, 2018).

While information about STIs in Islamic countries is limited, no accurate / limited data is available on the prevalence and epidemiology of syphilis in Iraq. According to the latest WHO data published in 2017 syphilis death in Iraq reached to 166 or 0.09% of the total death. Thus, in the present study, we aimed to determine the prevalence and epidemiology of syphilis among expatriate workers applying for various jobs in Baghdad, Iraq.

## **Aim of the study**

To detect the prevalence of syphilis diseases among some expatriates.

## **Materials and methods**

A total of 70 blood samples were collected from patients of Kenyan, Bengali and Ethiopian nationalities admitted to a private labs in Baghdad, Iraq between August and December 2018.





Blood was centrifuged at 2500 rpm for 10 minutes and supernatant (serum) was taken to carry on the required tests. Detection of specific antibodies to syphilis was performed by both non-treponemal test using CTK Syphilis kit (USA), according to the manufacturer's recommendations and results were confirmed by treponemal tests *Treponema pallidum* hemagglutination (TPHA) using miniVIDAS device (Markos *et al.*, 2018).

## Results

Out of 70 samples, the positive cases were seen in 21 cases (30%) while the negative cases were 49 (70%) as seen in Table 1. The gender of the positive cases included males 15 (71%) and females 6 (29%).

**Table 1 Total and Percentages of Syphilis Disease**

Total Number of cases	No. positive cases	No. negative cases	Male	Female
70	21 (30%)	49 (70%)	15 (71%)	6 (29%)

## Discussion

The number of expatriates arriving to Iraq from different countries with sexual infections showed how much dangerous the spread of these infections. In this research, the percentage of positive syphilis patients admitted to a private labs in Baghdad was 30% and this is a high percentage and requires immediate action to be taken to limit their spread. This information about spread of syphilis is limited in Iraq and since they are known to work as janitors in schools, colleges, shopping centers, baby sitters, and coffee shops, more research should be conducted to assess protective measures and limit the spread of STIs.



A similar study in UAE has showed for the first time that the infection rate with *T. pallidum* was 51% (Aziz *et al.*, 2016). The highest rate of infection was observed in individuals from India 32/105 (30.5%), followed by Pakistan 27/105 (25.7%) and Bangladesh 16/105 (15.2%) (Makroo *et al.*, 2015).

An Egyptian study on the prevalence of syphilis antibodies in blood donors reported an overall prevalence of 13% (Hussein, 2014).

Due to lack of awareness and knowledge, there is always a high risk factor for exposure to infectious agents such as *T. pallidum* and HIV since the majority of the people tested come from low socioeconomic states of their original countries and might be uneducated (Aziz *et al.*, 2016).

In this study, there was some difficulties in identifying whether these expatriates arrived recently to the country or have been screened again for the STIs. Furthermore, there is an urgent need for further studies within the native Iraqi population before any conclusion can be made about expatriates transmitting STIs to the local community.

This study also emphasize the necessity of preventive measure for STIs, screening, diagnosis, and treatment. Moreover, it also gives attention to the strict follow up on the treatment regimens for people identified as syphilis positive to prevent spread of the disease. It is also important to educate the workers how to deal with such cases in their gatherings since most of them come from low self-esteem societies.

The present study provides for the first time the epidemiology and rate of infection with *T. pallidum* among expatriates in Iraq, providing policy makers with data which can be used to develop appropriate prevention and control strategies.



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# Exposed Root Coverage After Soft Tissue Tumor Removal Using Two-Step Surgery Technique (Case Report)

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تغطية الجذر المكشوف بعد إزالة ورم الأنسجة الرخوة  
باستخدام تقنية الجراحة ذات الخطواتين (تقرير حالة)

نفحات المسك عامر صالح و د. يوسف ليث محمود

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## **Abstract**

When intra-oral lesions in soft tissue reach the gingival margin, they can produce aesthetic problems during its presence and after its removal. Periodontal plastic surgery can be used in the correction of the gingival contour using many different techniques. This is a case report of a peripheral ossifying fibroma removal in the interproximal area between maxillary left central and lateral incisors in addition to the coverage of the exposed root of the affected area by using two surgical stages: first one is keratinized gingival tissue augmentation surgery with free gingival graft concurrent with removal of the lesion and, in a second stage, root coverage by performing coronally repositioned flap technique with a follow-up of one year. The initial results achieved, which were root coverage of 100% after 6 months, promoted an adequate gingival contour and prevented the development of a mucogingival defect or a root exposure with its functional and aesthetic consequences. After one year, the results showed long term success of the techniques, where the margin remained stable with complete root coverage and tissues were stable and normal in color.

**Keywords: Mouth, Root, Tissue tumor and Two-step surgery technique.**



## المستخلص

عندما تصاب الأنسجة الرخوة داخل الفم و تصل الى حافات اللثة ، فإنها يمكن أن تسبب مشاكل جمالية أثناء وجودها وبعد إزالتها. يمكن اعتماد جراحة اللثة التجميلية في تصحيح محيط اللثة باستخدام العديد من التقنيات المعروفة عالمياً. هذا تقرير حالة لإزالة الورم الليفي المتعظم المحيطي في المنطقة البينية بين القواطع العلوية اليسرى الوسطى والجانبية بالإضافة إلى تغطية الجذر المكشوف للمنطقة المصابة باستخدام مرحلتين جراحيتين: الأولى هي جراحة تكبير أنسجة اللثة القرنية باستخدام التطعيم اللثوي الحر المتزامن مع إزالة الآفة ، وفي المرحلة الثانية ، تغطية الجذر عن طريق إجراء تقنية السديلة التاجية المعاد وضعها مع متابعة لمدة عام واحد. النتائج الأولية التي تم تحقيقها ، والتي كانت تغطية جذرية بنسبة 100 ٪ بعد 6 أشهر ، عززت محيط اللثة المناسب ومنع تطور عيب اللثة المخاطية أو التعرض للجذر مع عواقبه الوظيفية والجمالية. بعد عام واحد ، أظهرت النتائج نجاحاً طويلاً المدى للتقنيات ، حيث ظل الهامش مستقرًا مع تغطية جذر كاملة وكانت الأنسجة مستقرة وطبيعية اللون.

**الكلمات المفتاحية : الفم, الجذر, ورم نسيجي و تقنية جراحية ذو خطوتين**



## Introduction

Peripheral ossifying fibroma is characterized as a hyperplastic gingival mass with calcified foci, supposedly formed by metaplastic bone (Kaplan et al, 2008). The bone is found in the middle of a non encapsulated proliferation of bulky benign fibroblasts. The lesion may be derived from the connective tissue of the submucosa or the periodontal ligament. There is a tendency for the presence of inflammatory cells in the outer portion of the lesion. The surface often shows ulcerated areas and rarely causes erosion of adjacent bone (de Matos *et al.*, 2014).

The peripheral ossifying fibroma, also known as ossifying fibroid epulis, ossifying fibroma with calcification, peripheral cement-ossifying fibroma, and calcifying fibroblastic granuloma, is also part of the nonneoplastic proliferative lesions (Buchner *et al.*, 2010).

It is considered a reactive lesion, although its pathogenesis is uncertain. This pathology appears as a tissue response to chronic long term stimulation. This can occur when the gum tissue reacts in response to irritants such as biofilm and subgingival calculus, misplaced teeth, restorations over contour, ill-fitting dentures, root remnants, poorly preserved teeth, foreign bodies in the gingival sulcus, and orthodontic treatment. There is a mesenchymal cell of the periodontal ligament and/or cementum proliferation that are induced by such local irritants. The displacement and mobility of the teeth are uncommon, unless preexisting periodontal disease is found or in cases where the teeth are erupting (Choudary *et al.*, 2014)

Clinically, it appears as a nodular lesion, exophytic, pedunculated in most cases, of streaky reddish coloration of whitish areas, or similar in color to the adjacent mucosa. It features bright and opaque surface in some spots





and irregular texture and contours, with slow growth rate, although it is able to reach large dimensions (Buchner & Hansen, 1987)

This injury is located, preferably, in the attached gingiva or exceptionally in the free marginal gingiva. There is a predilection for the anterior portion of the jaws (Choudary *et al.*, 2014 ; Buchner & Hansen, 1987). Sometimes it extends throughout the teeth, involving both the facial and the lingual gum (Choudary, *et al.*, 2014). There may be bleeding when the lesion is touched or even spontaneously, but mainly when it is constantly traumatized. In most cases the patient is asymptomatic (Buchner *et al.*, 2010 ; Buchner & Hansen, 1987).

Women are affected more often than men by this injury, which occurs predominantly in the second decade of life (Choudary *et al.*, 2014 ; Buchner & Hansen, 1987), and in Caucasians (Buchner *et al.*, 2010 ; Buchner & Hansen, 1987), accounting for 9.6% of gingival lesions (Walters *et al.*, 2001)

Other injuries that have similar clinical appearance to peripheral ossifying fibroma include pyogenic granuloma, peripheral giant cells granuloma, fibrous hyperplasia, and giant cell fibroma (Kaplan *et al.*, 2008) (Buchner & Hansen, 1987). All these injuries are caused by low intensity chronic irritation.

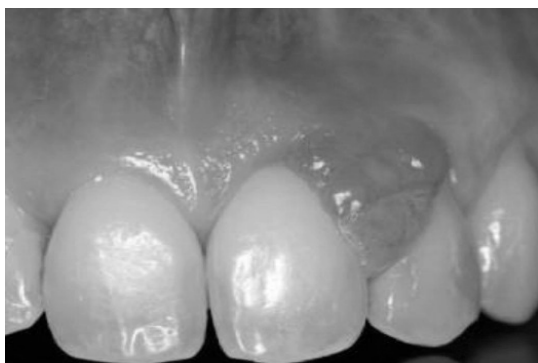
The treatment of choice is local excision, which should include the periodontal ligament, if it is also involved. Furthermore, one should remove any identifiable causative agent (Kaplan *et al.*, 2008) (Choudary *et al.*, 2014 ; Walters *et al.*, 2001). There may be recurrence (Choudary *et al.*, 2014) (Walters *et al.*, 2001), but its risk is diminished if the excision is performed under the periosteum (de Matos *et al.*, 2014 ; Walters *et al.*, 2001).

The literature provides several ways of removing the lesion, such as the use of Nd:YAG laser or conventional surgery with scalpel (Mergoni *et al.*, 2015).

The excisional biopsy necessary for this case is aggressive and may result in a severe periodontal defect because it can involve the entire keratinized adjacent tissue creating a similar Class I or II Miller defect. When trying to recreate the excised tissue, several approaches can effectively increase the present tissue, such as a graft of the subepithelial connective tissue, free gingival graft, derivatives of the enamel matrix, guided tissue regeneration, and coronal or lateral advanced flaps. The choice of technique will depend on the amount of tissue to be recreated (Hutton *et al.*, 2016).

## Case Report

A 31 years old female patient was attending to Al-Esraa university college/department of dentistry/periodontology clinics complaining of a lesion located between upper left central and lateral incisor teeth, painless but conflicts the esthetics of her smile (Figure 1a & 1b).



