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# From the Editor



**Ahmad Husari** (*Chief Editor*)

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I would like to take this opportunity to thanks the authors who support the journal and send us their valuable papers. This is our second issue in 2009 and Middle East Journal of Internal Medicine (MEJIM) accepted four original contributions/ clinical investigations. Amro et al questioned the medical necessity of urgent chest films obtained after intubation in more than one hundred patients at a tertiary medical center in Jordan. The study concluded that intubation conducted by experienced staff may be followed by a routine rather than urgent chest film for proper positioning of an endotracheal tube. The second original study tested the therapeutic benefit of intratympanic steroid therapy in idiopathic sudden sensorineural hearing loss (ISSNHL) and noted that steroid injection is a promising and a safe method for treatment for patients with ISSNHL. The third study was, a prospective study, conducted on one hundred and fifty patients with soft tissue injury of knee joint in Libya. The study concluded that therapeutic phonophoresis with Ketoprofen Gel is significantly more effective than Diclofenac Gel in reducing pain of soft-tissue injuries of knee joint. The fourth study examined the troubling

violence of gunshot wounds in Pakistan. More than 600 cases were included in the study. Mortality and morbidity was exceptionally high in patients who were treated in local community hospitals and then referred to tertiary centers. Septicemia and multi organ failure (MOF) was a common cause of fatality and the need for effective resuscitation, training and updated equipment cannot be over emphasized.

In the section of clinical research and methods, MEJIM accepted two papers. The first paper is a basic science research paper that examined the effects of Adenosine, ADP, and ATP on mechanical properties and the excitation, contraction and coupling process of the jejunum smooth muscles. The second paper science paper examined the ill effects of electromagnetic field on the reproductive system in an animal model.

Finally, our journal this month is also rich with two interesting case reports as well as letters to the editor.

# Should Routine Chest X-rays be Mandatory in Post Intubation, Intensive Care Patients

## ABSTRACT

**Background** Chest radiography is one of the most commonly performed investigations in critically ill patients. Endotracheal intubation is a common procedure in intensive care units (ICUs), and may be performed for numerous reasons and under varying circumstances, both elective and emergent. The aim is to determine the clinical usefulness of immediate chest radiographs after endotracheal intubation critical care unit.

**Methods** This was a prospective study. Endotracheal intubations in a 31-bed intensive care unit and a 12-bed intermediate intensive care unit were included. After intubations were performed by an experienced intensive care physician, data on that individual was recorded, both demographic and procedural, and predicted radiographic findings were recorded on a data collection sheet. Experience at intubation was stratified into four levels of lifetime experience: fewer than 10 procedures, 10-20 procedures, 20-50 procedures, and more than 50 procedures. Radiographic findings evaluated, included endotracheal tube position and procedure-related complications. The postintubation chest radiograph was then reviewed and the actual findings were also recorded.

**Results** A total of 101 evaluable intubations were recorded, two of which were predicted to show tube malposition. Actual radiographic findings revealed 10 malpositions, three of which were too high and seven were too low (one at the level of the carina). A single witnessed aspiration that occurred during intubation was not radiographically apparent until 24 hours later. Only the tube positioned at the carina was felt to be of acute clinical significance or to place the patient at any acute risk.

**Conclusions** The incidence of endotracheal tube malposition after intubation was underestimated.

However, when performed by experienced critical care personnel, acutely significant malpositions were rare (one out of 101 intubations). We conclude that, in the absence of specific pulmonary complications, endotracheal intubations performed by experienced operators may be followed by routine, rather than 'stat' chest radiographs.

**Keywords:** chest radiographs, complications, cost containment, endotracheal tube.

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## Introduction

Endotracheal intubation is a common procedure in intensive care units (ICUs), and may be performed for numerous reasons and under varying circumstances, both elective and emergent. This procedure is performed by individuals with disparate levels of training and experience, ranging from junior residents in various specialties to anesthesiology attending physicians. It is common practice to obtain an immediate (stat) chest radiograph (CXR) upon completion of an endotracheal intubation to assess parameters such as tube position and possible procedure-related complications. The preponderance of literature that addresses the utility of such films includes a significant amount of data on intubations performed by relatively junior, unskilled individuals<sup>[1,2,3]</sup>. The purpose of this investigation was to determine the clinical utility of stat CXRs after endotracheal intubations performed by experienced critical care personnel.

## Patients and Methods

This was a prospective, observational study of patients in a 31-bed pediatric with adult medical/surgical/neurosurgical ICU and a twelve-bed adult intermediate ICU. Intubations were performed on the basis of routine clinical criteria, with recording of procedure-related information. Consent was therefore not required. Our policy requires that intubations in the ICU and intermediate ICU ordinarily be performed by a member of the Critical Care Service (attending or fellow) or a member of the Department of Anesthesia. All patients intubated by a critical care fellow (medical, pediatric, or anesthesia in at least their fourth year of postmedical school training) or attending were eligible for inclusion.

After each intubation the operator completed a data collection form that included operator and procedural details such as level of training, intubation experience (level 1, <10 intubations; level 2, 10-20 intubations; level 3, 20-50 intubations; level 4, >50 intubations), nature of the procedure (elective or emergent), indication, medications used, tube and blade size, cord visualization, number of attempts, and number of operators who attempted intubation before a successful intubation was achieved. Predicted CXR findings (tube placement, pulmonary complications) were recorded before review of postintubation films, which were obtained stat, in accordance with our unit protocol.

Tube placement could be predicted as being high, low or

normal, and if low, whether above the carina or in a mainstem bronchus. Operators were also asked to predict the likelihood of an abnormality or complication other than tube malposition being radiographically apparent (none, unlikely, probable, certain). Films were subsequently reviewed by members of the critical care team, and the results as determined by the critical care physician were then entered on the data forms in a separate section. Our criteria for endotracheal tube malposition are as follows: an endotracheal tube tip less than 2cm above the carina was considered too low, and a tip higher than the clavicular heads was too high. Complications to be recorded were as follows: new infiltrate/aspiration, pneumothorax, or 'other' (to be described by the operator).

## Results

A total of 105 oral intubations were performed during the study period. Of these, 101 were performed by critical care personnel; the remaining four were performed by junior house staff at the 1 or -2 level and were excluded from evaluation. Ninety-eight of the 101 intubations were performed by individuals at experience levels 3 or 4. Two were performed by an individual who had previously done 10-20 intubations and one by a person at experience level one. Of the 101 evaluable patients, 53 were identified as females, 45 as males, and three data forms did not contain sex data. Endotracheal placement was confirmed in all cases by end-tidal carbon dioxide detection and physical findings (bilateral breath sounds, condensation within the tube). No endotracheal tube was secured at a distance of less than 20 cm or more than 24 cm at the lips. Of these 101 intubations, only two were predicted to show incorrect placement on CXR. One was predicted to show high tube placement, the other low. Actual CXR findings as interpreted by critical care physicians demonstrated 10 incorrect tube positions: three were too low and seven were too high. Of the two predicted position errors, the intubation predicted to be too high was confirmed by CXR. The predicted low intubation was felt to be in an appropriate position on CXR. Sensitivity of the clinician's predictions of technically incorrect tube position was poor, with sensitivity of zero for low tube placement (none out of three), 14% for high tube placement (one out of seven), and an overall sensitivity of 10% (one out of 10). None of the low intubations was into a mainstem bronchus, although one was noted to be at the level of the carina. None of the tube malpositions occurred in patients whose sex was unrecorded; all 98 patients whose sex was recorded were included in the evaluation of sex-related differences in frequency of tube malposition. Six out of seven high tube placements occurred in men and two out of three low placements occurred in women. Four complicated intubations were reported: three esophageal intubations, all of which were recognized at the time of intubation and which demonstrated no apparent clinical compromise, and one clinically observed aspiration.

No CXR abnormalities were identified in the cases of esophageal intubation. Although radiographically apparent 24 hours later, the stat CXR showed no abnormalities in the case of aspiration.

## Discussion

In the present study critical care clinicians predicted

incorrect endotracheal tube placement in only two out of 101 procedures (2%), although review of postintubation CXRs demonstrated a true incidence of 10 out of 101 (10%). Despite the relatively higher than predicted rate of 'incorrect' endotracheal tube positioning on CXR and the poor sensitivity of the clinical predictions, only one out of 101 intubations (the placement of one tube at the level of the carina) required intervention (repositioning the tube) acutely. Because of this, we favor the term 'suboptimal' to describe the great majority of cases in which the tube was not in the generally accepted appropriate position, but in which the patient is not at any significant acute risk. Although the ability of the operators to accurately predict tube position was limited, stat CXR did not provide information necessitating acute interventions when intubations were performed by experienced personnel. This is probably due to the ability of the operators to identify accurately intratracheal tube placement at a level above the carina based on physical and end-tidal carbon dioxide findings. Possible complications were actually overestimated by the clinicians, and no unexpected complications (aspiration, pneumothorax, etc) were identified on the stat films. In fact, although radiographically apparent 24 hours later, the clinically identified aspiration was not present on the stat CXR.

Formal radiologic evaluation of these films was not part of the design of the present study. These procedures are often performed during hours when a radiologist is not readily available, and clinical decisions are made based upon the clinician's interpretation of the CXR. For these reasons only the clinician's predictions and interpretations were considered. Existing literature suggests that the frequency of tube malposition after endotracheal intubation justifies the routine obtaining of stat CXR after such procedures. Schwartz et al[3] reported an overall incidence of 42 out of 271 malpositions, with 10 mainstem intubations (nine in women, one in a man). In a broader evaluation of post-procedural CXR in the ICU, Gray et al[2] reported an incidence of endotracheal tube malposition of 28 out of 112, although the number predicted by those performing the procedures was only six out of 112. Six unsuspected mainstem intubations were identified by the postintubation CXRs. Brunel et al[1] reported that 30 out of 219 intubations required repositioning, including 10 mainstem intubations. The rate of tube malposition we demonstrated (10 out of 101) is consistent with the data previously reported. In contrast, however, the present study demonstrated only one instance in which acute tube repositioning was necessary: a low tube placement that was still above the carina. We would characterize this as demonstrating one significant malposition requiring acute intervention, and nine suboptimal tube placements.

The difference in rates of clinically significant tube malpositions between the present study and the previous ones cited may be largely due to the experience of the operators performing the intubations. In our unit endotracheal intubations not performed by members of the Department of Anesthesia are all performed by critical care fellows or attendants. In the paper by Schwartz et al[3], 62% of intubations were performed by non-anesthesia house staff. The study by Brunel et al[1] included intubations performed by a variety of personnel. Most (62%) were performed by anesthesia residents, but 16% were performed by medical or pediatric residents. Of the 10

mainstem intubations reported, two occurred after intubation by an attendant of the anesthesia department, and six when performed by residents under attending supervision. Although not explicitly stated, presumably the other two occurred when intubations were performed by unsupervised residents. Although Gray et al<sup>[2]</sup> did not specifically report how many of their intubations were performed by house staff, they acknowledge that over half of all the procedures they reviewed (which also included a variety of vascular procedures) were performed by junior house staff. Although high endotracheal tube placement is potentially problematic because of the theoretic increased risk of inadvertent extubation or vocal cord injury, the studies on assessment of endotracheal tube positioning have not addressed this issue to any significant extent.

Specific data on the actual likelihood of such complications as a function of tube position are lacking. Neither of two recent studies of unplanned extubations<sup>[4,5]</sup> evaluated tube position as a risk factor for such events. An earlier literature review by Grap et al<sup>[6]</sup> similarly yielded no published data on this issue. The failure of studies that assessed risk factors for unplanned extubation to evaluate this parameter suggests that there is little clinical concern about high tube placement in most circumstances. Endotracheal tubes deemed to be too high appear to 'require' repositioning as a matter of protocol and on the basis of a theoretic concern rather than because of an active threat. Clinically, however, a low intubation appears to have a much greater potential for actual harm than does a high one.