(Figure 1b)



(Figure 1a)



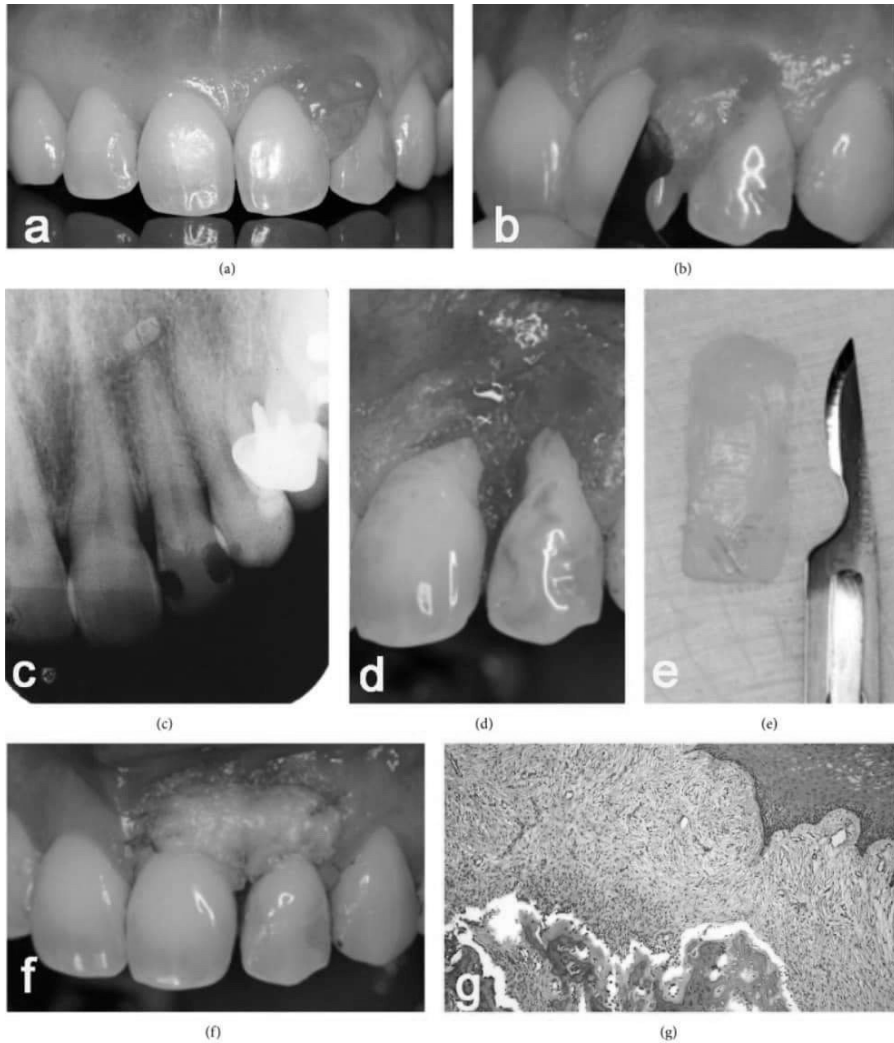
Intraoral physical examination showed an injury inserted in the interproximal gingiva, measuring  $12 \times 9 \times 5$  mm on the labial surface and  $7 \times 5 \times 3$  mm in the palatal surface, exophytic and nodular. The radiographical examination showed no related changes (Figure 2).



Surgical techniques were performed as follows:

after local anesthesia with 2% Lidocaine with epinephrine at a concentration of 1 : 100,000, the excision of the lesion was proceeded with a 15C scalpel blade (Figure 3e), removing all the gingival and periodontal tissue involved, followed by scaling and root planning of the same teeth (Figure 3d).

After excision of the lesion, the removal of a free gingival graft from the palate was performed, which was placed in the exposed tissue area to recreate the band of keratinized tissue lost as a result of the lesion itself and its excision. The graft was taken from the palate and its format was similar to the open area of the receiving tissue (Figure 3e). The apical and coronal dimension and thickness were measured so that it could be suitable and uniform. The graft was sutured along its entire length (Figure 3f). Digital pressure was performed with saline moistened gauze to remove any blood clot and maintain the graft in intimate contact with the recipient area.



The material obtained from excisional biopsy was sent for pathological analysis. Histologically, the lesion showed an intact squamous epithelium and, in the lamina, propria a highly cellular component of fibroblasts was observed with central area of calcification, setting the diagnosis for peripheral ossifying fibroma (Figure 3g).

Three months after the procedure (Figure 4), a second surgical procedure was performed in order to cover the exposed root of upper lateral incisor tooth.



(Figure 4)

The biomechanical preparation of the surface of the root was accomplished with scaling and root planning (Figure 3d) and application of EDTA 24% neutral pH (Pref-Gel®, Straumann). The coronally advanced flap technique, described by de Sanctis and Zucchelli (2007), was the selected technique: two horizontal beveled incisions were performed, mesial and distal to the recession, located at one end of the anatomical papillae and equal to the height of the recession plus 1 mm; two oblique incisions, slightly divergent, starting at the end of the two horizontal incisions and extending to the alveolar mucosa (Figure 5).



(Figure 5)

The coronal portion of the flap is partially divided, while the portion apical to the recession is a full thickness flap, exposing 3-4 mm of bone (Figure 6).



(Figure 6)

The relaxing vertical incisions are elevated in partial thickness. Apical bone exposure is held in the partial thickness flap, ending where it is possible to passively move the flap in coronal direction and coronally in the cementum-enamel junction. At this time simple sutures are performed throughout the flap (Figure 7).



(Figure 7)



After the initial results were achieved, root coverage of 100% was obtained after 6 months (Figure 8), and suitable gingival contour was promoted which prevented the development of a mucogingival defect or root exposure with its functional and aesthetic consequences.



**(Figure 8)**

After one year (Figure 9) the margin remained at its initial position, with no relapse in the exhibition of the cementum-enamel junction; and tissues were stable and characterized by color harmony.



**(Figure 9)**



## Discussion

When the gingiva is subjected to local chronic irritation or trauma reacts with localized hyperplasia that can be composed of mature collagen, cellular fibroblastic tissue, mineralized tissue, endothelial tissue, and multinucleated giant cells (Buchner *et al.*, 2010). Clinical and histological examinations are essential to achieve a diagnosis and ensure a complete treatment plan, which, in this case, included not only the removal of the lesion, but also reconstruction of the anterior esthetic zone impaired when performing the biopsy.

one-year follow-up of this case showed no recurrence of the lesion. Our findings are in accordance with (Silva *et al.*, 2007), who presented a case report of a surgical excision of a peripheral ossifying fibroma coincident with central odontogenic fibroma with an uneventful follow-up of one year.

Excisional biopsies when performed frequently result in mucogingival defects, which may produce esthetic problems and increase the chance of hyperesthesia (Bosco *et al.*, 2006).

(Bernimoulin *et al.*, 1975) first described a root coverage technique with free gingival graft placed to increase the zone of keratinized gingiva and flap coronally repositioned later.

Besides having an important role in maintaining gingival health, the attached gingiva protects the periodontium against external injuries, maintains a stable position of the gingival margin, and dispels the physiological forces made by the muscle fibers of the alveolar mucosa against the gum tissues. There is controversy regarding the amount of keratinized tissue to maintain gingival health. Mucogingival techniques are present in the





literature to increase the zone of attached gingiva. Among the alternatives, the free gingival graft is a widespread procedure, because of abundant donor site and the possibility of treating multiple teeth. As disadvantages we can cite postoperative discomfort, unpredictable color harmony, and the need for a second donor site (Carnio *et al.*, 2015).

During this treatment, biopsy and the free gingival graft were performed at the same surgical procedure. This decision was made to avoid repetitious postoperative discomfort for the patient and to make oral hygiene procedures more effective in accordance with (Anderegg & Metzler, 1996) (Keskiner *et al.*, 2016).

The decision of performing first the free gingival Keskiner *et al.*, (2016) graft found evidence in literature which points out that thin adjacent gingiva makes root coverage less predictable (Maynard , 1977) and an adequate amount of attached gingiva improves periodontal health (Lang & Löe , 1972). A systematic review (Thoma *et al.*, 2009) stated that the free gingival graft is a successful treatment concept to increase the width of attached gingiva around teeth. In this case report, as described also by other authors (de Matos *et al.*, 2007), clinical increases in the apicocoronal dimensions of keratinized tissue and attached gingiva were observed.

Root exposure, as a side effect of the biopsy, can be corrected after the recreation of keratinized tissue band. The coronally advanced flap technique (CAF) is a great alternative treatment because it presents satisfactory results in long term root coverage, good color harmony of the area treated with the surrounding tissues (Zucchelli *et al.*, 2014), without an excessive increase in the thickness of the tissue, and complete recovery of the original morphology of the marginal soft tissue. It also presents better postoperative course when



compared to coronally advanced flap with connective tissue graft (Zucchelli *et al.*, 2014). The only limiting factor to this technique is the need of a band of at least 1 mm keratinized tissue (Bosco *et al.*, 2006). A systematic review performed in 2008 (Cairo *et al.*, 2008) confirmed that the coronally advanced flap procedure is a safe and reliable approach in periodontal plastic surgery and is associated with consistent recession reduction and frequently with complete root coverage.

Coronally advanced flap can be associated with different materials as membrane barriers (Al Hezaimi *et al.*, 2014) (Rath *et al.*, 2016), grafts, subepithelial connective tissue (Zucchelli *et al.*, 2014), porcine collagen matrix (Moreira *et al.*, 2016) (Stefanini *et al.*, 2016), platelet-rich plasma (Biradar *et al.*, 2015) (Naik *et al.*, 2013) and platelet-rich fibrin (Keceli *et al.*, 2015) (Agarwal *et al.*, 2016).

Consensus Report of the European Workshop on Periodontology in 2014 (Tonetti & Jepsen, 2014), claimed that periodontal plastic procedures are complex, technique-sensitive interventions that require advanced skills and expertise. The choice of the technique should take in account increased morbidity when having a donor area or increased cost when using allograft materials. When there is enough tissue in the area to provide a well-designed flap for root coverage with stability, there is no need to use a soft tissue graft.

The treatment for gingival recession is considered completely successful when root coverage is associated with a gingival margin and a crevice probing depth that is coronal to the cemento-enamel junction (Pini-Prato *et al.*, 2015), as presented in this case report with one-year follow-up.



## Conclusion

Peripheral ossifying fibroma is a benign, slowly progressive lesion, with limited growth and histopathologic confirmation is mandatory. Complete surgical excision down to the periosteum is the preferred treatment and close postoperative follow-up is required. Surgical procedures with two stages using free gingival graft and coronally advanced flap present good results. In the presence of sufficient keratinized tissue, coronally advanced flap shows efficacy in root coverage.