Owen and Cheney<sup>[7]</sup> presented data in 1987 that indicated that mainstem intubation could be avoided if the endotracheal tube was positioned so that the 23 cm mark was at the level of the upper incisors in 'normal' sized males and the 21 cm mark was at that position in 'normal' sized females. Brunel et al<sup>[1]</sup>, however, reported two mainstem intubations with the tube at the 21 cm mark. Schwartz et al<sup>[3]</sup> reported similar results, noting that external markings were less predictive of good tube position in women than in men. The present study demonstrated a significantly higher rate of high tube position in men than in women, but, possibly because of its low incidence, could demonstrate no difference between men and women in the frequency of low intubations. Our results suggest that using the distance markings on an endotracheal tube may help to avoid low tube placement, but does not eliminate the possibility of high positioning. Although routinely obtained in settings such as the ICU and Emergency Department, stat CXR is seldom obtained when patients are intubated before undergoing general anesthesia, even if a prolonged anesthesia time is anticipated. 'Standard' techniques such as auscultation of bilaterally equal breath sounds, ballotment of the balloon in the suprasternal notch, and identification of the centimeter marking at the teeth or lips is usually deemed to provide adequate assessment of tube position under these conditions. Stat CXR for a commonly performed procedure may increase the cost of care by resulting in more radiographs than would have ordinarily been performed in an individual patient. In addition, unnecessarily ordered stat CXRs may divert personnel from other, potentially more important work.

Limitation of such orders can result in both cost savings and an overall increase in the quality of care provided. Although

the present results demonstrate a moderate rate of technically incorrect or suboptimal endotracheal tube placement as demonstrated by CXR, only a very small percentage (1%) required acute intervention.

Endotracheal tubes are often repositioned on the basis of CXR findings. It should be noted, however, that attempting to optimize tube position with an essentially elective repositioning should not be confused with urgent repositioning of a tube that is in a position likely to result in patient compromise. With regard to the identification of possible complications, the operators were actually over-cautious in their predictions. Based on these results we conclude that intubations may be followed by routine scheduled CXR if no specific pulmonary complications are anticipated or observed, the operator is experienced in the procedure, and findings consistent with suprasternal endotracheal position of the tube are documented.

## Conclusion

The changing spectrum of micro organisms involved in UTI and the emerging resistance requires continuous monitoring to guide empirical therapy. Results from developing countries are different than those from the developing countries due to antibiotic prescribing habits, as most of the antibiotics are readily available over the counter. *E. Coli*, *Klebsiella* and *Pseudomonas* remain the common pathogens causing UTI both in hospital and community acquired infections. Ampicillin, SMX/TMP, Pipracillin, Amoxycillin/Clavulanic cannot be used as first line treatment in *E. Coli* in both hospital and community infections. Cephalosporins except Ceftriaxone and Nitrofurantoin can be used as empirical therapy in these patients. Nitrofurantoin cannot be used for *Klebsiella* or *Pseudomonas* infections during pregnancy or for hospital and community acquired infections. Quinolones and Cephalosporins are the antibiotics of choice.

Treatment should as far as possible be based on local data and since that may also vary from time to time in the same hospital, periodic surveillance is recommended.

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# Intratympanic Injection of Dexamethasone for Idiopathic Sudden Sensorineural Hearing Loss

## ABSTRACT

**Objectives:** To determine the efficacy of Intratympanic steroid therapy in Idiopathic Sudden Sensorineural Hearing Loss at King Hussein Medical Center.

**Patients and methods:** A prospective study that was conducted at Royal Medical Services during the period between January 2006 and January 2008. Twenty-three patients with inner ear disease manifested as idiopathic sudden sensorineural hearing loss (ISSNHL) were enrolled in the study. All patients received 4 mg/cc of dexamethosone twice weekly administered by intratympanic route over 2 weeks period. Patients were followed up by pure tone audiometry (PTA) on each visit and before the administration of the drug on the first 2 weeks, then every 4 weeks for 6 months. Hearing recovery was defined as complete or partial, depending on the final pure-tone average tested 6 months following the onset of hearing loss. Patients were classified according to severity of the onset of hearing loss into mild, moderate and severe sudden sensory neural hearing loss.

**Results:** The mean age of patients was 48.7 years with age range between 28 and 73 years with female to male ratio of 1.3 to 1.0. Four patients were found to have mild degree of hearing loss, 6 had moderate and 13 had severe hearing impairment. The mean hearing level improved from an average of 66.2 dB (HL) before treatment to 40.6 dB (HL) after treatment. Patients with severe degrees of hearing loss showed less response to treatment than those with mild to moderate degrees of hearing loss.

**Conclusion:** Intratympanic steroid injection is a promising method of treatment for patients with ISSNHL. It is considered as a relatively safe method of treatment with no significant complications that also applies to patients with contraindications to systemic steroids.

**Keywords:** Intratympanic, steroids, idiopathic sudden sensorineural hearing loss.

## Introduction

Idiopathic sudden sensorineural hearing (ISSHL) can be a debilitating disorder with various degrees of hearing loss. The estimated incidence of it is 5 to 20 cases per 100,000 with viral infection being the most common etiological factor.<sup>1</sup> Other etiologies include vascular occlusion and inner ear membrane breaks.<sup>2,3</sup>

Spontaneous recovery occurs in a good percentage of patients whether or not they receive treatment, but it had been noticed in many studies that the earlier the onset of treatment the better the chance of recovery the patient has. It was also noticed that the severe progressive onset of hearing loss associated with other inner ear symptoms like vertigo, has poorer chance of recovery.

Systemic steroids have been used and proved to be an

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effective method of treatment and are by far the most agreed upon line of treatment for ISSNHL.<sup>4</sup>

Other proposed lines of treatment include vasodilators, antiviral agents, hyperbaric oxygen, and plasmapheresis. Steroid therapy for ISSNHL is usually given orally soon after the onset of the hearing loss. A newly proposed route of steroid therapy is intratympanic injection of steroids which has the ability to achieve higher concentration of steroid in the inner ear, as well as less side effects induced by systemic steroid therapy.<sup>5</sup>

The aim of this study was to determine the efficacy of intratympanic dexamethosone therapy in ISSHL patients as first line treatment.

## Patients and Methods

Twenty three patients were enrolled in this clinical prospective study over a two year period at King Hussein Medical Center of the Royal Medical Services (January 2006 to January 2008). All patients had ISSNHL as a cause of hearing loss with contraindication to systemic steroids as first line treatment. All patients received 4 mg/cc of dexamethosone twice weekly administered by Intratympanic route over a 2 week period. Patients were followed up by pure tone audiometry (PTA) on each visit and before the administration of the drug on the first 2 weeks, then monthly for 6 months. Hearing recovery was defined as complete or partial, depending on the final pure-tone average tested 6 months following the incidence.

Inclusion criteria included the following:

- Patients were seen during the first 14 days or less after the onset of the hearing loss.
- Had unilateral hearing loss of more than 30 dB (HL) on more than 3 consecutive frequencies.
- Had no previous treatment of systemic steroids for the same illness.
- Had contraindication to systemic steroid therapy.
- Demonstrated a normal MRI scan with gadolinium of the retrocochlear region.

Any patient who didn't meet the above mentioned criteria was not included in the study. Other exclusion criteria included patients with otitis media or middle ear effusion or with ongoing medical illness that requires chemotherapy or

radiotherapy.

Patients were classified into three groups according to the degree of hearing loss. Mild ISSNHL was considered if the average hearing loss was = 40 dB (HL), moderate if between 41 dB (HL) and 60 dB (HL), and severe if > 60 dB (HL).

## Results

The mean age of patients was 48.7 years with age range between 28 and 73 years with female to male ratio of 1.3 to 1.0. Four patients were found to have mild degree of hearing loss, 6 had moderate and 13 had severe hearing impairment. The mean hearing level improved from an average of 66.2 dB (HL) before treatment to 40.6 dB (HL) after treatment. Patients with severe degrees of hearing loss showed less response to treatment than those with mild to moderate degrees of hearing loss (Table 1). Results are comparable to other studies in the literature using systemic steroids as first line of treatment for patients with ISSNHL.

## Discussion

ISSNHL is a sign of inner ear disease. It occurs in 5-20 per 100,000 population. However, only in approximately 10% of cases can a specific cause be identified.<sup>2</sup> The prevalent etiopathogenic theories in the literature include viral infection, membrane rupture, vascular alterations, and immune response.<sup>6</sup> In addition to the loss of hearing, ISSNHL is often accompanied by tinnitus and vertigo.

The interval between ISSNHL's onset and medical care appears critical to recovering hearing. Investigators found the proportion of patients experiencing spontaneous recovery declined after 30 days, and with a small proportion regaining hearing spontaneously after six months.<sup>1</sup>

If there is no improvement of hearing after a period of 2-3 months, with or without treatment, amplification and supportive audiology rehabilitation to the patient should be considered.

Steroids as a treatment for ISSNHL have emerged due to the work done by Wilson et al in the early 1980s who demonstrated a recovery rate of 61%.<sup>4</sup>

Different lines of treatment are still under investigation due to the significant number of failures encountered with whatever modality of therapy used. One line of treatment emerged to be of interest a few years ago, which is the subject of our study, the intratympanic steroid therapy.

The goal of intratympanic therapy is to improve hearing recovery by targeting treatment to the inner ear through the round window membrane.

Intratympanic corticosteroids treatment modality for ISSHL appears attractive because it avoids the side effects of systemic steroids and obtains higher inner-ear concentrations. It was shown that the permeability

of the round window by dexamethasone in an animal experiment resulted in a 72% increase in blood flow. These effects lasted throughout the duration of the experiment (two hours).<sup>7</sup>

The mechanism of steroid action on the inner ear is still not fully understood, although as a potent anti-inflammatory agent, steroids are suspected to cause vasodilatation with increased microvascular blood flow in the cochlea resulting in decreasing the endolymphatic hydrops, decreasing inflammation, or other unknown effects which are still under investigation.

Our study was designed for patients receiving intratympanic steroids as first line of treatment and showed almost similar results to those who received systemic steroids as first line of treatment.

The results of the present study revealed that nearly half of the patients in the treatment group (47.8%) showed significant hearing improvement with intratympanic administration of dexamethasone. Parnes et al in a study on intratympanic steroids treated 13 patients over a period of 1 to 6 weeks; seven patients (53.8%) improved by more than 10 dB after treatment.<sup>8</sup>

Studies in the literature suggest that intratympanic steroid administration is effective in patients with ISSHL as a second line of treatment for patients who have failed traditional systemic steroid administration. And around 60% of steroid-treated cases did not improve, or their hearing worsened over the treatment period and their losses remained permanent.<sup>9</sup>

Arriaga MA and Goldman S. suggested in their study that steroid administration after failure of systemic steroids is safe and effective in the treatment of ISSNHL.<sup>10</sup>

In another study done by Rauch SD<sup>11</sup>, it was found that steroid toxicity is reduced in intratympanic administration compared to systemic route with the advantage of achieving higher concentration in the perilymph of the inner ear. Their use as secondary-line therapy in non-responding ISSNHL cases has been approved in many other studies.<sup>12,13</sup>

## Conclusion

The results of the present study suggest that intratympanic dexamethasone administration is safe and as effective as systemic steroids for the treatment of ISSHL. Any patient with ISSNHL who has a contraindication to systemic steroid therapy is a candidate for intratympanic dexamethasone therapy as long as the inclusion criteria are met.

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**Table 1** Response to treatment according to severity of hearing loss

Patient Category	Average hearing loss prior to treatment	Average hearing loss post treatment
Mild ISSNHL	38.7	18.1
Moderate ISSNHL	55.6	25.7
Severe ISSNHL	80.3	54.4

# Phonophoresis with Diclofenac versus Ketoprofen for Knee Joint Injuries

## ABSTRACT

**Aim:** To comparatively assess the response in pain control after use of two drugs, Diclofenac versus Ketoprofen, in the process of phonophoresis.

**Methodology:** One hundred and fifty Libyan patients with soft-tissue injuries of knee joint were randomly assigned to receive phonophoresis with Diclofenac (group A) or Ketoprofen (group B) in the process of phonophoresis. Both groups received ultrasound three times per week for two weeks. The patient indicated their pain level by marking on a visual analog pain scale (VAS) at the start of treatment and at the end of the second week. ANOVA for repeated measures was used to analyze data.

**Results:** At the end of two weeks of treatment, both groups showed a significant decrease in pain level but for group B pain level decreased more significantly.

**Conclusion:** We conclude that the process of therapeutic phonophoresis with Ketoprofen Gel is significantly more effective than Diclofenac Gel in reducing pain of soft-tissue injuries of knee joint.