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# Nefopam Versus Ketorolac for Post-operative Pain Control in Cesarean Section

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## نيفوبام و كيتورولاك للتحكم في الالم بعد الولادة القيصرية

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## **Abstract**

More than 230 million people undergo surgery each year worldwide and the number is increasing annually. Surgery causes commonly postoperative pain that should be alleviated as soon and as effective as possible to reduce suffering, to promote the healing process and rehabilitation and to prevent complications. However, clinical pain management after surgery is far from being successful despite dramatically increased scientific evidence in this area. Many patients suffer from severe pain after surgery. Aim: The aim of this study is to compare between ketorolac and nefopam when administered intravenously as post-operative analgesia in cesarean section. Patients and methods: 60 patients, who were candidates for elective & emergency cesarean section, Patients were randomly assigned to receive intravenous infusion of Nefopam (Group A) or an intravenous infusion of Ketorolac (Group B) with induction of anesthesia. All patients received Tramadol ampule 100 mg after delivery of baby as analgesia. The patients were also observed for development of sweating, nausea and vomiting with the vital signs during recovery phase. Results: there are a significant difference between group A (Nefopam) and group B (Ketorolac) regarding Numerical rating scale (NRS) and patient satisfaction. Conclusions: Nefopam is more effective than ketorolac in controlling pain for patients undergoing cesarean section.

**Keywords: Ketorolac, Nefopam, Cesarean section, Pain.**



## المستخلص

يخضع أكثر من 230 مليون شخص للجراحة كل عام في جميع أنحاء العالم ويزداد العدد سنويًا. تسبب الجراحة ألمًا شائعًا بعد الجراحة يجب تخفيفه بأسرع ما يمكن وبفعالية قدر الإمكان لتقليل المعاناة وتعزيز عملية الشفاء وإعادة التأهيل ومنع المضاعفات. ومع ذلك ، فإن إدارة الألم السريرية بعد الجراحة بعيدة كل البعد عن النجاح على الرغم من الأدلة العلمية المتزايدة بشكل كبير في هذا المجال. يعاني العديد من المرضى من ألم شديدة بعد الجراحة ، الهدف من هذه الدراسة هو المقارنة بين كيتورولاك و نيفوبام عند تناولهما عن طريق الوريد كمسكن بعد الجراحة في الولادة القيصرية. عرض 60 مريضًا ، كانوا مرشحين للولادة القيصرية الاختيارية والطارئة و الذين تم تعيينهم عشوائياً لتلقي اما التسريب الوريدي من مادة Nefopam (المجموعة أ) أو التسريب الوريدي من مادة كيتورولاك (المجموعة ب) مع تعريض الى التخدير. تلقى جميع المرضى ترامادول أمبول 100 ملغ بعد ولادة الطفل كمسكن للألم. كما لوحظ على المرضى تطور التعرق والغثيان والقيء مع العلامات الحيوية أثناء مرحلة الشفاء. بينت النتائج وجود فرق كبير بين المجموعة أ (نيفوبام) والمجموعة ب (كيتورولاك) فيما يتعلق بمقياس التصنيف العددي (NRS) ورضا المريض. استنتج من هذه الدراسة ان Nefopam أكثر فعالية من كيتورولاك في السيطرة على الألم المرضى الذين يخضعون لعملية قيصرية.

الكلمات المفتاحية: كيتورولاك ، نيفوبام ، ولادة قيصرية ، ألم.



## Introduction

More than 230 million people undergo surgery each year worldwide and the number is increasing annually (Weiser *et al.*, 2008) (Nalini *et al.*, 2017). Surgery causes commonly postoperative pain that should be alleviated as soon and as effective as possible to reduce suffering, to promote the healing process and rehabilitation and to prevent complications. However, clinical pain management after surgery is far from being successful despite dramatically increased scientific evidence in this area. Many patients suffer from severe pain after surgery (Gerbershagen *et al.*, 2014).

Pain which is considered as the most common symptom that brings patients to see a physician is nearly always a manifestation of a pathological process. This symptom may have a wide variety of causes ranging from relatively benign conditions to acute injury, myocardial ischemia, degenerative changes, or malignancy. Pain relief has significant physiological benefits; hence, monitoring of pain relief is increasingly becoming an important postoperative quality measure. The goal for postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects (Richard, 2013). Various agents (opioid vs. non-opioid), routes (oral, intravenous, neuraxial, regional) and modes (patient controlled vs. "as needed") for the treatment of postoperative pain exist. Pain needs to be quantified to be treated effectively. The gold standard is the patient's self-assessment done routinely after surgery to measure the efficacy of pain management. Several scoring tools are available but a 10-point pain assessment scale, where 1 is no pain and 10 is the worst possible pain imaginable, has been nationally accepted. The key to adequate pain control is to reassess the patient and determine if he or she is satisfied with the



outcome. A satisfaction score should be obtained together with a pain score so as to minimize the chances that inadequately treated pain goes unnoticed. Responsive analgesia management with good patient communication is the key to a successful program (Garimella & Cellini, 2013 ; Haefeli, 2006).

Nefopam is a benzoxazocine compound that is structurally related to orphenadrine and diphenhydramine. It is a centrally acting analgesic with both supra-spinal and spinal sites of action. Nefopam is neither an opiate nor a non-steroidal non-inflammatory drug. Nefopam does not induce respiratory depression, even in postoperative patients (Alfonsi *et al.*, 2004). It was developed in the early 1970s as an antidepressant and myorelaxant but has been shown to be effective in preventing acute postsurgical hyperalgesia and nonsurgical neuropathic pain. Oral and intravenous forms of Nefopam are used, and the drug has an oral bioavailability of 40% and a plasma half-life of 3-5 h. Plasma peak concentrations are reached 15-20 min after intravenous injection and at 30 min during continuous infusion. Nefopam hydrochloride is a centrally acting antinociceptive compound that inhibits the reuptake of serotonin, norepinephrine and dopamine, the three most important substances in the transmission of pain resulting in reduced glutaminergic transmission by decreasing the activation of postsynaptic glutamatergic receptors and it also has supraspinal and spinal sites of action (Jin *et al.*, 2016). In addition to its analgesic effect, it also reduces postoperative shivering, making it favorable for perioperative use. Given that postoperative pain is acute nociceptive, inflammatory and even neuropathic in nature (Choi , 2016).

Despite the above-mentioned properties favoring Nefopam for perioperative use, adverse effects such as confusion and tachycardia have been



well noted. Furthermore, unexpected side effects including neuropsychiatric (related with abuse), cutaneous, or anaphylactic reactions have been reported. Therefore, extensive use of Nefopam in the perioperative period should wait until further research establishes the safety of the intraoperative use of Nefopam, defines the analgesic mechanisms, and provides good quality strategies for Nefopam in the multimodal analgesic approach (Choi, 2016).

Ketorolac tromethamine is the first NSAID approved for parenteral use. It is used for a variety of clinical indications but is mainly administered for the management of postoperative pain. It can also be used for treatment of cancer-related pain, for pain after cesarean delivery, and in the emergency department for treatment of migraine headaches, renal colic, musculoskeletal pain, and sickle cell crisis. Ketorolac has been used safely and effectively in select pediatric populations but at present is not recommended for use in children under the age of 17. Routes of administration include intravenous (IV), IM, oral (PO), ophthalmic, and intranasal (IN). Ketorolac primarily exerts its effects through inhibition of the cyclooxygenase (COX) -1 and -2 isozymes, with a greater affinity for COX-1.

All forms of Ketorolac are rapidly absorbed with a mean half-life for absorption of 3.8 minutes, and duration of action of approximately 6 to 8 hours. It is metabolized by the liver into hydroxylated and conjugated forms. The primary route of excretion is renal with 92% of the administered dose being found in the urine. Ketorolac crosses the placenta and is also excreted into breast milk in small quantities. The adverse events associated with ketorolac are similar to those of other NSAIDs, which include gastrointestinal (GI) bleeding, renal impairment, liver dysfunction, and possible allergic reactions. Use of ketorolac disrupts platelet aggregation through the inhibition of thromboxane A<sub>2</sub>.



The use of ketorolac is associated with a small increased risk of GI and possibly operative site bleeding, and it is advisable to always communicate with the surgeon before administering this drug preoperatively.

The aim of this study was to comparison between Ketorolac and Nefopam when administered intravenously with Tramadol during induction of anesthesia as post-operative analgesia over a 12 h period following surgery in patients who had undergone cesarean section.

## Materials and Methods

This study is prospective, randomized, double-blinded clinical trial. The study was conducted in operating theatres in Al-Imamaien Al-Kadhumaen Medical City in Baghdad, Iraq, from August 2017 till January 2018. Sixty patients were prepared to cesarean sections; patients were divided into two equal groups. Group A received slow intravenous Nefopam and group B received slow intravenous ketorolac and both group received tramadol intravenously to compare the potency of these analgesic drugs in post-operative measures as a plan for post-operative pain management. Approval were obtained from Iraqi Committee for medical specializations as well as written informed written consent for participation in the study was signed by investigated subjects according to the Helsinki principles.

### The inclusion criteria:

1. Elective or emergency cesarean sections under general anesthesia.
2. ASA class two.
3. Weight between 70-110 Kg
4. Age between 20-40 years old.



## The exclusion criteria:

1. Patient refusal.
2. Patient with history of renal impairment.
3. Diabetic patients.
4. Patient with history of hypertension.
5. Patients in which her wound infiltrated by local anaesthesia.
6. Cases with allergy to medications used in the study.
7. Patient already on analgesics treatment.

## Study procedure

Before induction of anesthesia name, age, patient identification number, weight, ASA class, and initial vital signs all were recorded. Anesthesia were induced with medications mentioned above, then Endotracheal intubation was performed by direct laryngoscopy. Then slow intravenous administration of Nefopam was given to (group A) and slow intravenous administration of Ketorolac was given to (group B). Sevoflurane was used. Both groups received Tramadol to ensure analgesia.

The blinded technique was ensured by preparing the medication by my colleague, so he was handling as 10 ml syringe of either Nefopam diluted or ketorolac diluted solution. We both do not know which one was Nefopam or Ketorolac. All patients received from 20 IU to 40 IU of Pitocin after delivery of fetus. After skin closure, Sevoflurane was turned off; neuromuscular blockade was reversed with neostigmine and atropine. Oral suction was done before extubation. During the emergence phase 100 percent oxygen was administered and the patients were extubated when they met the standardized extubation criteria.



On recovery, observer starts to record the mean arterial blood pressure (MAP), heart rate (HR), O<sub>2</sub> saturation and estimate the blood loss at the end of operation. Also, patient evaluated for the presence of Nausea, vomiting and sweating. Then we documented data after 1 hr., 6hr. and 12 hr. Post-operative which include Numerical Rating Scale (figure1), Nausea and vomiting and finally patient satisfaction by the following parameters:

Very satisfied 5

Somewhat satisfied 4

Neither satisfied nor dissatisfied 3

Somewhat dissatisfied 2

Very dissatisfied 1

## **Data analysis**

The statistical analysis of this prospective study performed with the statistical package for social sciences (SPSS) 20.0 and Microsoft Excel 2013. Numerical data described as mean and standard deviation, Analysis of variance (ANOVA) used for comparison among study groups. Categorical data were described as count and percentage. Chi-square test or fisher exact test used to estimate the association between variables. The lower level of accepted statistical significant difference is bellow or equal to 0.05.

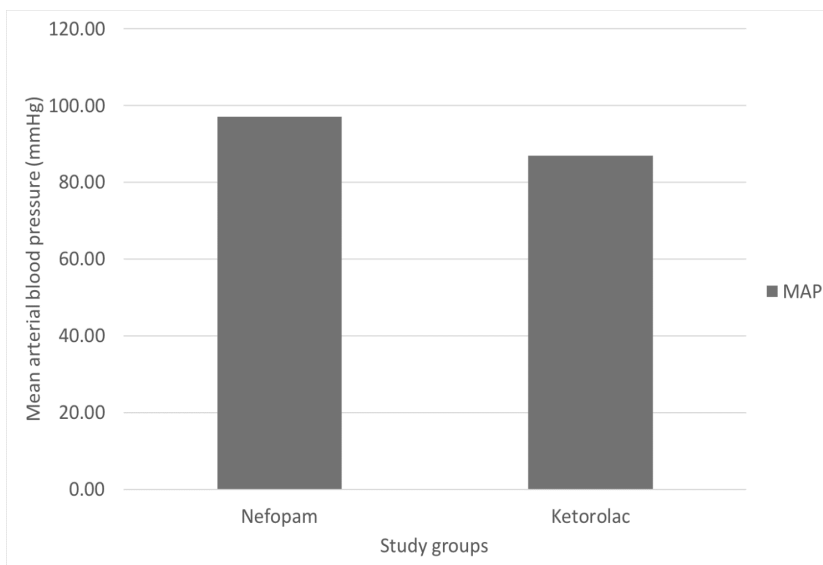
## **Results**

This study included 60 patients; divided into two groups, 30 for each group all of them met the entry criteria of the study. Patients were able to complete the entire study and their data were included in the final analysis.

There are no statistical differences between Ages, weight; Dose of Pitocin, blood loss and heart rate with p values are 0.703, 0.334, 0.325, 0.810 and 0.371 respectively. There is decrease in mean arterial blood pressure in group B (86.97 mmhg) more than group A (97.10 mmhg). With a significant p value less than 0.001. (Figure 3-1)

**Table 1: Patient Characteristics**

	Group		P value
	Nefopam	Ketorolac	
Age	27.90±4.69	28.37±4.76	0.703
Weight	83.10±7.82	85.47±10.78	0.334
Pitocin	23.00±5.96	26.00±7.70	0.325
Blood loss	860.00±310.84	841.67±275.46	0.810
MAP	97.10±8.17	86.97±10.34	<0.001
HR	88.53±12.80	91.50±12.67	0.371



**Figure 1: Difference in mean arterial pressure between two groups**





The incidence of pain according to the numerical rating scale After 1 hr. post-operative for group A was 0 % no pain, 3.33 % mild pain, 76.67 % moderate pain and 20 % was severe pain, while in group B was 0% no pain, 0 % mild pain, 50 % moderate pain and 50 % was severe pain. With p value less than 0.001. After 6 hrs. The incidence of pain according to numerical pain scale for group A was 0 % no pain, 20 % mild pain ,76.67 % moderate pain and 3.33 % was severe pain, while in group B was 0% no pain, 3.33 % mild pain, 93.3 moderate pain and 3.33 % was severe pain with p value less than 0.001. After 12 hrs. The incidence of pain according to numerical pain scale for group A was 3.33 % no pain, 40 % mild pain, 56.67 % moderate pain and 0% severe pain, while in group B was 3.33 % no pain, 26.67 % mild pain, 70 % moderate pain and 0 % severe pain.

The incidence of nausea and vomiting After 1 hr. post operatively was higher in group A 36.67 % rather than group B 23.33 % with p value less than 0.001. After 6 hr. The incidence of nausea and vomiting was 6.67 % in group A and 0 % in group B. with p value less than 0.001. After 12 hr. The incidence of nausea and vomiting was 0 % in both groups with p value less than 0.001.

**Table 2: Numerical rating scale post operatively**

Numerical rating scale		Nefopam	Ketorolac	P value
After 1 hr.	0	0 (0)	0 (0)	<0.001
	2	1 (3.33)	0 (0)	<0.001
	4	9 (30)	4 (13.33)	<0.001
	6	14 (46.67)	11 (36.67)	<0.001
	8	4 (13.33)	12 (40)	<0.001
	10	2 (6.67)	3 (10)	<0.001



Numerical rating scale		Nefopam	Ketorolac	P value
After 6 hrs.	0	0 (0)	0 (0)	<0.001
	2	6 (20)	1 (3.33)	<0.001
	4	20 (66.67)	18 (60)	<0.001
	6	3 (10)	10(33.3)	<0.001
	8	1 (3.33)	1 (3.33)	<0.001
	10	0 (0)	0 (0)	<0.001
After 12 hrs.	0	1 (3.33)	1 (3.33)	<0.001
	2	12 (40)	8 (26.67)	<0.001
	4	17 (56.67)	17 (56.67)	<0.001
	6	0 (0)	4 (13.33)	<0.001
	8	0 (0)	0 (0)	<0.001
	10	0 (0)	0 (0)	<0.001

**Table 3: Incidence of nausea and vomiting**

Nausea & vomiting		Nefopam	Ketorolac	P value
After 1 hr.	No	19 (63.33)	23 (76.67)	<0.001
	Yes	11 (36.67)	7 (23.33)	<0.001
After 6 hrs.	No	28 (93.33)	30 (100)	<0.001
	Yes	2 (6.67)	0 (0)	<0.001
After 12 hrs.	No	30 (100)	30 (100)	<0.001
	Yes	0 (0)	0 (0)	<0.001

The incidence of patient satisfaction After 1 hr. post operatively in group A was 0 % very dissatisfied, 16.67 % was somewhat dissatisfied, 66.67 % was neither satisfied nor dissatisfied, 16.67 % was somewhat satisfied and 0 % was very satisfied while in group B was 13.33 % very dissatisfied, 40 % was somewhat dissatisfied, 33.33 % was neither satisfied nor dissatisfied, 13.33 % was somewhat satisfied and 0 % was very satisfied. With p value less than 0.001. After 6 hr. The incidence of patient satisfaction in group A was 0 % very dissatisfied, 3.33 % was

somewhat dissatisfied, 40 % was neither satisfied nor dissatisfied, 53.33 % was somewhat satisfied and 3.33 % was very satisfied while in group B was 3.33 % very dissatisfied, 32.33 % was somewhat dissatisfied, 56.67 % was neither satisfied nor dissatisfied, 13.33 % was somewhat satisfied and 3.33 % was very satisfied. With p value less than 0.001. After 12 hr. The incidence of patient satisfaction in group A was 0 % very dissatisfied, 0 % was somewhat dissatisfied, 26.67 % was neither satisfied nor dissatisfied, 56.67 % was somewhat satisfied and 16.67 % was very satisfied while in group B was 0 % very dissatisfied, 6.67 % was somewhat dissatisfied, 43.33 % was neither satisfied nor dissatisfied, 40 % was somewhat satisfied and 10 % was very satisfied with p value less than 0.001.

**Table 4: Incidence of patient satisfaction**

Patients satisfaction		Nefopam	Ketorolac	P value
After 1 hr.	1	0 (0)	4 (13.33)	<0.001
	2	5 (16.67)	12 (40)	<0.001
	3	20 (66.67)	10 (33.33)	<0.001
	4	5 (16.67)	4 (13.33)	<0.001
	5	0 (0)	0 (0)	<0.001
After 6 hrs.	1	0 (0)	1 (3.33)	<0.002
	2	1 (3.33)	7 (23.33)	<0.002
	3	12 (40)	17 (56.67)	<0.002
	4	16 (53.33)	4 (13.33)	<0.002
	5	1 (3.33)	1 (3.33)	<0.002
After 12 hrs.	1	0 (0)	0 (0)	<0.001
	2	0 (0)	2 (6.67)	<0.001
	3	8 (26.67)	13 (43.33)	<0.001
	4	17 (56.67)	12 (40)	<0.001
	5	5 (16.67)	3 (10)	<0.001



## Discussion

This study examined the analgesic efficacy of Ketorolac and Nefopam that was co-administered with tramadol via IV route for analgesia in patients undergoing cesarean section (Son *et al.*, 2017). Patient characteristics (age, weight, dose of Pitocin, blood loss and heart rate) showing no significant differences between the two treatment groups as seen in table 1, P – value for age, weight, dose of Pitocin, blood loss and heart rate were 0.703, 0.334, 0.325, 0.810 and 0.371 respectively and all of them more than 0.05. Numerical rating scale After 1 hr., 6 hr., and 12 hrs. Post operatively for group A show less pain than group B, with p value less than 0.001. This makes Nefopam better than ketorolac in controlling pain according to Numerical rating scale (NRS). Ji-Seon *et al.*, One hundred and sixty patients scheduled for laparoscopic cholecystectomy were randomly assigned to ketorolac (Group K) or Nefopam (Group N) groups. The anesthetic regimen was standardized for all patients. The analgesic solution contained fentanyl 600 µg and ketorolac 180 mg in Group K, and fentanyl 600 µg and Nefopam 120 mg in Group N, showing there were no significant differences in postoperative analgesics consumption and pain intensity between the Ketorolac-fentanyl and Nefopam-fentanyl combinations, this due to ketorolac and Nefopam have been used in high doses with high dose of Fentanyl.

Boo-Young *et al.*, 120 patients undergoing gynecologic surgery were divided randomly into two groups: Nefopam group treated with oxycodone 1 mg and Nefopam 1 mg bolus; and Ketorolac group treated with oxycodone 1 mg and ketorolac 1.5 mg bolus. After the operation, a blinded observer assessed the pain with a numeric rating scale (NRS) showing there were no



significant differences in NRS between both groups (Hwang *et al.*, 2015). This difference from our study may be due to the use of a different combination with low doses of Nefopam / Oxycodone, Ketorolac / Oxycodone while in our study we used Nefopam / Tramadol, Ketorolac / Tramadol. Kumar *et al.* (1996) prospective double blind randomized clinical trial was conducted in 181 patients after single intravenous (I.V.) bolus dose of these two drugs for relieving acute post-operative pain following upper abdominal surgery. 100 patients received 30 mg Ketorolac (group A) while 81 patients received 20 mg Nefopam (group B). Both the groups were comparable in terms of age and sex. Showing 30 mg Ketorolac provides progressively increasing and lasting pain relief compared to 20 mg Nefopam when used as single I.V. bolus dose in immediate post-operative period following upper abdominal surgery.