**Key Words:** Phonophoresis, ultrasound, Ketoprofen, Diclofenac, knee joint.

## Introduction

Soft tissue injuries at the knee joint are responsible for more than 12 million orthopedic visits per year. They are classified into sprains, strains, contusions, tendonitis, and bursitis. These manifest as pain around knee joint, reduced range of motion, and difficulty in activities of daily living. The sports related knee joint injuries are responsible for around 10% of time off-work. Medical treatment is started per RICER protocol (rest, ice pack, compression, elevation, and rehabilitation). After stabilization, rehabilitation includes use of rest, NSAIDs, physiotherapy. The surgical repair is reserved for advanced and non-responding patients. One of the rehabilitation measures is ultrasound. Ultrasound has been used for treatment of knee injuries for over 40 years now; however, the optimal dose schedule still remains to be defined<sup>(1)</sup>. In this, a high frequency acoustic wave is applied to the tissue leading to both thermal and non-thermal effects<sup>(2-5)</sup>. The therapeutic benefit of ultrasound is probably related to the increased blood flow, increased tissue extensibility leading to analgesia and relief of spasm<sup>(6-8)</sup>. In addition, changes in cellular permeability and metabolism may also contribute to the effect<sup>(6-11)</sup>. Local application of anesthetics including NSAIDs and steroids is the standard of care for these patients<sup>(19-22)</sup>. This application can be enhanced by use of ultrasound and involves both thermal and non-thermal mechanisms of ultrasound<sup>(5-10)</sup>. This technique in which ultrasound is used along with a pharmaceutical agent is known as phonophoresis<sup>(24)</sup>. Earliest evidence of benefit of phonophoresis has been well documented

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since 1967; with some of showing penetration up to 7 cm into tissues, but more recent studies have been doubtful<sup>(12-18)</sup>. Most of these studies had methodological shortcomings like randomization and assessment protocols. Papers have reported that common cream-based agents may hinder adequate transmission of acoustic waves as compared to gel-based agents. Controlled clinical studies comparing various agents are still rare. Studies are still awaited to establish the appropriate agent, concentration, type of vehicle, ultrasound frequency, and regimens.

The rationale of this study was to compare the efficacy of ultrasound driven gel-based phonophoresis using Diclofenac versus Ketoprofen for treatment of patients suffering from soft tissue injuries of knee joint at Department of Physiotherapy at Zawia Central Hospital. The subjective pain response was evaluated using Visual Analog Scale (VAS)<sup>(23)</sup>.

The primary objective was to evaluate relief of pain in these patients. This was accomplished using VAS checked before treatment and on the last day of phonophoresis.

Statistical analysis included comparison of mean score in both groups and their standard deviation. From this, t-test and p-value of the difference was obtained.

## Patients and Methods

One hundred and fifty patients who attended outpatient physiotherapy department at Zawia Central Hospital were included. All of these cases had been examined by the orthopedician at Zawia Central Hospital, Orthopedics Department. A diagnosis of soft tissue injury of knee joint

and subsequent stabilization was established by clinical and radiological parameters before referral to Department of Physiotherapy. Range of motion, musculoskeletal strength, and specific provocative testing were also assessed by the physical therapist at the initiation of phonophoresis and at the end of the study. The exclusion criteria are as listed in Table 1. The distribution of patient's characteristics in both groups is presented in Table 2 in brief. Informed consent was obtained from each patient in Arabic language.

All patients (150) included in study were randomized to either the Diclofenac or Ketoprofen group. All included patients received phonophoresis which included eight minutes of pulsed mode (50% duty cycle) ultrasound treatments with the ULTRASONIC -1200 (TEMA Srl, Pesaro, Italy) at a frequency of 1 MHz with intensity of 1 W/cm<sup>2</sup>, 3 times a week for 2 continuous weeks. In this process of phonophoresis, two drugs were used. Group A received Diclofenac gel (Diclofenac 1% gel, HERMOFARM, KONCERN A. D, Serbia, Montenegro). Group B received Ketoprofen gel (FASTUM gel, Ketoprofen 2. 5%, A. MENARINI International, Florence, Italy).

All male patients received phonophoresis on Monday, Wednesday, and Saturday while female patients were treated on Sunday, Tuesday, and Thursday. All patients continued with their activities of daily living without any significant changes. No other medication or intervention was required for any of them during the course of study specifically the use of oral NSAIDs. These patients continued with their advice and home exercise schedules.

**VISUAL ANALOG SCALE:** The patients indicated the pain with VAS from 0 to 10 points at the time of registration and at the end of sixth session. This was accomplished by subjective assessment by patients using standard bar chart extending from 0 to 10 with digital increments (1-10). No pain was scored at 0 and most severe pain at 10. This was assessed for pain during routine walking (activity-associated) and not rest pain at both observations.

## Results

At completion of study, 126 patients completed their phonophoresis as per schedule. These also included 17 patients who completed their planned 5 courses beyond 2 weeks but in less than 3 weeks. The remaining 24 patients did not complete their planned 6 courses and these were not included in final analysis. Out of these, 18 patients had delayed completion beyond 3 weeks, five patients dropped out and could not be traced for continuation of treatment, and one patient had interruption for 17 days due to an episode of fever which was diagnosed to be due to chest infection and unrelated to his orthopedic condition.

Out of 126 analyzed patients, 61 patients (48. 4%) were in the Diclofenac group while 65 patients (51. 6%) were in the Ketoprofen group. The patient characteristics are shown in Table 2. In both groups males predominated with 1. 3:1 ratio. The minimum age was 15 and the maximum age was 65 years while the mean age was around 30 years. The mean and median ages were slightly lower in Ketoprofen group (about 2 years). Right side was relatively less involved although equally randomized to both groups while there was discordance in distribution for left sided disease. This may be due to a smaller

strength of study.

The Ketoprofen group showed more significant fall in VAS as compared to the Diclofenac group. The mean score in the Diclofenac group fell from 5. 672 to 3. 639 while in the Ketoprofen group it fell from 6. 015 to 1. 831 (Figure 1). The mean±S. D. for pre-treatment score was 5. 85 ± 1. 644 while that for post-treatment was 2. 71 ± 1. 855 with a t value of 14. 17 and p value <0. 01. There was no observed complication of treatment reported in any of the patients during this study.

## Discussion

Residual pain and inflammation from knee joint soft tissue injuries are often treated by ultrasound. Counterirritants, anesthetics, and steroids are used to improve the efficacy of treatment<sup>(13,14,16,19,20,21)</sup>. The routes used for these agents include oral, injectable, as well as local application. Transdermal application of these agents is one of the safest measures and is widely used for these conditions<sup>(11,12,13,14,19,20,21)</sup>. A concurrent use of these agents with ultrasound may increase permeability of these agents through the skin by both thermal and non-thermal mechanisms<sup>(4-9)</sup>. The exact mechanism for this enhancement is currently under investigation. This enhancement in drug permeation by ultrasound and its mechanisms is still unclear.

Various studies have revealed conflicting results with use of various agents. Still, phonophoresis is current treatment of choice for various pathological conditions of knee joint, e. g., arthritis including tendonitis, bursitis, and ligamentous and meniscal injuries. Its efficacy over conventional ultrasound has been established by various authors<sup>(2,4,6,7,10,11,12,13,14,19,20)</sup>. Various agents tested for phonophoresis include opioids, NSAID'S, anesthetics, corticosteroids, and antibiotics<sup>(15-22)</sup>. To our knowledge, to date, no randomized trial has been published which compared any of these agents. In our center, the two most easily available agents include Diclofenac and Ketorolac. Both of these agents were currently in use before inception of this study at our center but the efficacy of one over another was never tested in a protocolized manner. We undertook this study to compare the efficacy of these two agents in our setup.

We noted a statistically significant decline in VAS for Ketoprofen group at end of phonophoresis as compared to Diclofenac group. Since there were no reported complications, these results indicate that Ketoprofen is a safe and therapeutically useful agent for phonophoresis and may be a better agent than Diclofenac when used for phonophoresis in patients with knee joint injuries. The major limitations of our study are the short duration of follow-up (2 weeks) and the lack of objective assessment tool. Another limitation is the lack of a control group which can surrogate for the process of natural resolution of soft tissue injuries. Hence, our results should be viewed in light of existing data from other studies and can be used as a baseline for further evaluations.

The mean age was around 30 years depicting that mainly the younger population is seeking physiotherapeutic intervention for conditions related to knee joints. This stresses the need for more effective physiotherapeutic measures for earlier rehabilitation for this younger population. Further studies are warranted to evaluate more efficacious treatment modalities.

## Conclusions

Both Diclofenac and Ketoprofen are effective agents for phonophoresis when used as physiotherapeutic modality for rehabilitation of adult patients with soft tissue injuries of knee joint. Ketoprofen has a statistically significant advantage over Diclofenac when used for phonophoresis. A long-term evaluation is required to see if this advantage is maintained over a longer period of time.

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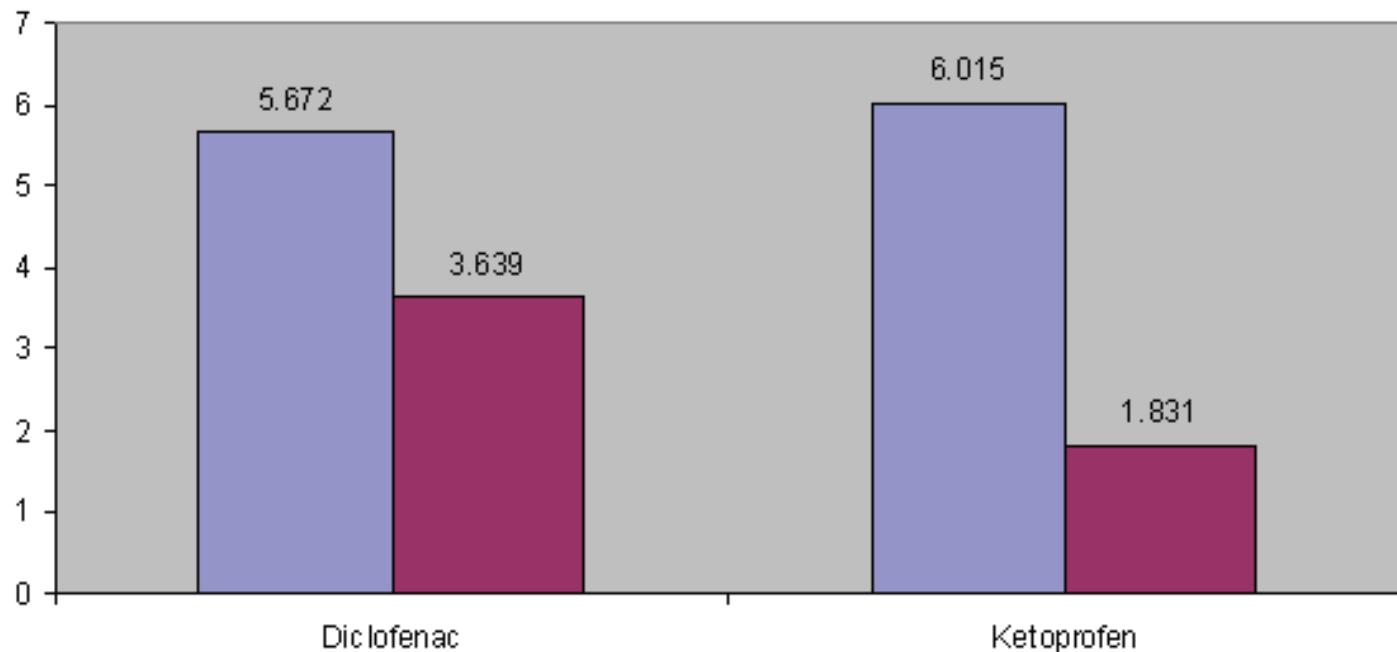
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**Table 1** Exclusion criteria

Infection at treatment site
Known allergy to drugs
Steroid injection within previous 3 months
Any co-morbid condition including peripheral vascular disease, cardiac pacemakers, malignancy, local hemorrhage, and pregnancy

**Table 2** Patient characteristics

	<b>Diclofenac</b>	<b>Ketoprofen</b>
Total patients (n)	61	65
Males	35 (57.4%)	37 (56.9%)
Females	26 (42.6%)	28 (43.1%)
Age (years)		
Range	15-63	16-63
Mean	31.1	28.9
Median	30	28
Side		
Right	30	30
Left	31	35
Pre-score		
Total	346	391
Mean	5. 672	6.015
Post-score		
Total	222	119
Mean	3.639	1.831

**Figure 1:** Mean VAS reduction (Diclofenac versus Ketoprofen)

# Abdominal Gunshot Wounds; Analysis of 626 Cases Managed in a Single, Surgical Unit at Tertiary Care Hospital of North West Frontier Province (NWFP), Pakistan; A Pilot Study

## ABSTRACT

**Objective:** To conduct a pilot study of demography and management of abdominal gunshot wounds. To identify the causes of morbidity and mortality and to find out the areas where more work is needed to be done.

**Material and methods:** This pilot project was conducted in a single surgical unit for a period of 4.5 years. Patients coming to casualty surgical department with gunshot injuries to abdomen alone or associated with other parts of the body are included in the study. Demographic aspects were noted in a proforma.

Organs injured and their management was recorded in detail. Morbidity and mortality was calculated. Reasons for mortality are analyzed. Any deficiency in the management of such patients is highlighted. Descriptive statistics is applied for analysis of the data.

**Results:** Total patients managed in 4.5 years were 626. Out of these 532 (85%) were male patients. Four hundred and forty (70%) were of 15 to 39 years of age. The reason was attempted homicide in 447 (71.4%), attempted suicide in 21 (3.35%), accidental injuries were 97 (15.4%) while stray bullets were the cause in 51 (8.14%) cases. Klashnikove guns (AK-47) were used in 365 (58%) cases, Kalashnikove (bore 222) in 27 (4.31%), 32-bore pistol in 72 (11.5%), 5mm rifle (gun) in 83 (13.25%) while shotgun was used in 55 (9%) cases. In 24 cases the type of gun used was unknown. Single bullet injury was the cause of wounds in 235 (37.5%) cases and multiple bullets in 336 (53%) cases. Out of six hundred and twenty three, 528 cases were operated on in Casualty Operation Theatre (COT) while 95 were operated on in the main surgical O.T. Ten (1.6%) were operated on by Professor, 22 (3.5%) by Associate Professor, 40 (6.4%) by Assistant Professor, 153 (24.5%) by Senior Registrar, 398 (64%) by Senior Residents. Morbidity was 342. Mortality was 62 (10%). Most of the patients who died had injury to duodenum, pancreas and liver.

Mortality was high in those patients who were operated on initially in a peripheral hospital and then referred to Lady Reading Hospital with complications. Septicemia and multi organ failure (MOF) was a common cause of mortality.

**Conclusion:** Gun shot wounds are very common in this part of the world. Klashnikove is the commonest gun used. Younger age group people are affected by this type of trauma. Attempted homicide is the commonest mode of injury. Injuries of the duodenum, pancreaticoduodenal area and liver are associated with high mortality. Peripheral hospitals need to be upgraded with better equipment and trained and experienced surgeons.

**Key words:** Gunshot wounds, abdomen, demography,

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management, morbidity, mortality, North West Frontier Province (NWFP), Pilot study.

## Introduction

North West of Pakistan has a long belt of tribals which separates Pakistan from Afghanistan. Weapons are manually manufactured and sold at cheaper rates in this part of the country. By culture we are Pathans. Disputes run in families as a cultural belief in tit for tat. The government machinery can do little to solve these disputes<sup>(1)</sup>.

Lady Reading Hospital is a tertiary level hospital in the province. It has a bed complement of 1500, and all the specialties of various disciplines are established here. We have separate units for vascular surgery, cardiac surgery, thoracic surgery, pediatric surgery, urology, orthopedic surgery, and department of traumatology etc etc.

Firearm injuries are very frequently seen and managed in various departments of this hospital including general surgery. The burden of such injuries on the public is enormous. The word ‘prevalence’ of Firearm Injury usually means the estimated population of people who are managing Firearm Injury at any given time (i.e. people with Firearm Injury). The term ‘incidence’ of Firearm Injury means the annual diagnosis rate, or the number of new cases of Firearm Injury diagnosed each year (i.e. getting Firearm Injury). In Pakistan according to US census report 2004 the incidence of firearm injuries out of a total of population estimated used 159,196,336, recorded were 16,899<sup>(2)</sup>.

By searching the English literature, no reference could be found to any such study conducted in NWFP. The idea is to get insight of such injuries and conduct more research work in future on various aspects of this type of trauma. Various aspects like the gender, types of weapons, the way the wounds are inflicted, the various organs injured, the surgical procedures performed in various situations and post operative morbidity and morality may all be addressed.

## Materials and Methods

This pilot study was conducted in a single surgical unit of the Post Graduate Medical Institute, Lady Reading Hospital Peshawar. A retrospective analysis of all patients admitted with gunshot wounds of abdomen in fifty four months period has been carried out. Data was recorded from the time of admission till the time of discharge. Most of the patients below the age of 15 years went to pediatric surgery unit and so are not included. However few cases below 15 years of age came to our unit as these children did not have a lady attendant as required by the pediatric surgical unit of the hospital. Patients who were initially operated at other hospitals and referred to the unit post operatively are included. A proforma was designed where all the necessary information was recorded.

Operation notes were written by the principal surgeon who operated on patients. Various grades of surgeons from Senior Trainee to Professor were involved in the care of these patients. Any morbidity during the hospital stay was noted and treated accordingly. Data has been analyzed by applying descriptive statistics.

## Results

In 4.5 years the total number of patients with abdominal gunshot wounds managed in a single surgical unit was 626. Out of 626 patients 94 (15%) were female while 532 (85%) were male patients. Twenty Six (4%) were below the age of 15 years. While 440 (70%) were between 15-39 years of age. One hundred and thirty one (21%) were 40-70 years old while 29 (5%) were above 70 years (table-1). Out of 626 cases 447 (71.5%) were attempted homicide, 21 (3.35%) suicidal, 51 (8.14%) stray bullet while 97 (15.5%) were accidental injuries. In 10 (1.6%) patients the intentions was not disclosed by the patient/ attendants (table - 2). Single bullet injury was recorded in 235 (37.5 %). Three hundred and thirty six (54%) patients had sustained multiple bullet injuries. The weapon used was Kalashnikov (AK47) in 365 (58%) cases, Kalakov in 27 (4%), shotgun in 55 (9%), pistol in 72 (11.5%) while 83 (13.5%) patients had bullet injury with 5 mm rifle. In 24 (4%) patients the nature of the gun was unknown (table-3).

Three cases did not need surgical intervention. Out of 623 cases, 398 (64%) were operated by Senior Residents, 153 (24.5%) were operated by Senior Registrar, 40 (6.4%) by Assistant Professor, 22 (3.5%) by Associate Professor and 10 (1.6%) by Professor, as a principal surgeon (table - 4). Out of 623 patients, 489 (78%) were operated in Casualty O.T while 134 (21%) were operated in main OT. Out of 134 patients operated in main OT, 40 (30%) were redo.

Among the hollow visceral organs; 153 stomach, 324 small gut, 190 large gut, 35 duodenal, 56 rectal and 9 anal canal injuries had been recorded. Stomach and small gut had been repaired. Large gut wounds were repaired with proximal diverting stomas. Intraperitoneal rectal injuries had been repaired with a diverting sigmoid colostomy. Part 1 duodenum was injured in 20 cases, part 2 in 4, part 3 in 5, part 4 in 6 cases. Part 1 and 2 had been repaired while part 3 and 4 had been repaired along with diverting Gastrojejunostomy Anastomosis (GJA). In 5 patients combined Pancreaticoduodenal injuries had been recorded. These had been repaired with diverting GJA. Among the 9 anal canal injuries; 3 patients had loss of

sphincter control mechanism, secondary to direct injury to the sphincter. In these 3 patients primary repair of the sphincter with diverting sigmoid colostomy had been done.

Among the solid visceral injuries, various grades of liver injuries were seen in 297 patients, spleen in 177 and pancreas in 43. Among 297 liver injuries, 4 patients had ligation of hepatic artery to get control of profuse bleeding from liver lacerations. Out of 177 splenic injuries, 70 patients had splenectomy for grade III and IV injuries. Out of 43 pancreatic injuries, 6 were in head, 7 in body and 30 in tail. All had been repaired with silk suture and external drainage instituted.

Diaphragm had been injured in 112 patients. In 38 patients laceration was on right side, 57 on left side while in 17 it was bilateral. All had been repaired with silk suture. In the urological tract various grades of kidneys laceration were found. One hundred and forty five patients had their Kidneys injured. Fifty-six were on right side, 88 on left side while 1 patient had both kidneys injured. In 26 patients Nephrectomies were done for grade III and IV injuries. Rest of the kidneys had been repaired with absorbable sutures. Ureteric injuries were recorded in 31 patients.

Right ureter was perforated in 16, left in 15 cases. All these had been repaired on DJ stents. Urinary bladder was injured in 142 cases. It was intraperitoneal in 110 and extraperitoneal with bladder neck and proximal urethral injuries in 32 cases. Intraperitoneal wounds were repaired while in extraperitoneal injuries suprapubic cystostomies were done. Long bones fractures were seen in 132 cases. These were the direct injuries due to bullets. In 42 cases upper limbs long bones were fractured while in 90 cases, lower limbs bones were fractured. Orthopaedic team managed all these. Haemothorax was recorded in 136 cases. It was on right side in 54, left side in 57 and bilateral in 25 cases. All these were managed with chest drains. However 4 needed thoracotomies for continuous bleeding. Thoracic team managed these. Direct spinal cord bullet injuries were seen in 34 cases. 32 had paraplegia and 2 monoplegia. These patients were later transferred to neurosurgical unit. Pelvic bones fractures were seen in 44 patients. Orthopaedic team treated all these conservatively. Vascular injuries were seen in 14 cases. In 8 Inferior Vena Cava, 3 external iliac vein, 1 common iliac vein, 1 femoral artery and 1 brachial artery injuries had been recorded. Vascular team operated all these at the time of laparotomy. In 2 cases sciatic nerve injury, in 2 radial nerve, in 1 median nerve, 1 ulnar nerve and in 3 peroneal nerve injuries were recorded.

Neurosurgical team initially treated all these conservatively. Soft tissue injuries were seen in 419 patients. Soft tissue, injuries of neck were recorded in 14 cases, abdominal wall in 115, chest wall in 30, torso 48, upper limbs 89, lower limbs 102, pelvic area in 6 and perineum in 9 cases. In two male patients soft tissue of scrotum and penis were injured. In 2 female patients breasts were wounded, in one right breast and in other one left side. One 30 years old female sustained gun shot wound lower abdomen. She was 3 months pregnant. She had perforation anterior wall of uterus, through and through perforation body of the foetus and then posterior wall of the uterus.

Foetus was found dead at the time of exploration. Another

female of 25 years age had lacerated uterus as a result of gunshot, 4 months old dead foetus was found lying free in the peritoneal cavity. Total complications recorded in this study were 342 (Table-5). Mortality was 10% (Table-6).

## Discussion

In this study 626 patients with gunshot wounds were managed in a 40 beded General Surgical Unit in a period of 56 months. Comparatively low prevalence of gun shot wounds have been reported from Western Europe and South America. In this study 626 patients with Firearm wounds were managed in a 40 beded General Surgical Unit in a period of 56 months. In a study from Sweden 1559 patients (including all the hospitals of the country) with gunshot wounds were managed in 8 years<sup>(3)</sup>. Eleven percent of these were homicidal in nature and 3.35% were suicidal. Van-Haarst EP et al reported 48 gunshot wounds in 10 years period<sup>(4)</sup>. Cornwell et al reported 848 patients with gunshot wounds of abdomen, from January 1995 to December 1996<sup>(5)</sup>. Zantut LF et al reported 194 gunshot wounds of abdomen from three larger urban trauma centers<sup>(6)</sup>. Demetriades D et al reported 309 patients with abdominal gunshot wounds in a period of 16 month<sup>(7)</sup>. A national study (Pakistan) has reported 63 patients with FAI abdomen in a period of 2 years<sup>(8)</sup>. From Jamaica 37 patients were reported in 1995 with gunshot wounds of abdomen in a period of 12 months<sup>(9)</sup>. Sosa J L reported 121 patients with abdominal gunshot wounds<sup>(10)</sup>.