(Oh YN *et al.*, 2018) Ninety-two patients were randomly divided into two groups to receive intravenous PCA. Patients were assigned to either the Nefopam group (Nefopam 120 mg and Fentanyl 20 µg/kg) or the Ketorolac group (Ketorolac 2 mg/kg and fentanyl 20 µg/kg). Pain was assessed on a visual analogue scale (VAS) and a numeric rating scale (NRS). Additionally, patient satisfaction, adverse events, and vital signs were monitored showing There were no significant differences in VAS score ( $P = 0.48$ ) or NRS score ( $P = 0.15$ ) between the two groups. Similarly, patient satisfaction did not differ between the two groups [8.5(0.8) vs. 8.2(1.0),  $P = 0.14$ ]. There were no statistically significant differences in the incidence of nausea ( $P = 0.72$ ), vomiting ( $P = 0.46$ ).in conclusion Nefopam is an appropriate alternative for co-administration with Fentanyl-based PCA in patients who have difficulty using non-steroidal anti-inflammatory drugs.



Incidence of nausea and vomiting after 1 hr., 6 hrs. and 12 hrs. was higher in group A than group B with p value less than 0.001. (Yoon *et al.*, 2015) Sixty patients undergoing laparoscopic gynecologic surgery received IV-PCA. Group A (n = 30) received IV-PCA with a combination of morphine 60 mg and Ketorolac 180 mg, while group B (n = 30) received Nefopam 200 mg (basal rate 1 ml/h, bolus 1 ml, and lockout time 15 min for both). The primary outcome evaluated was analgesic efficacy using the visual analogue scale (VAS).

Other evaluated outcomes included the incidence rate of postoperative nausea and vomiting (PONV) showing the incidence rate of vomiting was not statistically different between the two groups in contrast to our study which showing a statistical significant difference regarding the incidence of nausea and vomiting , this may be due to correlated to the side effects of Nefopam (Lu *et al.*, 2013). Chung *et al.* Patients undergoing gynecological laparoscopic surgery were randomly allocated to receive either Nefopam- (non-opioid; N group) or Fentanyl-based (F group) PCA. PONV and postoperative pain were assessed during the 72 hours following discharge from the post-anesthetic care unit (PACU). The adverse effects of Nefopam were also evaluated. Show the PONV incidence was significantly lower in the N group than the F group at all measured times.

The incidence of patient satisfaction in group A was higher than group B at all times of measures with p value less than 0.001. Boo-Young *et al.* (Hwang *et al.*, 2015). 120 patients undergoing gynecologic surgery were divided randomly into two groups: Nefopam group treated with oxycodone 1 mg and Nefopam 1 mg bolus; and Ketorolac group treated with oxycodone 1 mg and Ketorolac 1.5 mg bolus. After the operation, a blinded observer



assessed the pain with a numeric rating scale (NRS), infused PCA dose and sedation score at 1, 4, 24, and 48 h, nausea, vomiting, headache, shivering, pruritus and delirium at 6, 24 and 48 h, and satisfaction at 48 h after the operation. Show there is no significant difference in the patient satisfaction between both groups; this may be due to the use of oxycodone as adjuvant in this study rather than tramadol in our study.

## Conclusion

The use of Nefopam as analgesic drug for post-operative analgesia is significantly more effective than Ketorolac.

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# Betamethasone Gel Compared with Lidocaine Gel to Reduce Tracheal Tube Related Post-operative Airway Symptoms

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مقارنة بيتاميثازون جل مع ليدوكائين جل في تقليل أعراض  
مجرى الهواء في القصبة الهوائية بعد الجراحة

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## Abstract

**Background:** The commonest method to secure airway in general anesthesia is the use of cuffed Endotracheal Tube (ETT), However the recovery are often complicated by ETT induced airway and circulatory reflexes which can lead to potentially dangerous complications. A lot of studies and researches have been focused on prevention of these emergence phenomena (EP); nevertheless, the problem is still far from final solution. **Aim:** To compare the efficacy of Lidocaine gel vs. Betamethasone gel in attenuating the ETT induced EP. **Patients and methods:** 51 patients who were been chosen for elective intermediate average duration operations and were in class 1 & 2 of American society of anesthesiologist (ASA). Patients were randomly assigned to receive Betamethasone gel or Lidocaine gel or normal saline (NS.) as a lubricant to the endotracheal tube. Coughing &/or bucking at emergence of anesthesia was evaluated as either present or not by blinded observer. The patients were also observed for development of hoarseness of voice and laryngeal spasm along with the vital signs during recovery phase and observed for sore throat, hoarseness of voice after 1 hr., 6 hrs. and 12 hrs. post-operative .**Results:** the incidence of sore throat, hoarseness of voice and cough was lowest in group B (Betamethasone) rather than group A (Lidocaine) and control group C (Normal saline). **Conclusions:** Applying Betamethasone and lidocaine gel on the endotracheal tube is a simple and effective method of reducing the incidence of post-operative laryngeal spasm, sore throat, cough and hoarseness of voice in patients under general anesthesia with endotracheal intubation.

**Keywords:** Endotracheal tube, Lidocaine, Betamethasone, Extubation.

## المستخلص

إن الطريقة الأكثر شيوعاً لتأمين مجرى الهواء في التخدير العام هي استخدام أنبوب القصبة الهوائية المقيد (ETT) ، ومع ذلك فإن التعافي غالباً ما يكون معقداً بسبب مجرى الهواء الناجم عن الانعكاسات الدورانية التي يسببها ETT والتي يمكن أن تؤدي إلى مضاعفات خطيرة محتملة. لقد ركزت الكثير من الدراسات والأبحاث على الوقاية من هذه الظواهر الناشئة (EP) ؛ ومع ذلك ، لا تزال المشكلة بعيدة عن الحل النهائي. هدفت الدراسة الحالية الى مقارنة فعالية ليدوكائين جل مقابل بيتاميثازون جل في تخفيف EPT المحرض. اختير 51 مريضاً لإجراء عمليات اختيارية متوسطة المدة وكانوا في الفئة 1 و 2 من المجتمع الأمريكي لأطباء التخدير (ASA) . هؤلاء المرضى اختيروا عشوائياً لتلقي بيتاميثازون جل أو ليدوكائين جل أو محلول ملحي عادي (NS). كمواد تشحيم للأنبوب الرغامي. قيم السعال و / أو الجماع عند ظهور التخدير على أنه إما موجود أو غير موجود بواسطة مراقب أعمى. كما لوحظ أن المرضى يعانون من بحة في الصوت وتشنج الحنجرة إلى جانب العلامات الحيوية أثناء مرحلة الشفاء ، كما لوحظ وجود التهاب في الحلق ، وبحة في الصوت بعد ساعة واحدة ، 6 ساعات و 12 ساعة. بينت النتائج حدوث التهاب الحلق وبحة الصوت والسعال أقل في المجموعة ب (بيتاميثازون) مقارنة مع المجموعة أ (ليدوكائين) والمجموعة الضابطة (محلول ملحي عادي). استنتج من هذه الدراسة ان تطبيق بيتاميثازون جل و يدوكائين جل على الأنبوب الرغامي هو طريقة بسيطة وفعالة للحد من حدوث تشنج الحنجرة بعد الجراحة والتهاب الحلق والسعال وبحة الصوت في المرضى تحت التخدير العام مع التنبيب الرغامي.

**الكلمات المفتاحية:** الأنبوب الرغامي ، ليدوكائين ، بيتاميثازون ، نزع الأنبوب.



## Introduction

Emergence from general anesthesia implies liberation of the patient from the state of anesthesia. The indication for anesthetic state no longer exists at the end of surgery; the patient should ideally be free from effects of anesthetics and only analgesia needs to be continued. The emergence should happen in a short-time, smooth and free from undesirable effects, a consequence of residual effects of anesthesia and altered physiology related to airway, respiration, autonomic, metabolic and endocrine functions. Along with the advent of newer anesthetic agents, reversal agents/antidotes and monitoring devices, there have been improved understanding of arousal pathways in the nervous system contributing to faster and smoother emergence from anesthesia (Bhaskar, 2013). Many problems may occur as a result of intubation and extubation that include cardiovascular response, coughing and laryngospasm, regurgitation and aspiration of gastric contents, airway obstruction and Laryngeal trauma (Yentis, 2013) (Karmarkar & Varshney, 2008).

Lidocaine hydrochloride (Lignocaine) which is an amide local anaesthetic agent, introduced in 1947 used mainly as local anesthesia. Often combined with adrenaline, since lidocaine tends to produce local vasodilatation and administration intravenously to depress laryngeal and tracheal reflexes (e.g. during tracheal intubation/extubation) (Mitchell *et al.*, 2012) (DDJ & DB, 2005) . Moreover, it is commonly used to reduce the increase in intracranial pressure (ICP) caused by laryngoscopy. Possibly reduces muscle pains and potassium increase after suxamethonium. It has been also used to produce analgesia and general anesthesia (although its



therapeutic ratio is low). 4–10% lidocaine has been used instead of air to inflate the tracheal tube cuff, thereby reducing postoperative sore throat and hoarseness. Furthermore, it is also considered as class I antiarrhythmic drug in ventricular Tachyarrhythmia. Lidocaine is thought to be more toxic to nerve tissue when directly applied than other local anesthetic, hence the increased incidence of transient radicular irritation syndrome following its use for spinal anesthesia than with other drugs (hyperbaricity of the solution and use of very thin needles/catheters are also thought to contribute by encouraging pooling of drug around spinal nerves). This has led to revision of the drug's data sheet to specify dilution to 2.5% before administration (even this concentration has been implicated in causing transient symptoms) (Haas *et al.*, 2014 ; Yentis, 2017).

Topical corticosteroids are widely used for inflammatory and hyperproliferative disorders in dermatology. Numerous topical corticosteroids with high local activity have been developed over the years, with a focus to develop drugs with high efficacy locally and minimum risk for adverse drug reactions. They are available in a number of formulations. Their therapeutic effects are a result of their anti-inflammatory, immunosuppressant, vasoconstrictive and anti-proliferative actions. An appropriate topical corticosteroid is selected on the basis of the dermatological condition to be treated, patient-related factors and the physicochemical properties of the drug. Their use is associated with mainly local adverse drug reactions, but prolonged use and/or use of high potency topical corticosteroids may cause systemic effects (Kazemi & Amini, 2007 ; Lahir, 2018).

This study was aimed to compare the efficacy of Lidocaine gel versus Betamethasone gel in attenuating the ETT induced EP.



## Methods

This study is prospective, randomized, double-blinded clinical trial. The study was conducted in the elective operation theatres in Madenat Al-Imamaein Al-Kadhumain Medical Centre in Baghdad, Iraq, from November 2017 till January 2018. In this study 51 patient were candidate to elective surgery, patient were divided into three equal groups. Group A received Lidocaine gel as a lubricant to ETT, group B received Betamethasone gel as a lubricant and group C lubricated with normal saline (NS.) in testing for attenuating the ETT induced EP. The types of surgery. Approval were obtained from Iraqi Committee for medical specializations as well as written informed written consent for participation in the study was signed by investigated subjects according to the Helsinki principles.

### The inclusion criteria:

1. Elective operation in which patient will need ETT.
2. ASA class one and two.
3. Length of operation between 30 min and two hours.