We recorded male to female ratio of 5.6: 1. In a study conducted in South Africa the male and female ratio of 4.5: 1 has been reported<sup>(11)</sup>. In our study 70.3 % cases (440 out of 626) were in the age group of 15 - 39 years and the elderly population (i.e. 70 years and above) was affected by gunshot wounds is 4.63% only. In a study from Karachi (Pakistan) 4091 attempted homicide cases have been reported in 2002. The study was conducted in 29 months and authors reported that 95% (n=3864) were male patients<sup>(12)</sup>. In a study from Bangladesh suicide was found to be more common in female of 10-50 years age group<sup>(13)</sup>.

In this study 71% were due to homicide. Three major causes (firearm, blunt trauma and sharp force) of homicide were recognized in a study of 4122 cases in 6 years when data from all around the country was collected in Bangkok and its provinces. Maximum cases were in the 3rd decade of life<sup>(14)</sup>. Homicide has been reported as the major cause of death in Brazil in persons age 15 - 44 years<sup>(15)</sup>. This is in contrast to our study. The reason may be that elderly people are still given due respect in our society and that young, active people are involved in disputes and homicidal tendency.

The decision to explore patients with gunshot wounds of abdomen in our setup is clinical. Many researchers have reported the role of Laparoscopy both for diagnosis and treatment<sup>(10,16)</sup>. Some authors have reported that diagnostic laparoscopy may reduce the number of negative laparotomies<sup>(10)</sup>. The importance of serial clinical examination cannot be ignored. In our set up laparoscopic facility is not available in Accident and Emergency department and therefore we rely on clinical examination of the patients with abdominal gunshot wounds. A sensitivity of 100% and specificity of 71.4% of clinical assessment has been reported in the literature for laproscopic surgery<sup>(17)</sup>. Diagnostic peritoneal lavage (DPL)

has been reported to be 99.98% sensitive and 98% specific<sup>(18)</sup>. DPL has been found to be highly predictive of intra-abdominal injury particularly in wounds of the gut<sup>(19)</sup>. In gunshot wounds a policy of mandatory laparotomy WAS adopted in our study.

Surgery of the solid viscera depends on the grade of injury to that organ. In our study among 297 (47.7%) liver injuries, four patients had their hepatic artery ligated to minimize hemorrhage from the liver wounds. We treated our grades I, II, and III injuries with sutures. In grade III we also did perihepatic packing. Similar approach have been reported by others<sup>(20,21)</sup>. Penetrating injuries to liver present a therapeutic challenge, because these patients die of continuous bleeding. Balloon tamponade has been reported to be especially effective in gunshot wounds of liver<sup>(22)</sup>. In a study of 304 patients with gunshot wounds of liver; resectional debridement and perihepatic packing has been strongly recommended in grades III, IV and V wounds<sup>(23)</sup>.

One hundred and seventy seven (28.5%) patients out of 623 had splenic wounds. Grade-I and grade-II were repaired while in grade-III and grade-IV splenectomies were done. The same approach is suggested in literature<sup>(24)</sup>. Most of the time it is difficult to know about pancreatic injury preoperatively. In gun shot wounds of the upper abdomen such injuries may be considered as there is not much time to perform diagnostic tests for pancreatic wounds because these patients are in hypovolumic shock. In our study 43 (7%) patients were found at the time of laparotomy to have pancreatic wounds. All these were repaired with non-absorbable sutures and external drainage. This has been the practice in this hospital at least for the last 30 years (opinion of the senior surgeons in the province,unpublished). Small numbers of pancreatic gun shot wounds have been reported by various authors diagnosed mostly at laparotomy. External drainage only, pancreaticoduodenectomy and distal pancreatectomy have been reported as the procedures performed<sup>(1,25)</sup>. All 112 (18%) diaphragmatic wounds were repaired with silk suture. These patients had thoraco-abdominal gunshot wounds. One hundred and nineteen patients have been reported in a study with penetrating thoracoabdominal trauma with 42% incidence of diaphragmatic injuries<sup>(26)</sup>.

One hundred and forty five (23.3%) patients had their kidneys injured with gunshot. Traditionally gunshot wounds of kidneys are managed by surgical exploration. Grade I and II were repaired while in 26 patients of grade III and IV nephrectomies (2%) were done. Grade III&IV renal injuries carries significant risk of delayed bleeding.

Nephrectomy rate as high as 55% and as low as 16% have been reported in the literature<sup>(27,28)</sup>. Some authors have suggested conservative management of renal gun shot wounds in hemodynamically stable patients of grade I and II injuries<sup>(29)</sup>. In our study 31 (5%) patients had ureteric wounds, which were repaired over DJ Stents.

A study reported 15 gunshot wounds of the ureter. In 4 patients they did ureteroneocystostomy and in the rest they did repair with DJ Stent<sup>(30)</sup>. Preoperatively; it is not always easy to diagnose ureteric injury. Most of the time these injuries are found at the time of exploration for gunshot wounds of abdomen. Some authors recommend exploration of the retroperitoneum as the "only" definitive method of excluding

gun shot wounds of ureters<sup>(30,31)</sup>.

In our study 142 (23%) cases of urinary bladder wounds were recorded. One hundred and ten intraperitoneal wounds were primarily closed and urethral catheter drainage instituted. In 32 cases of extraperitoneal bladder neck injuries or proximal urethral injuries; suprapubic cystostomies were done and definitive procedures were performed at a later date. Similar approach has been reported by other authors<sup>(32)</sup>. Tiguert R reported 5 patients with gunshot wounds of urinary bladder, 2 with concomitant complete posterior urethral transection. All were treated operatively<sup>(33)</sup>. In our study two male patients had gunshot wounds of the external genitalia.

These patients were managed with wound excision and secondary closure. In one patient left testicle was lost and the right was saved by putting it in an artificial pouch made surgically in the groin. After 3 months when all the wounds had healed, the testis was brought down into the scrotal neopouch. In our study 2 pregnant female patients sustained gunshot wounds to uterus. In both cases uterine perforation were noted with dead fetuses in peritoneal cavity. Both mothers survived. A case of gunshot wound to the second trimester gravid uterus has been reported with dead foetus. Mother was treated for the injuries at laparotomy while the foetus was not removed at the time.

She delivered normally a dead foetus per vaginum on 2nd post operative day<sup>(34)</sup>.

Stomach injuries were recorded in 143 (23%) cases out of 623. All these wounds were repaired primarily with no morbidity. A study by Croce MA et al reported that gastric injuries are equivalent to colonic wounds in their contribution to intra-abdominal abscess/sepsis (35fresh). However we did not come across any such complication. We recorded 35 (5.6%) cases of duodenal wounds. In 5 patients combined duodenal and pancreatic wounds were recorded. Wounds of first and second parts were primarily closed. Wounds of third and fourth parts were closed with diverting gastrojejunostomy anastomoses (GJA). Wounds of pancreas in these patients were separately sutured. We recommend that complicated high risk duodenal injuries should be managed by duodenal diversion. All jejunal and ileal wounds were primarily closed in our study. This is the world recognized practice<sup>(36)</sup>. In our study 190 (30.5%) patients had colonic wounds. These were primarily closed with proximal diverting stomas. However more recently studies have shown that primary closure of colonic gunshot wounds may be undertaken without diverting stoma. Primary repair of penetrating colonic injury has been recommended in haemodynamically stable patients<sup>(37,38,39)</sup>. Colostomy has been found to be safe and effective method of treating patients with gunshot wounds and other penetrating injuries of the colon. We have been practicing diversions as these patients are hypovolumic, has multiorgan injury and mostly come late(more than 6 hrs). Segmental resection of badly lacerated colon and end to end anastomosis is also reported<sup>(40)</sup>.

Other research workers have reported that if colonic gunshot wounds are associated with one of the risk factors i.e PATI of 25 or more, 6 units or more blood transfusion, 6 hours or longer time elapsed between injury and surgery then diversion still has a room for consideration<sup>(14)</sup>. Fifty-six (9%) patients had rectal wounds.

Thirty eight patients had intra-peritoneal perforation which were repaired with diverting sigmoid colostomy.

Twelve had middle 1/3rd perforations. These were primarily closed transperitoneally after mobilization and diverting sigmoid colostomy done. Drainage of the extraperitoneal space was done transperitoneally. In 6 patients with extra peritoneal lower 1/3rd rectal trauma, diverting sigmoid colostomy along with wash outs and presacral drainage was done. Almost similar approach is recommended in the world literature<sup>(8,41,42)</sup>. In our study 9 patients had wounds of the anal canal, anal orifice and sphincter. Sphincters were repaired primarily with diverting stomas. The wounds of the anal canal and orifice without sphincter damage were managed operatively conservatively. Total complications recorded in our study were 342 (table 5). These patients were treated accordingly. Biliocutaneous fistula dried up with conservative treatment in 6-8 weeks time. Proton pump inhibitors were used in hematemesis. Duodenal fistula occurred in 6 patients. Out of these 5 (8.06%) died. One recovered with redo surgery where Roux-En-Y was done. Total parenteral nutrition was instituted to these patients for 6 weeks. Vesicocutaneous fistula was recorded in 2 patients. Both were managed conservatively.

Small bowel fecal fistula occurred in 22 patients. All except 8 low output fistulas were managed conservatively. In the rest of the eight patients 7 (11.30%) died secondary to mal nutrition while one recovered after re-exploration and resection anastomosis. Out of 626 patients, 623 were operated, 62 died, a mortality of 10%.

Three patients died of pulmonary embolism secondary to DVT. Twelve (19.35%) patients died of continuous hemorrhage from hepatic wounds while 1 had extensive soft tissue wound of the left buttock and he also died of continuous bleeding. Twenty eight patients died of septicemia. Eighteen of these were those who were initially operated in a peripheral hospital. On arrival to our care, they were re-explored and all of them had missed injuries to the colon and small gut. Six (9.68%) patients of pancreatico-duodenal wounds died. In our study mortality was found to be very high in patients with liver wounds. Twelve (19.35%) of 623 patients died of continuous bleeding from liver wounds. Liver related mortality of 9.6% has been reported in a study<sup>(23)</sup>. In this study pancreatico-duodenal/duodenal wounds were responsible for death of 6 patients. Ten percent (10%) mortality has been reported in a study, in patients with pancreatic or pancreaticoduodenal wounds. In severe injury of the pancreas and duodenum, pancreatico-duodenectomy has been suggested<sup>(43)</sup>. Complicated duodenal injuries require sophisticated techniques to be dealt with, as suture line dehiscence is a common and dreadful complication. Diversion and pancreatico-duodenectomy may be considered for better results<sup>(44)</sup>. More work is needed to be done to improve the management of duodenal and pancreatic wounds. Another common cause of mortality in our study was septicemia. Twenty-eight out of 623 patients died of this cause. Most of these patients (24/28) had multi-organ injuries. Third generation cephalosporin (Ceftriaxone, Rocephin, Roche UK) was used in all these patients (as per culture report) but they could not survive. Antibiotics may need to be instituted immediately after abdominal gunshot wounds to prevent development of septicemia in such injuries.

Peripheral hospitals need to be upgraded with equipments and expertise. This will help to manage these patients immediately after they sustain injury. Patients take longer time to reach Lady Reading Hospital for management. Trained surgeons especially in abdominal trauma need to be posted in peripheral hospitals. This will greatly improve the care of the patients and may result in decrease in mortality and morbidity from gunshot wounds of abdomen.

## Conclusion

Gunshot wounds are more common in young male individuals. Kalashnikov (AK-47) is the commonest gun used in cases of homicide. Mortality is high in patients of duodenal and pancreaticoduodenal wounds and extensive lacerations of liver. More research work is being planned to improve care of such patients. Patients operated initially in a peripheral hospital had high mortality secondary to septicemia. The type, the exact time and the dosage of antibiotics need to be reassessed.

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**Table 1.** Age wise distribution (n=626)

Age	No	% age
Less than 15 years	26	04.15%
15 —39 years	440	70.28%
40 —70 years	131	20.92%
More than 70 years	29	4.63%

**Table 2.** Intension of the gunshot wounds (n=626)

	No	% age
Attempted Homicide	447	71.40%
Attempted Suicide	21	03.35%
Accidental	97	15.49%
Stray bullet	51	08.14%
Unknown	10	01.59%

**Table 3.** Type of gun/ weapon used (n=626)

	No	% age
Klashnikov	365	58%
Kalakove	27	04%
32 bore pistol	72	11.5%
5mm rifle	83	13.5%
Shotgun	55	09%
Unknown	24	04%

**Table 4.** Grades of surgeons who operated as a principal surgeon (n=626)

Grade of surgeon	No	% age
Senior Residents	398	64%
Senior Registrar	153	24.5%
Assistant Professor	40	06.4%
Associate Professor	22	03.5%
Professor	10	01.6%

**Table 5.** Post operative complications (n = 342)

Morbidity	Frequency	% age
Wound infection	118	34.50%
Wound dehiscence	56	16.38%
Chest infection	45	13.16%
Urinary tract infection	78	22.80%
Retention of urine	22	06.43%
Intravenous-line phlebitis	25	07.30%
Deep veins thrombosis	16	04.68%
Deep veins thrombosis, resulting into Pulmonary Embolism	03	00.88%
Confusion / irritability	42	12.29%
Psychiatric disorders	18	05.27%
Haemetemesis	05	01.46%
Biliocutaneous fistula	06	01.75%
Jaundice 20 blood transfusion	16	04.68%
Duodenal fistula	06	01.75%
Vesicocutaneous fistula	02	0.58%
Small gut fistula	22	06.43%

**Table 6.** Causes of Mortality (n = 62)

Mortality	No	% age
Pulmonary embolism	03	04.38%
Bleeding hepatic wounds	12	19.35%
Bleeding soft tissue buttock wound	01	01.61%
Septicemia	28	45.16%
Pancreaticoduodenal wounds	06	09.68%
Small gut fistula	07	11.30%
Duodenal fistula	05	08.06%

# Effects of some Purines and Their Antagonistic Compounds on Eabbit Intestinal Smooth Muscle Contraction Induced by KCl and Ach

## ABSTRACT

**Objective:** This study was designed to evaluate the mechanical properties and the excitation- contraction coupling process of the jejunum smooth muscles and the role of purines (Adenosine, ADP, and ATP) and their antagonistic compounds in intestinal smooth muscle contraction induced by KCl and Ach.

### Methods

The effect of adenosine and ATP on KCl and ACh contractures of isolated rabbit jejunum preparations was carried out to determine the effect of these compounds on the excitation-contraction (E-C) coupling mechanism. Responses to adenosine and theophylline in isolated rabbit jejunum smooth muscle preparations were studied in order to determine the existence of P1- purinoceptors in these preparations. In order to determine the existence of P2- purinoceptors in isolated rabbit jejunum smooth muscle preparation, the effects of quinidine and ATP (different concentrations) on KCl and Ach contractures were studied.

### Conclusion

- 1-The spontaneous mechanical activity of the intestinal smooth muscles heavily depends on the influx and efflux of calcium ions through cell membranes.
- 2-The presence of P1 and P2 receptors in jejunum muscles of rabbit is suggested by the action of agonist and antagonist on spontaneous mechanical activity.
- 3-The inhibitory action of adenosine on the contraction of rabbit jejunum smooth muscles indicates the presence of A1 receptors.
- 4-The theophylline antagonized effect on adenosine action in rabbit jejunum smooth muscles is confirming the presence of A1 in rabbit jejunum.
- 5-Presence of P2X receptors on rabbit jejunum is concluded by the potentiated responses of ATP on contraction of jejunum smooth muscles.
- 6-The antagonistic effect of quinidine on the action of ATP in the rabbit jejunum smooth muscles confirmed the presence of P2x receptors.

**Key Words:** intestinal smooth muscle, adenosine, adenosine triphosphate, Theophylline, quinidine

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## Introduction

Extracellular purines (Adenosine, ADP, and ATP) are important signaling molecules and have intense biological and physiological effects on smooth muscle contraction, neurotransmission in the peripheral and central neurons system, exocrine and endocrine secretion, the immune response, inflammation, platelet aggregation, pain and modulation of cardiac function<sup>(1)</sup>.

The concept of purines as extracellular signaling molecules was instigated by Drury & Szent<sup>(2)</sup>, in a comprehensive report showing that adenosine and adenosine 5 monophosphate (AMP) extracted from heart muscle, have pronounced biological effects, including heart block, arterial dilatation, lowering of blood pressure, and inhibition of intestinal contraction.

The realisation that purine compounds have potent actions on excitable membranes came during the first half of the previous century<sup>(2,3,4)</sup>.

There are two main families of purine receptors, adenosine or P1 receptors, and P2 receptors, recognizing primarily ATP, ADP, UTP, and UDP.

Purines such as adenosine are known to act as neurotransmitters as well as neuromodulators in the central, peripheral, and enteric nervous system<sup>(5,6)</sup>.

The pharmacological actions of adenosine on smooth-muscle preparations are well established, and the effects are mediated via receptors that have been classified as P1-purinoceptors (adenosine receptors<sup>(7)</sup>).

Segmentation contractions are a common type of mixing motility seen especially in the small intestine - segmental rings of contraction chop and mix the ingesta. Alternating contraction and relaxation of the longitudinal muscle in the wall of the gut also provides effective mixing of its contents<sup>(8)</sup>.

The intestine is commonly divided into two proximal-to-distal segments; the, small and large. Their functions are to absorb water, electrolytes, nutrients, and other non dietary components (such as drugs) necessary to maintain health.

To do this, the intestinal contents must be moved in a manner that not only brings them in contact with the intestinal mucosa but also propels them along this tubular organ<sup>(9)</sup>. Normal intestine motility results from coordinated contractions of smooth muscle, which in turn derive from two basic patterns of electrical activity across the membranes of smooth muscle

cells - slow waves and spike potentials.

This study was undertaken to investigate the mechanical properties and the excitation-contraction coupling process of the smooth muscles in jejunum and the role of purines (Adenosine, ADP, and ATP) in spontaneous jejunum muscle contraction.

## Results

**Effect of KCl and ACh on the rabbit's jejunum smooth muscle contractures**

Rabbit jejunum smooth muscle preparations give a pronounced biphasic contractile response when exposed to KCl and ACh. The response is characterized by a fast initial contracture (the phasic component) being followed by slow maintained response (the tonic component). In order to determine the maximum response in these preparation, concentrations of (10, 20, 40, 60, 80, 100mM) of KCl were employed.

Preparations were maximally activated by 80 mM KCl. Concentrations up to 60mM caused only tonic contracture.

Above 80Mm the contracture consists of an initial phasic contracture is shown in (Figure 1).

In (Figure 2) potassium contracture tension has been plotted against log external potassium concentration.

In the case of ACh, preparations reached the maximum contracture response at ( $10^{-5}$ M). Increasing the external ACh concentration up to ( $10^{-7}$ M) caused only a tonic contracture. Above ( $10^{-6}$ M) the contracture consists of an initial phasic contracture as is shown in (Figure 3).

A plot of ACh induced contracture tension against external log concentration is shown in Figure 4.

**Effect of P1 & P2 agonist and antagonist on spontaneous mechanical activity of the rabbit jejunum smooth muscle**

Adenosine and ATP exert potent extracellular action on a variety of tissues; many of these actions are mediated via purinoceptors. Responses to adenosine and ATP in isolated rabbit jejunum smooth muscle preparations were studied in order to determine the existence of P1 and P2 purinoceptors in these preparations.

Exogenously applied adenosine to isolate a rabbit jejunum smooth muscle produced inhibitory effects on the spontaneous mechanical activity in a dose dependent manner.

In rabbit jejunum smooth muscle theophylline at ( $10^{-4}$ M) was found to inhibit the action of adenosine on the spontaneous mechanical activity in this preparation.

Unlike adenosine, ATP caused a significant enhancement in spontaneous mechanical activity.

Quinidine at ( $10^{-4}$ M) was also found to inhibit the excitatory action of ATP on the spontaneous mechanical activity in this preparation and it was also employed in these studies as a P2 purinoceptor antagonist.

**Effect of agonist and antagonist on KCl -induced and ACh-induced contractures**

An investigation of the effect of adenosine and ATP on KCl

and ACh contractures of isolated rabbit jejunum preparations was carried out to determine the effect of these compounds on the excitation-contraction (E-C) coupling mechanism. In rabbit jejunum smooth muscle 80mM KCl and  $10^{-5}$  Ach gave near maximum contracture responses. Rabbit jejunum preparations were pretreated with adenosine for a period of 3 minutes before KCl or Ach were added to the bath medium. Adenosine inhibited the phasic component of jejunum smooth muscle of KCl-induced contractures (Figure 5). However with  $10^{-5}$  ACh responses the phasic component was inhibited (but in a reverse dose-dependent manner) (Figure 6).

Purinoceptors were classified into two major types using selective antagonists to reveal the difference in the nature of various responses. Responses to adenosine and theophylline in isolated rabbit jejunum smooth muscle preparations were studied in order to determine the existence of P1- purinoceptors in these preparations.

Theophylline antagonizes the effect of adenosine on the phasic phase of contraction in a concentration dependent manner. Theophylline not only abolishes the effect of adenosine at all concentrations but in addition it causes increases in the phasic component of KCl and ACh induced contractures (Figure 7 & Figure 8).

ATP potentiated the phasic KCl-induced contractures (Figure 9). In contrast this agent potentiated tonic component of the ACh-induced contractures (Figure 10).

In order to determine the existence of P2- purinoceptors in isolated rabbit jejunum smooth muscle preparation the effect of quinidine ( $10^{-4}$  M) and ATP (different concentrations) on KCl and Ach contractures were studied.

The results have also shown that quinidine greatly reduced the excitatory effect of ATP on jejunum smooth muscle. Quinidine antagonized the effect of ATP on the tonic contraction in a concentration dependent manner.

Quinidine not only inhibits the effect of ATP but in addition it causes decreases in the tonic component of KCl and ACh induced contractures (Figure 11 & Figure 12).

## Discussion

**Effect of (KCl and ACh) on spontaneous mechanical activity of the rabbit jejunum smooth muscle**

It is now established that most smooth muscle preparations exhibit spontaneous mechanical activity. These activities were found to be very dependent on extracellular calcium<sup>(10-12)</sup>.

The results presented here show that rabbit jejunum smooth muscle exhibits regular spontaneous mechanical

activity when incubated in normal Kreb's saline. This confirmed by the results of the previous studies<sup>(13,14)</sup>, while the irregular spontaneous mechanical activities of the rabbit colon smooth muscle shows similar results to that of rat<sup>(15)</sup> and that of human<sup>(16)</sup>.

The mechanical events of the myogenic spontaneous activity do not depend on the cholinergic and adrenergic receptors, but are influenced by activation of calcium channels (Long lasting calcium channels) (Ltype),

blocking potassium channels<sup>(16)</sup>, and also is influenced by

the polarization and depolarization which lower frequency of the spontaneous activity. This is in agreement when the results from a number of studies on other smooth muscles<sup>(17,18,8)</sup>.

Potassium chloride and Acetylcholine showed a potentiation effect on these spontaneous activities that may be explained by the opening of L-type of Ca channel by KCl and the depolarization of smooth muscle by ACh that facilitates such type of contraction<sup>(18)</sup>.

Rabbit jejunum smooth muscles develop biphasic contractures in response to KCl or to stimulates such as ACh response, induced by this agonist provided valuable information regarding the source of activator calcium utilized during contraction. The results showed that rabbit jejunum smooth muscles went into contracture when exposed to KCl. However, it was well documented that potassium ions induced membrane depolarization in all muscle types; one of the consequences is an activation of calcium channels in the muscle membrane<sup>(13)</sup>. This is consistent with results presented here which showed that contractile activity was enhanced by KCl.

It was found that 80mM KCl caused a depolarization. This concentration of the agonist induced maximum force development in jejunum smooth muscle, it would appear that this agonist uses distinct types of calcium channels. These results support the view that inward calcium movement is a necessary factor in maintenance of contraction of the smooth muscle.

The jejunum smooth muscle has A biphasic response depending on the concentration of KCl. The reason is that KCl depends on increasing intracellular calcium ions through its action on the opening of voltage dependent calcium channels. This is explained by others<sup>(19,20,14)</sup>.

Potassium chloride produces dose - dependent increases in tonic phase of the jejunum smooth muscle. This effect is due to an increase in opening calcium channels (L.type). However the phasic phase response was low because this phase initiates from activation of sensitive and fast calcium channels (T type)<sup>(13)</sup>. The important step of the muscle excitation contraction coupling (E-C coupling) is increasing cytoplasmic free calcium ion<sup>(21)</sup>.