### The exclusion criteria:

1. Cases with allergy to medications used in the study.
2. Patient with cough or had asthma or chronic obstructive airway disease.
3. Recent respiratory infection.
4. Patient at risk of aspiration like pregnant lady, morbid obesity, Active gastro esophageal reflux and hiatal hernia.



5. Laryngeal or tracheal surgery or pathology.
6. If nasogastric tube were anticipated after surgery.
7. Anticipated difficult intubation.
8. Patient with history of smoking.
9. Pharyngeal, oral and nose surgeries.
10. Patient refusal.

### **Study procedure:**

Before induction of anesthesia name, age, gender, patient identification number, weight, American society of anesthesiologist (ASA) class, name of operation and initial vital signs all were recorded. Anesthesia was induced with medications mentioned above, and then endotracheal intubation with a high volume low pressure cuffed ETT was performed by direct laryngoscopy. At the end of surgery, neuromuscular blockade was reversed with neostigmine and atropine. After skin closure, Sevoflurane was turned off. Oral suctioning was done before extubation. During the emergence phase 100 percent oxygen was administered. The patients were extubated when they met the standardized extubation criteria.

Once Sevoflurane was discontinued, a blinded observer starts to record. The mean arterial blood pressure (MAP), heart rate (HR), all been recorded after extubation as well as the duration of the operation. Presence of spasm, bucking, cough and hoarseness of voice also recorded. Also patient evaluated for the presence of sore throat, hoarseness of voice, coughs in the post anesthesia recovery unit, 1hr, 6hr and 12 hr. post-operative and graded as below.



## **Grading system for sore throat, hoarseness, and cough 1 hour to 24 hours after surgery**

### **Sore throat**

- 0 No sore throat
- 1 Mild (less than what is seen in common cold)
- 2 Moderate (like what is seen in common cold)
- 3 Severe (more than what is seen in common cold)

### **Hoarseness**

- 0 No hoarseness
- 1 Mild (no hoarseness in the time of interview but had it previously)
- 2 Moderate (only is felt by the patient)
- 3 Severe (recognizable in the time of interview)

### **Cough**

- 0 No cough
- 1 Mild (less than what is seen in common cold)
- 2 Moderate (like what is seen in common cold)
- 3 Severe (more than what is seen in common cold)

### **Data analysis:**

The statistical analysis of this prospective study performed with the statistical package for social sciences (SPSS) 20.0 and Microsoft Excel 2013.





Numerical data described as mean and standard deviation, Analysis of variance (ANOVA) used for comparison among study groups. Categorical data were described as count and percentage. Chi-square test or fisher exact test used to estimate the association between variables. The lower level of accepted statistical significant difference is bellow or equal to 0.05.

## Results:

This study included 51 patients, Divided into three groups, 17 for each group all of them met the inclusion criteria of the study. Patients were able to complete the entire study and their data were included in the final analysis. There is no statistical difference in patient's characteristics (Age, weight, duration of operation, mean arterial pressure, heart rate and size of ETT) with p value 0.332, 0.847, 0.271, 0.120, 0.283 and 0.310 respectively in all groups. Regarding Type of surgery and ASA show, there are no statistical difference between type of surgery, ASA in all groups with p value 0.058 and 0.396 respectively.

**Table 1: Patient Characteristics**

		Range	Mean	P value
Age	Ns. (n=17)	26-65	43.06±11.95	0.332NS
	Betamethasone (n=17)	11-65	44.71±13.67	
	Lidocaine (n=17)	26-55	39.00±7.77	
	Total (n=51)	11-65	42.25±11.43	
Weight	Ns. (n=17)	65-135	86.35±17.12	0.847 NS
	Betamethasone (n=17)	40-145	87.82±21.18	
	Lidocaine (n=17)	50-110	84.35±13.76	
	Total (n=51)	40-145	86.18±17.32	



Duration	Ns. (n=17)	60-120	78.82±24.97	0.271 NS
	Betamethasone (n=17)	45-90	74.41±16.38	
	Lidocaine (n=17)	45-120	67.35±19.54	
	Total (n=51)	45-120	73.53±20.74	
MAP	Ns. (n=17)	86-134	100.53±11.03	0.120 NS
	Betamethasone (n=17)	75-115	97.41±10.69	
	Lidocaine (n=17)	79-105	93.71±5.67	
	Total (n=51)	75-134	97.22±9.68	
HR	Ns. (n=17)	71-115	85.53±10.70	0.283 NS
	Betamethasone (n=17)	68-110	86.71±11.46	
	Lidocaine (n=17)	60-100	81.12±9.79	
	Total (n=51)	60-115	84.45±10.73	
Size	Ns. (n=17)	7-8	7.47±0.33	0.310 NS
	Betamethasone (n=17)	7-8	7.59±0.32	
	Lidocaine (n=17)	7.5-8	7.62±0.22	
	Total (n=51)	7-8	7.56±0.29	

During recovery phase the incidence of spasm was highest in group C (23.53%) while in group A was lowest ( 0%) . in group B was 5.88 % with p value 0.049 .The incidence of cough was lowest in group B (11.67 %) rather than other groups. In group A incidence of cough was (41.18%) and was highest in group C (64.71%). with significant p value 0.006.Incidence of hoarseness of voice was highest in group C (47.06%) and the same in both group A and B (5.88%). With p value 0.002. There is no statistical significance between all groups regarding incidence of bucking, Nausea & vomiting. With p value more than 0.05.

**Table 2: Type of surgery and ASA**

	Type	Ns.	Betamethasone	Lidocaine	P value
ASA	1	17 (100)	12 (70.59)	14 (82.35)	0.058NS
	2	0 (0)	5 (29.41)	3 (17.65)	
Surgery	breast mass	1 (5.88)	1 (5.88)	0 (0)	0.396
	herniaotomy	0 (0)	5 (29.41)	2 (11.76)	
	Hydrocele	0 (0)	0 (0)	1 (5.88)	
	lab coli	10 (58.82)	7 (41.18)	12 (70.59)	
	mastectomy	1 (5.88)	1 (5.88)	1 (5.88)	
	pelvic mass	2 (11.76)	1 (5.88)	0 (0)	
	Hysterectomy	2 (11.76)	2 (11.76)	0 (0)	
thyroidectomy	1 (5.88)	0 (0)	1 (5.88)		

**Table 3: incidence of bucking, nausea and vomiting, cough, spasm and hoarseness of voice**

	Groups	NS.	Betamethasone	Lidocaine	P value
Spasm	No	13 (76.47)	16 (94.12)	17 (100)	0.049*
	Yes	4 (23.53)	1 (5.88)	0 (0)	
Bucking	No	14 (82.35)	13 (76.47)	14 (82.35)	0.884NS
	Yes	3 (17.65)	4 (23.53)	3 (17.65)	
Nausea & vomiting	No	12 (70.59)	12 (70.59)	14 (82.35)	0.582NS
	Yes	5 (29.41)	5 (29.41)	3 (17.65)	
Cough	No	6 (35.29)	15 (88.24)	10 (58.82)	0.006*
	Yes	11 (64.71)	2 (11.76)	7 (41.18)	
Hoarseness of voice	No	9 (52.94)	16 (94.12)	16 (94.12)	0.002*
	Yes	8 (47.06)	1 (5.88)	1 (5.88)	

NS: none statistical significance ( $p>0.05$ ).

\*: Statistical significant difference ( $p<0.01$ )



The incidence of sore throat (ST) After one hour from surgery was highest in Group C (Severe 11.8%, moderate 17.6%, mild 70.6 and 0% no sore throat) while in the Group B was lowest (severe 0%, moderate 0%, mild 11.8% and no sore throat 88.2%) . in group A the incidence was ( severe 0%, moderate 5.9% , mild 52.9% and no sore throat 41.2%) . p value > 0.001. After six hour from surgery The incidence of sore throat was highest in group C ( moderate 5.9%, mild 82.4% , no sore throat 11.8% ) , while was lowest in group B ( moderate 0%, mild 11.8% , no sore throat 88.2% ) . In group A was (moderate 0%, Mild 17.6% and no sore throat 82.4%).p value > 0.001. After 12th hour from surgery The incidence of sore throat was highest in group C ( moderate 5.9%, mild 47.1% , no sore throat 47.1% ) , while was lowest in group B ( moderate 0%, mild 0% , no sore throat 100 % ) . In group A was (moderate 0%, Mild 11.8% and no sore throat 88.2%). P value 0.003.

The incidence of hoarseness of voice After one hour from surgery was highest in Group C (moderate 47.1%, mild 29.4% and 47.1% no hoarseness of voice) while in the Group B was lowest (moderate 0%, mild 5.9% and no hoarseness of voice 94.1%) . in group A the incidence was moderate 0% , mild 23.5% and no hoarseness of voice 76.5%) . not significant p value 0.01 . After six hour from surgery The incidence of hoarseness of voice was highest in group C (mild 17.6%, no hoarseness of voice 82.4%), while was lowest in group B (mild 5.9%, no hoarseness of voice 94%). In group A was (Mild 0% and no hoarseness of voice 100%). Not significant p value 0.150. After 12th hour from surgery the incidence of hoarseness of voice was highest in group C (mild 11.8%, no hoarseness of voice 88.2%), while was lowest in group B and A (mild 0%, hoarseness of voice 100 %). In group A was (Mild 0% and no hoarseness of voice 100%). Not significant p value 0.125.

**Table 4: incidence of sore throat**

Sore Throat (ST)		Groups			P value
		Betamethasone	Xylocaine		
Nil					
1 hr.	no ST	0	15	7	<0.001
	%	0.0%	88.2%	41.2%	
	Mild ST	12	2	9	
	%	70.6%	11.8%	52.9%	
	Moderate ST	3	0	1	
	%	17.6%	0.0%	5.9%	
	Severe ST	2	0	0	
	%	11.8%	0.0%	0.0%	
	Total	17	17	17	
%	100.0%	100.0%	100.0%		
6 hr.	no ST	2	15	14	<0.001
	%	11.8%	88.2%	82.4%	
	Mild ST	14	2	3	
	%	82.4%	11.8%	17.6%	
	Moderate ST	1	0	0	
	%	5.9%	0.0%	0.0%	
	Total	17	17	17	
%	100.0%	100.0%	100.0%		
12 hr.	no ST	8	17	15	0.003
	%	47.1%	100.0%	88.2%	
	Mild ST	8	0	2	
	%	47.1%	0.0%	11.8%	
	Moderate ST	1	0	0	
	%	5.9%	0.0%	0.0%	
	Total	17	17	17	
	%	100.0%	100.0%	100.0%	

**Table 5: Incidence of hoarseness of voice**

NS.		Hoarseness of voice (HOV)	Groups			p value
			Betamethasone	Lidocaine		
1hr.	No HOV	8	16	13	0.010	
	%	47.1%	94.1%	76.5%		
	Mild	5	1	4		
	%	29.4%	5.9%	23.5%		
	Moderate	4	0	0		
	%	23.5%	0.0%	0.0%		
	Total	17	17	17		
%	100.0%	100.0%	100.0%			
6hr.	No HOV	14	16	17	0.150	
	%	82.4%	94.1%	100.0%		
	Mild	3	1	0		
	%	17.6%	5.9%	0.0%		
	Total	17	17	17		
%	100.0%	100.0%	100.0%			
12 hr.	No HOV	15	17	17	0.125	
	%	88.2%	100.0%	100.0%		
	Mild	2	0	0		
	%	11.8%	0.0%	0.0%		
	Total	17	17	17		
%	100.0%	100.0%	100.0%			

The incidence of cough After one hour from surgery was highest in Group C (severe 11.8%, moderate 23.5%, mild 29.4% and 35.3 % no cough) while in the Group B was lowest (severe 0%, moderate 5.9%, mild 5.9% and no cough 88.2%). in group A the incidence was severe 0% moderate 0%, mild 23.5% and no cough 76.5%). not significant p value 0.015. After six hour from surgery the incidence of cough was highest in group C (mild 47.1%, no cough 52.9%), while was lowest in group B (mild 0%, no cough 100%). In group A

was (Mild 0% and no cough 100%). significant p value 0.001. After 12th hour from surgery the incidence of cough was highest in group C (mild 29.4%, no cough 70.6%), while was lowest in group B and A (mild 0%, no cough 100%). In group A was (Mild 0% and no cough 100%). significant p value 0.004.