Depolarization of preparations with ACh induced increase in tension development. It is well known that the increase in myoplasmic calcium associated with contraction may be due to either an influx of calcium or to release of intracellular calcium or both<sup>(22)</sup>. The results revealed that contraction was evoked when ACh is applied as an exogenous action. This increase in tension is mediated as an enhancement of the activity of L-type calcium channels<sup>(23)</sup>.

ACh binds muscarinic receptors that present in smooth muscle membrane which leads to increasing cytoplasmis free calcium ions, and induction of muscle contraction through three different mechanisms. The first mechanism represents the ability of depolarization in cell membrane. This assumes calcium entry through potential dependent calcium channels (PDCs)<sup>(13)</sup>. The second mechanism represents calcium ion entry from extracellular calcium sources through calcium channels that are opened by receptors. The calcium channels opened as a result of special receptor activation by ACh.

Activation of M1 and M3 receptors stimulates the formation of inositol triphosphate (IP3) and diacylglycerol (DAG) in most smooth muscles, whereas activation of M2 receptors increases potassium efflux or decreases cyclic adenosine monophosphate (cAMP )<sup>(24-26)</sup>.

**Effect of (P1 & P2) agonist and antagonist on spontaneous mechanical activity of the rabbit jejunum and colon smooth muscle**

The result showed that ATP had an excitatory effect at high concentration on spontaneous activity of rabbit jejunum smooth muscles. This may be due to increasing of intracellular calcium concentration through own ATP receptor mechanism. These findings support that of<sup>(12)</sup>, which suggest that jejunum muscle may possess P2-purinoceptors which were active in the ion channels in the cell membrane. Both theophylline and quinidine leads to inhibition of spontaneous activity. This means that these two compounds lead to decreases of spontaneous activity and this may be referred to their relaxant effect on smooth muscle, as found by<sup>(19)</sup>, since they terminate these support activities. These finding support that of<sup>(27,19)</sup> in rat ileal preparation.

The antagonistic effect of theophylline on adenosine responses of rabbit jejunum smooth muscle strongly suggests the presence of P1 type purinoceptors in this preparation. Quinidine may thus have the same effects on ATP action in rabbit jejunum in smooth muscle as a P2- antagonist, strengthening the view that jejunum smooth muscle may possess a P2-purinoceptors population.

**Effect of P1 and P2 agonist and antagonist on KCl and ACh induced contracture of the rabbit jejunum and colon smooth muscle.**

Numerous studies have demonstrated that adenosine is capable of elevating intracellular (cAMP) levels in a number of tissues<sup>(28,29,30)</sup>. Reports indicate that cAMP plays a major role in the relaxant effects of catecholamines and other sympathomimetic drugs on smooth muscle<sup>(31,32)</sup>. Our results show that adenosine has an inhibitory effect of jejunum smooth muscle. On the other hand Mostwin<sup>(18)</sup>, has claimed that in guinea-pig taenia coli, adenosine compounds do not stimulate adenylate cyclase which is responsible for conversion of ATP to cAMP. However, Wakade and Wakade<sup>(33)</sup> suggested that the relaxation induced by adenosine is due to a reduction of the influx of extracellular calcium. Significantly some actions of adenosine can be overcome by raising extracellular calcium<sup>(34,35,36)</sup>.

The inhibitory effect of adenosine responses induced by KCl and ACh, is due to presence of A1 receptor in rabbit jejunum smooth muscle. This probably may attribute to the decrease of the intracellular calcium ions in the smooth muscle cells<sup>(22,11)</sup> while the inhibitory effect on the tonic response may be explained by the blocking of the L-type calcium ion channels<sup>(37)</sup>. On the other hand Adenosine reduces the contractility induced by ACh in the intestine smooth muscle. This effect is due to physiological antagonism of Adenosine to ACh because each of them act on different receptors<sup>(25)</sup>.

An investigation into the effect of ATP on KCl and ACh contractures of isolated rabbit's jejunum smooth muscle preparations was carried out to determine the effect of this

compound on the E-C of coupling mechanism. The reported responses of smooth muscle to ATP is variable, depending upon the tissue, occurring as relaxations in some instances and contraction in others(38).

ATP in rabbit jejunum smooth muscle potentiate the contraction induced by both KCl and Ach. This may strengthen the view that indicates the presence of P2x receptor in jejunum and colon smooth muscle. P2x receptor activation leads to an increase in calcium influx. Calcium can enter directly through calcium-permeable P2x receptor channels opened in response to membrane depolarization. This is in agreement with the results of(39).

P2X activation leads to membrane depolarisation and calcium influx directly through P2X receptor channels<sup>(40)</sup> and through voltage-dependent L-type calcium channels<sup>(41)</sup>.

P2x receptors mediate rapidly (within 10 minutes) and selective permeability to cations Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup><sup>(42-44)</sup>. They are distributed on excitable cells (muscle cells, neurons, and glial cells) and their role is mediators of fast excitatory neurotransmission ATP in both the central and peripheral nervous systems. The present work showed that the theophylline was more specific in antagonising the effect of adenosine in rabbit jejunum smooth muscle. This is in a good agreement with the results of<sup>(22,19,12)</sup>.

Theophylline has several actions at the cellular level, including inhibition of phosphodiesterase (PDE) isoenzyme, antagonism of adenosine receptors, inhibition of calcium influx, and enhancement of Catecholamine secretion.

All of these effects are in patients with asthma<sup>(45-47)</sup>.

It is clear that there is a similarity between the effects of theophylline and procyanidine (a new drug for the treatment of heart failure) in reversing the inhibitory effects of adenosine on the smooth muscle of the jejunum of the rabbit<sup>(48)</sup>, this is in agreement with<sup>(49)</sup> who used computer-assisted model analysis to observe the structural similarity of flavanoid extracted from Hawthorn to papaverine and theophylline (Adenosine receptor antagonism), two chemical agents which are known to inhibit phosphodiesterase<sup>(50,49)</sup>. This indicates that procyanidine, a flavanoid derivative, has some antagonist activity on adenosine receptors. Theophylline is a selective antagonist for adenosine on P1 receptors<sup>(51)</sup> so it reduces the action of adenosine which supports our previous conclusion that the jejunum smooth muscles have A1 receptors.

Quinidine was used to identify the properties and activities of P2 receptors through antagonizing the contractile activity of ATP on smooth muscle<sup>(11)</sup>. Several compounds including Quinidine, 2-substituted imidazolamines have been shown to antagonise responses to ATP in various preparations, but none of these compounds have a specific action<sup>(52)</sup>. Low concentrations of apamin were shown by Shuba Vladimiron, 1980(53) to block ATP, but not adenosine, nevertheless, it is a useful agent to distinguish P1 and P2 receptors. The results have also shown that 10-4M Quinidine greatly reduced the excitatory effect of ATP on jejunum smooth muscle. Burnstock<sup>(51)</sup>, showed that Quinidine blocked contraction induced by ATP or by non-adrenergic, noncholinergic nerves in bladder smooth muscle.

Furthermore quinidine could block the excitation of

urinary smooth muscle of Guinea pig induced by electrical stimulation of the nervous system or by addition of ATP, while it reversed only 15% of the smooth muscle contraction induced by acetylcholine. This effect of quinidine is thought to be due to blocking of calcium channels<sup>(51)</sup>. In addition Quinidine has been shown to block the excitatory actions of ATP on the gut of lower vertebrates<sup>(54)</sup>, Quinidine may thus have the same effects on ATP action in jejunum and colon smooth muscle as a P2-purinoceptor antagonist, strengthening the view that jejunum and colon smooth muscle may possess a P2-purinoceptors population. It was reported that quinidine is a selective antagonist to ATP on P2 receptors<sup>(11)</sup>.

The results of inhibitory effect of Quinidine on KCl and ACh induced contraction, supported the suggestion of the presence of P2X receptors in jejunum and colon smooth muscles<sup>(55)</sup>.

## Conclusion

The spontaneous mechanical activity of the intestinal smooth muscles heavily depends on the influx and efflux of calcium ions through cell membranes.

The presence of P1 and P2 receptors in jejunum muscles of rabbit is suggested by the action of agonist and antagonist on spontaneous mechanical activity.

The inhibitory action of adenosine on the contraction of rabbit jejunum smooth muscles indicates the presence of A1 receptors.

Presence of P2X receptors on rabbit jejunum is concluded by the potentiated responses of ATP on contraction of jejunum and colon smooth muscles.

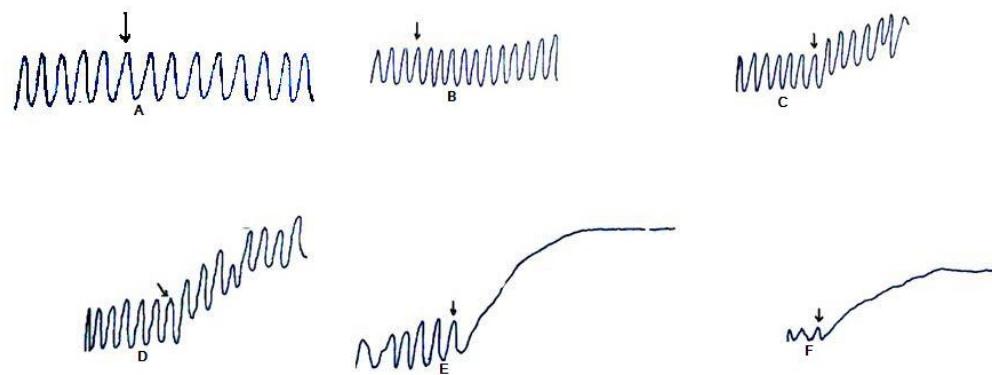
The theophylline antagonized effect on adenosine action in rabbit jejunum smooth muscles is confirming the presence of A1 in rabbit jejunum.

The antagonistic effect of quinidine on the action of ATP in the rabbit jejunum smooth muscles confirmed the presence of P2x receptors.