**Table 6: Incidence of cough**

NS	Cough	Groups			P value
		Betamethasone	Lidocaine		
1hr.	No cough	6	15	13	0.015
	%	35.3%	88.2%	76.5%	
	Mild	5	1	4	
	%	29.4%	5.9%	23.5%	
	Moderate	4	1	0	
	%	23.5%	5.9%	0.0%	
	Severe	2	0	0	
	%	11.8%	0.0%	0.0%	
	Total	17	17	17	
%	100.0%	100.0%	100.0%		
6 hr.	No cough	9	17	17	<0.001
	%	52.9%	100.0%	100.0%	
	Mild	8	0	0	
	%	47.1%	0.0%	0.0%	
	Total	17	17	17	
	%	100.0%	100.0%	100.0%	
12 hr.	No cough	12	17	17	0.004
	%	70.6%	100.0%	100.0%	
	Mild	5	0	0	
	%	29.4%	0.0%	0.0%	
	Total	17	17	17	
	%	100.0%	100.0%	100.0%	



## Discussion

Sore throat, cough and hoarseness of voice are a common complication after surgeries involving induction of general anesthesia. During tracheal intubation, trauma, irritation and inflammation of the laryngeal mucosa are considered to be the responsible factors for the development of post-operative sore throat, cough and hoarseness of voice (Fayyaz *et al.*, 2017). Patient characteristic (age, weight, Duration of surgery, MAP heart rate, size of ETT) showing no significant differences between the three treatment groups as seen in table?, P – value for age, weight, duration of surgery, MAP, Heart rate and size of ETT were 0.332, 0.847, 0.271, 0.120, 0.283, 0.310 respectively and all of them more than 0.05. Similarly, the ASA and type of surgery showing p-value of 0.058, 0.396.

On recovery the incidence of spasm in group A was 0 %, while in group B was 5.88% and in group C was 23.35%. With a significant p value less than 0.05. This is may be due to a local anesthetic effect of Lidocaine. The incidence of cough was lowest in group B (11.67 %) rather than other groups. In group A incidence of cough was (41.18%) and was highest in group C 64.71%. with significant p value less than 0.05. This is due to local anesthetic effect of Xylocaine and anti-inflammatory effect of betamethasone. Incidence of hoarseness of voice was highest in group C (47.06%) and the same in both group A and B (5.88%). There is no statistical significance between all groups regarding incidence of bucking, Nausea & vomiting. With p value more than 0.05.

After one hour from surgery the incidence of sore throat was highest in Group C while in the Group B was lowest. in group A the incidence was ( severe 0%, moderate 5.9% , mild 52.9% and no sore throat 41.2%) . p value > 0.001





.After six hour from surgery The incidence of sore throat was highest in group C, while was lowest in group B . In group A was (moderate 0%, Mild 17.6% and no sore throat 82.4%).p value > 0.001. After 12th hour from surgery the incidence of sore throat was highest in group C, while was lowest in group B. In group A was (moderate 0%, Mild 11.8% and no sore throat 88.2%). P value 0.003.

Incidence of hoarseness of voice after one hour from surgery was highest in Group C while in the Group B was lowest. in group A the incidence was moderate 0% , mild 23.5% and no hoarseness of voice 76.5%) . not significant p value 0.01 . After six hour from surgery the incidence of hoarseness of voice was highest in group C while was lowest in group B. In group A was (Mild 0% and no hoarseness of voice 100%). Not significant p value 0.150.After 12th hour from surgery the incidence of hoarseness of voice was highest in group C, while was lowest in group B and A. In group A was (Mild 0% and no hoarseness of voice 100%). Not significant p value 0.125.

Incidence of cough after one hour from surgery was highest in Group C while in the Group B was lowest. in group A the incidence was severe 0% moderate 0% , mild 23.5% and no cough 76.5%) . Not significant p value 0.015. After six hour the incidence of cough was highest in group C, while was lowest in group B and A. Significant p value 0.001. After 12th hour from surgery the incidence of cough was highest in group C. while was lowest in group B and A (mild 0%, no cough 100 %). In group A was (Mild 0% and no cough 100%). significant p value 0.004.

Nadia *et al.*, Ninety women with an ASA I or II and undergoing elective mastoidectomy were randomized into three groups of 30 patients. The endotracheal tubes in each group were sprayed with 50% Beclomethasone,



10% Lidocaine hydrochloride, or normal saline (control group) before endotracheal intubation. Patients were examined for sore throat (none, mild, moderate, or severe), cough, and hoarseness at 1 and 24 h after extubation. This study agreed with our study by Showing the incidence bucking, spasm was not significantly different among the groups in the present study (Ayoub *et al.*, 1998).

Parineeta *et al.*, 120 ASA I and II patients undergoing elective surgery under general anesthesia with endotracheal intubation. Patients were divided into three groups of 40 patients each. Endotracheal tube used for patients in group C was unlibricated, while that for group B and group L were lubricated betamethasone gel or 2% Lidocaine jelly respectively. Incidence and severity of postoperative sore throat, hoarseness and cough were observed. This study agreed with our study by showing Severity of postoperative sore throat at all times was less with betamethasone compared with Lidocaine and control group. This may be due to the prolonged anti-inflammatory action of betamethasone gel (Ayoub *et al.*, 1998).

Ayoub *et al.*, With institutional review board approval, written, informed consent was obtained from 87 ASA physical statuses I-III patients scheduled for elective surgery under general endotracheal anesthesia with propofol and a non-depolarizing relaxant. Subjects were informed that we would be inquiring about ST, C, and H. Exclusion criteria included operations involving the head and neck, anticipated rapid-sequence induction or airway difficulty, and patients who were ~16 yr old or who were using steroids preoperatively. Patients were randomly assigned so that before intubation, the endotracheal tube was lubricated uniformly by a un blind investigator from the cuff to the 15-cm mark with 3 mL of a water-soluble gel containing



chlorhexidine gluconate alone or with the addition of betamethasone 0.05% (equivalent to 3 mg of prednisone). Proving that widespread application of betamethasone gel significantly reduces the incidence of postoperative hoarseness of voice. This is disagreed with our study. The beneficial effect of Betamethasone gel application was observed in subsequent studies because of wide spread application of betamethasone gel to all portions of the tube that came in contact with the posterior pharyngeal wall, vocal cords, and trachea and not just confined to the tip and cuff of the tracheal tube (Sumathi *et al.*, 2008) .

One hundred patients (ASA I-II) to undergo Endo tracheal intubation, were randomly divided equally into two groups; 50 Case (Group A). 50 Control (Group B). The tracheal tubes for Case Group A were lubricated with 0.05% betamethasone gel and for the Control Group B with KY gel. Patients were interviewed at end of Procedures and 1 and 24 hour after extubation. Showing The incidence and severity of sore throat, hoarseness and cough, 1 and 24 hours postoperatively was reduced significantly in Case Group A. So Betamethasone gel, when was used for lubrication of endotracheal tubes pre-operatively, was shown to be effective in decreasing postoperative sore throat, hoarseness, and cough (Yentis, 2007).

This prospective, randomized, double blind, controlled study compares the incidence of postoperative sore throat, cough, and hoarseness of voice after general tracheal anesthesia when applying betamethasone gel (betamethasone group) or Lidocaine jelly (Lidocaine group) on the tracheal tube. One hundred and fifty ASA classes I and II patients undergoing elective surgeries under general oro tracheal anesthesia were randomized into three groups: Betamethasone gel, Lidocaine jelly, and control groups. In the



post-anesthesia care unit (Sumathi *et al.*, 2008). A blinded anesthesiologist interviewed all patients on postoperative sore throat, cough, and hoarseness of voice at 1, 6, 12, and 24 h after operation. Resulted in A wide spread application of betamethasone gel on the tracheal tube decreases the incidence and severity of postoperative sore throat, cough, and hoarseness of voice. (Fayyaz *et al.* , 2017). this clinical study was conducted at the Nishtar Hospital and Medical College, Multan, Pakistan, from July to December 2015, and comprised patients who were set to undergo elective surgery under general anesthesia. The patients were divided into two equal groups. In group 1, endotracheal tube was lubricated with betamethasone

gel (0.05%). In group 2, endotracheal tube was lubricated with 4.0% Lidocaine gel. SPSS 20 was used for data analysis. Generalized estimating equation was used to see the association between the treatment methods and severity of sore throat over time. Resulted in Local application of betamethasone gel was associated with reduced risk of post-operative sore throat as compared to local application of Lidocaine gel on the endotracheal tube.

This was a prospective, randomized, single-blind comparative study carried out among 120 ASA I and II patients aged 18-65 years undergoing elective surgery under general anesthesia with endotracheal intubation. Patients were randomly divided into three groups of 40 patients each. Endotracheal tube used for patients in group C was un lubricated, while that for group B and group L were lubricated up to 15 cm mark with 2.5 ml of 0.05% Betamethasone gel or 2% Lidocaine jelly respectively. Incidence and severity of postoperative sore throat, hoarseness and cough were observed at 1, 6 and 24 h following extubation. Resulted in Wide spread application



of 0.05% betamethasone gel to lubricate the endotracheal tube significantly reduces the incidence and severity of sore throat at 24 h of extubation but not of hoarseness or cough (Thapa *et al.* , 2017 ).

## Conclusion:

Applying Betamethasone and Lidocaine gel on the endotracheal tube is a simple and effective method of reducing the incidence of post-operative laryngeal spasm, sore throat, cough and hoarseness of voice in patients under general anesthesia with endotracheal intubation.

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**(تعهد الملكية الفكرية)**

إني الباحث ..... صاحب البحث الموسوم (.....)

(.....)  
اتعهد بان البحث قد انجز من قبلي ولم ينشر في مجلة اخرى في داخل وخارج  
العراق وارغب بنشره في مجلة (مجلة كلية الاسراء للجامعة للعلوم الطبية) في كلية  
الاسراء الجامعة.

التوقيع:

التاريخ:

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**(تعهد نقل حقوق الطبع والتوزيع)**

اني الباحث ..... صاحب البحث الموسوم (.....)

(.....)  
اتعهد بنقل حقوق الطبع والتوزيع والنشر الى مجلة (مجلة كلية الاسراء الجامعة  
للعلوم الطبية) في كلية الاسراء الجامعة.

التوقيع :

التاريخ :

3. تكتب الاسماء العلمية (اللاتينية) للنباتات والحيوانات وغيرها بحروف مائلة لتمييزها عن باقي النص وتسمى اسماء المواد الكيميائية (المبيدات، الادوية.... الخ) بأسمائها العلمية وليست التجارية.
4. يشار الى المصادر في متن البحث كما يلي:  
اللقب او الاسم الثالث للمؤلف والسنة اذا كان البحث بإسم باحث واحد، واذا كان مؤلفين فيذكران والسنة واذا كانوا ثلاثة فاكثر فيذكر اسم الاول واخرون والسنة.
5. ترتب المصادر حسب الصيغة العالمية (APA) وكما بالامثلة المذكورة :
  - أ. بحث في مجلة.  
اسم الباحث أو الباحثون، (السنة)، عنوان البحث، اسم المجلة، المجلد، العدد وصفحتي البدء والانتهاه للبحث.
  - ب. كتب.  
اسم المؤلف أو المؤلفون، (السنة) عنوان الكتاب، الطبعة، دار النشر وعدد الصفحات.
  - ج. الرسائل والاطاريح الجامعية.  
اسم الباحث، (السنة)، عنوان الرسالة او الاطروحة، العنوان (الكلية والجامعة) وعدد الصفحات.
  - د. بحث في وقائع مؤتمر او ندوة علمية.  
اسم الباحث أو الباحثون، (السنة)، عنوان البحث، اسم المؤتمر او الندوة العلمية، مكان الانعقاد، صفحتي البدء والانتهاه للبحث.

ترسل البحوث الى مجلة كلية الاسراء الجامعة للعلوم الطبية على العنوان الاتي:

كلية الاسراء الجامعة – قسم التوثيق والنشر

بغداد / العراق

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## دليل المقيّم Reviewer Guidelines

أدناه الشروط والمتطلبات الواجب مراعاتها من قبل المقيم للبحوث المرسلة للنشر في

هذه المجلة

1. ملّ استمارة التقييم المرسلة رفقة البحث المطلوب تقييمه بشكل دقيق وعدم ترك أي فقرة بدون اجابة.
2. على المقيّم التأكد من تطابق وتوافق عنوان البحث باللغتين العربية والانكليزية وفي حالة عدم تطابقهما اقتراح العنوان البديل.
3. أن يبين المقيّم هل ان الجداول والاشكال التخطيطية الموجودة في البحث وافية ومعبرة.
4. أن يبين المقيّم هل ان الباحث اتبع الاسلوب الإحصائي الصحيح.
5. أن يوضح المقيّم هل ان مناقشة النتائج كانت كافية ومنطقية.
6. على المقيّم تحديد مدى استخدام الباحث للمراجع العلمية الرصينة وحداثتها.
7. أن يؤشر المقيّم بشكل واضح على واحد من ثلاث اختيارات وهي:
  - البحث صالح للنشر بدون تعديلات.
  - البحث صالح للنشر بعد اجراء التعديلات.
  - البحث غير صالح للنشر.
8. يجب أن يوضح المقيّم بورقة منفصلة ما هي التعديلات الأساسية التي يقترحها لغرض قبول البحث.
9. للمقيّم حق طلب إعادة البحث إليه بعد إجراء التعديلات المطلوبة للتأكد من التزام الباحث بها.
10. على المقيّم تسجيل اسمه ودرجته العلمية وعنوانه وتاريخ اجراء التقييم مع التوقيع على استمارة التقييم المرسلة له رفقه البحث المرسل له للتقييم.

## المصادر

1. يستخدم النظام القياسي الدولي للوحدات (SI) ويمكن استعمال مختصرات المصطلحات العلمية المعتمدة عالميا على ان تكتب بشكل كامل اول مرة ترد في النص.
2. ترقم الجداول والاشكال على التوالي حسب ورودها في البحث وتزود بعناوين دالة على مضمون الجدول او الشكل ويشار الى كل منها بالترسل نفسه في متن البحث.

## دليل المؤلف Author Guidelines

- ادناه الشروط والمتطلبات الواجب مراعاتها من قبل الباحث للنشر في هذه المجلة بشرط أن لا يكون البحث قد نشر أو سينشر في أية مجلة علمية أخرى ولم يمض على انجازه أكثر من أربع سنوات .
1. يجب ان يكون عنوان البحث موجزاً قدر الامكان ومعبر عن البحث.
  2. اسماء الباحثين: تكتب اسماء الباحثين وعناوين عملهم بصورة واضحة مع البريد الالكتروني للباحث الاول.
  3. يجب ان يتضمن المستخلص موجزا واضحا عن البحث مكون من -250 300 كلمة متبوعا بكلمات مفتاحية 4-6. اذا كان البحث باللغة العربية فيكون المستخلص متبوعا بالكلمات المفتاحية اولا ثم المستخلص متبوعا بالكلمات المفتاحية باللغة الانكليزية ثانيا و العكس صحيح.
  4. المقدمة: تتضمن مراجعة المعلومات وثيقة الصلة بموضوع البحث الموجودة في المصادر العلمية وتنتهي المقدمة باهداف الدراسة وأساسها المنطقي.
  5. المواد وطرائق العمل : تذكر طرائق العمل بشكل مفصل ان كانت جديدة اما اذا كانت منشورة فتذكر بشكل مختصر مع الاشارة للمصدر وتستعمل وحدات النظام العالمي (S.I.Us) System International of Units
  6. النتائج والمناقشة : تعرض بشكل موجز وهادف وبنظام متوالي وتعرض النتائج بافضل صورة معبرة وتوضع الجداول والاشكال في أماكنها المخصصة بعد الاشارة إليها في النتائج.
  7. يستعمل نظام الارقام العربية وهكذا في البحوث المرسله للنشر وتمثل مناقشة النتائج تعبيراً موجزاً عن النتائج وتفسيراتها.
  8. تكون كتابة المصدر في القائمة المصادر متضمنة الآتي : اسم او أسماء الباحثين، سنة النشر وعنوان البحث كاملاً واسم المجلة ورقم المجلد والعدد وعدد الصفحات، مثال: حمزة، عصام شاكر و جارالله، عزيز لطيف و رشيد، فرقد عبدالله وسلمان، سرحان علي (2018)، تقدير مستويات الزئبق في مصل دم مستخدمين لحشوات الاسنان. مجلة كلية الاسراء الجامعة، المجلد الاول\العدد الاول: 281-294.
  9. المستخلص الانكليزي يجب أن يكون وافياً ومعبراً عن البحث بصورة دقيقة وليس بالضرورة ان يكون ترجمة حرفية للمستخلص العربي ومتبوعا بكلمات مفتاحية 4-6.

- يعرض البحث قبل النشر للتدقيق من قبل مقيّم لغوي (اللغة العربية واللغة الانكليزية) ويجب على الباحث الالتزام بهذه التعديلات.
- تلتزم المجلة بسياسة نشر تعكس التزامها بأخلاقيات البحث العلمي وبنود لجنة أخلاقيات النشر Committee of Publication Ethics
- تلتزم المجلة بجميع الضوابط الصادرة من وزارة التعليم العالي والبحث العلمي / دائرة البحث والتطوير الخاصة بالمجلات العلمية.
- تحتفظ هيئة التحرير بحقها باجراء التعديلات الشكلية واللغوية اللازمة.
- تحتفظ هيئة التحرير بحقها في عدم نشر أي بحث دون ابداء الاسباب وتعتبر قراراتها نهائية.
- لا ترد البحوث لا صاحبها سواء قبلت للنشر او لم تقبل.
- يزود صاحب البحث بنسخة ورقية واحدة من العدد الذي نشر فيه بحثه.

### شروط النشر

1. يطبع البحث بواسطة الحاسوب بمسافات مفردة بين الاسطر وبحجم خط 12 ونوع (Simplified Arabic)، اما العنوان باللغتين العربية والانكليزية فيكون بحجم خط 14 شريطة الا يزيد عدد صفحاته عن 15 صفحة بما في ذلك الجداول والاشكال والمراجع وعلى وجه واحد على ورق قياس A4 مع ترك هامش في حدود 2 سم من الاعلى والاسفل وهامش بحدود 3 سم من الجانبين الايمن واليسر.
2. لا يفضل نشر البحوث من قبل رئيس واعضاء هيئة التحرير في المجلة سواء كان البحث منفرداً أو مشتركاً.
3. يقدم البحث بثلاث نسخ ورقية ونسخة الكترونية بعد قبول البحث للنشر، يسلم البحث بشكله النهائي مطبوعاً بالنظام الاعتيادي بمسافة منتظمة لكافة الصفحات عدا الصفحة الاولى التي تتضمن عنوان البحث و اسماء الباحثين و عناوينهم و البريد الالكتروني للباحث الاول باللغتين العربية والانكليزية وعلى قرص مرن CD ببرنامج Microsoft / 2010Word .
4. تقبل البحوث باللغتين العربية و الانكليزية ويفضل كتابة البحث باللغة الانكليزية.

## تعليمات النشر

### في مجلة كلية الاسراء الجامعة للعلوم الطبية

- تصدر كلية الاسراء الجامعة (مجلة كلية الاسراء الجامعة للعلوم الطبية) في مجلد سنوي يضم عددين.
- تقوم المجلة بنشر البحوث العلمية للباحثين في تخصصات العلوم الطبية التالية:
  - الطب العام وطب الاسنان
  - الصيدلة
  - تقنيات المختبرات الطبية
  - تقنيات الاجهزة الطبية
  - التمريض
- يشترط في البحث المقدم للنشر أن لا يكون قد نشر أو أرسل لجهة اخرى للنشر .
- تخضع البحوث المقدمة للنشر في المجلة للتقييم حسب الاصول العلمية المتبعة من قبل اثنين من المختصين في موضوع البحث ومن ذوي الكفاءة، وقد يستشار بثالث عند الضرورة مع حجب أسماء المقيمين عند ارسال الملاحظات للباحثين.
- يلتزم الباحث باجراء جميع التعديلات التي يراها المقيمون ضرورية ويرفض البحث اذا اتفق المقيمون على رفضه، أو رفض من احدهما وتعديلات جوهرية من الاخر، أو تعديلات جوهرية من كلا المقيمين.
- يلتزم الباحث عند النشر في هذه المجلة بمليء استمارة التعهد الخاص ببيان فيها ملكيته الفكرية للبحث وعدم نشره سابقا في اي مجلة علمية او مؤتمر علمي.
- تخضع البحوث المقدمة للنشر لتحديد نسبة الاستلال (الانتحال) Plagiarism باستعمال برنامج Turnitin.



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