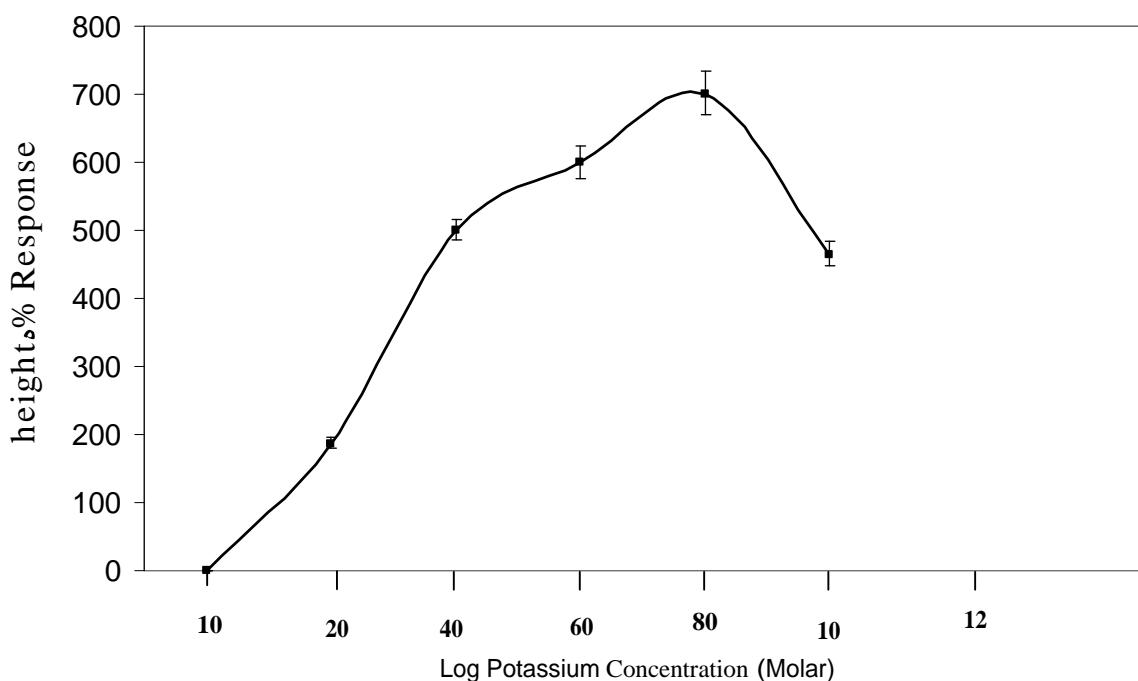
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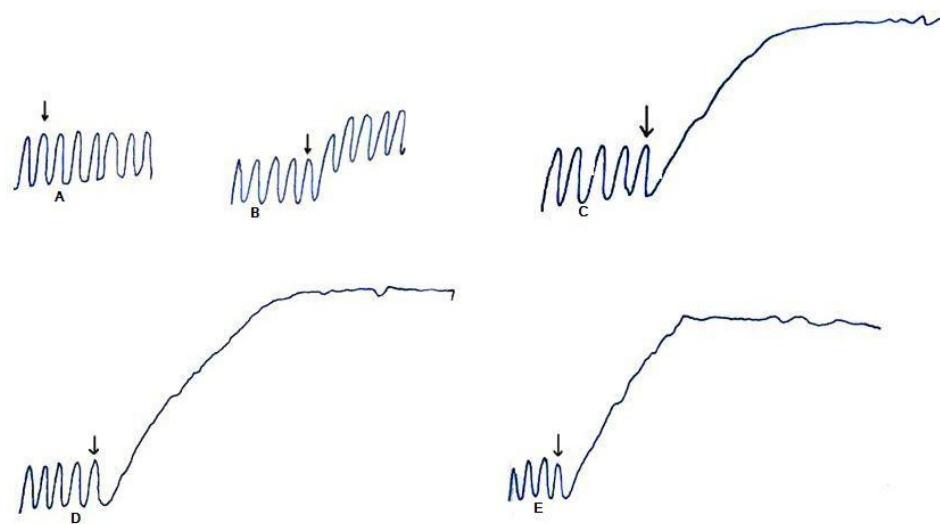
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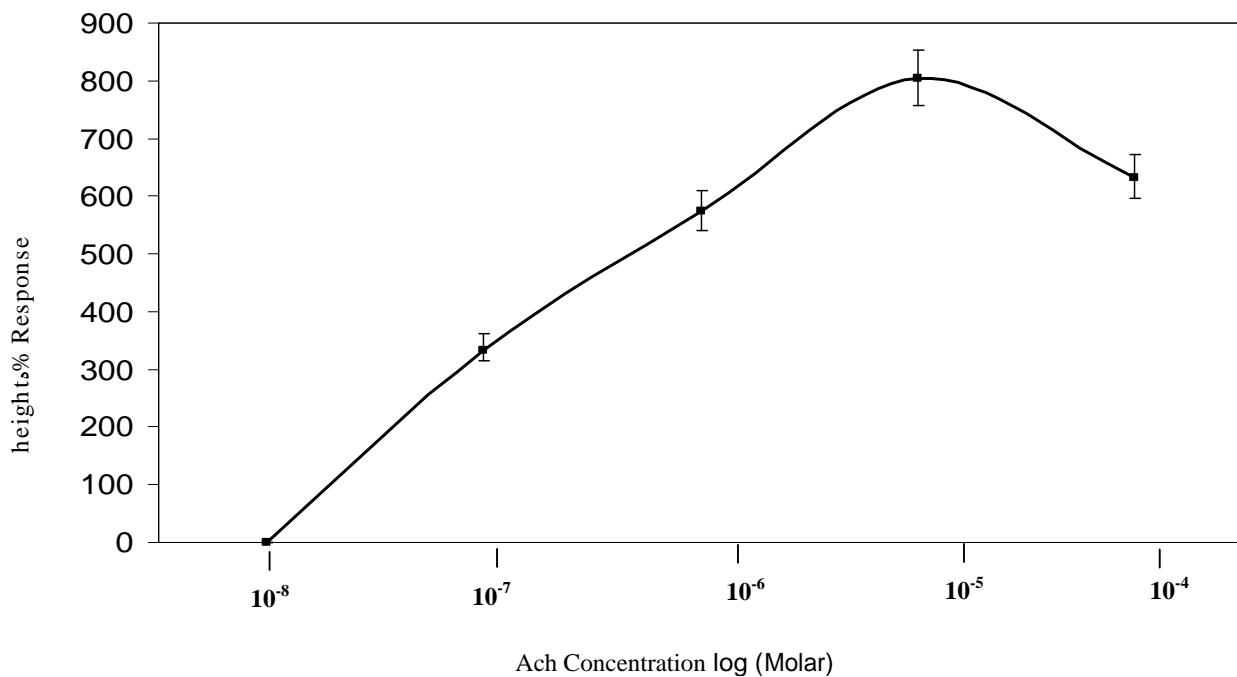
**Figure (1): The response of the rabbit jejunum smooth muscle to various KCl concentrations (added at the arrows) A- 10mM KCl B- 20mM KCl C- 40mM KCl D- 60mM KCl E- 80mM KCl F- 100mM KCl**



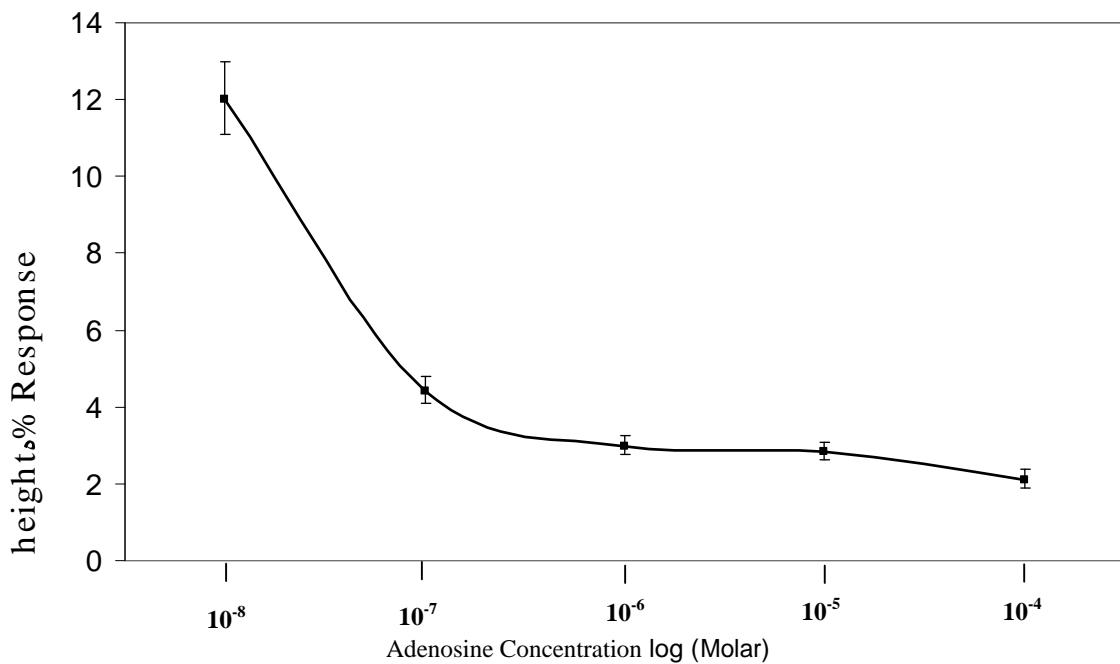
**Figure (2): relationship between log external potassium concentration and response height in rabbit jejunum smooth muscle. Each point represents the mean  $\pm$  SE ( $n=6$ ).**



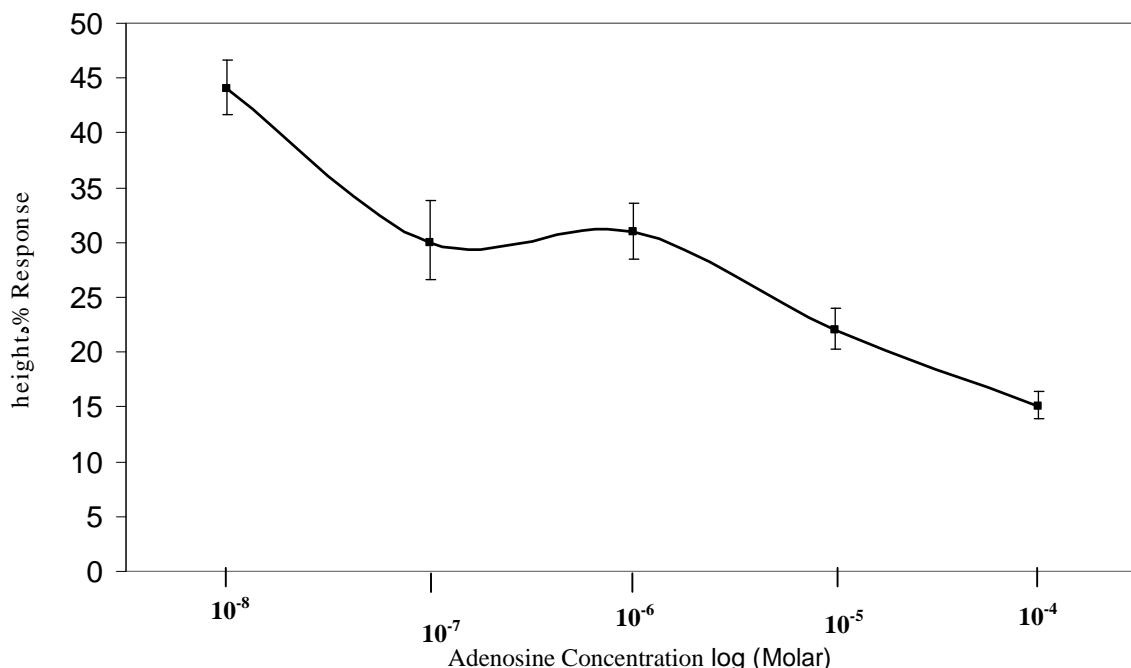
**Figure (3)** the response of the rabbit jejunum smooth muscle to various ACh concentrations (added at the arrows) A-  $10^{-8}$ M ACh B-  $10^{-7}$ M ACh C-  $10^{-6}$ M ACh D-  $10^{-5}$ M ACh E-  $10^{-4}$ M ACh



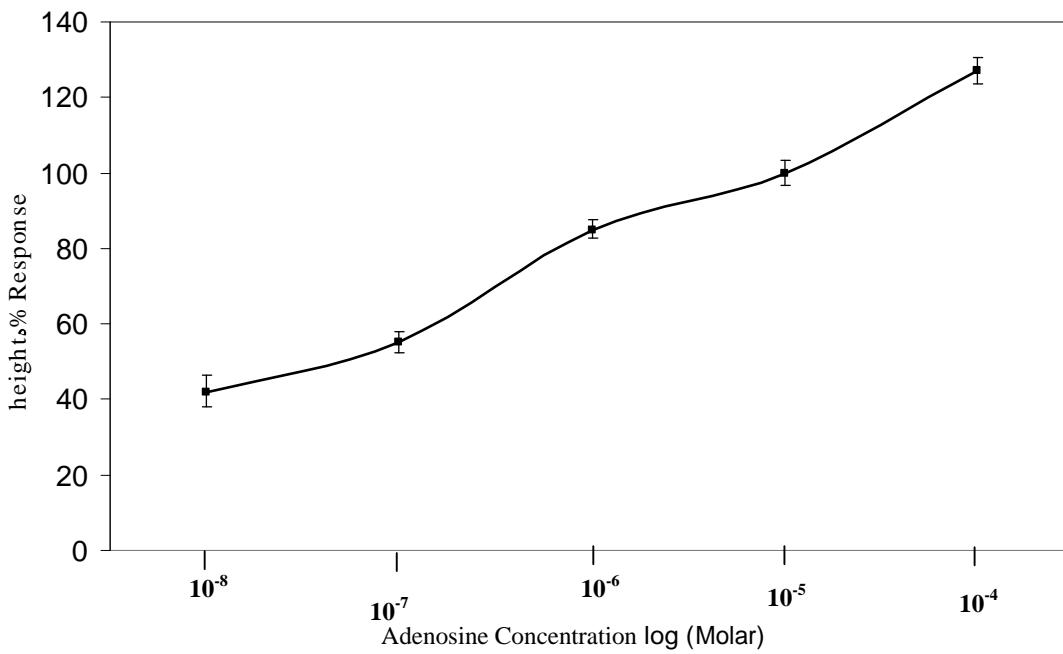
**Figure (4):** relationship between log external ACh concentration and response SE  $\pm$  height in rabbit jejunum smooth muscle. Each point represents the mean (n=6)



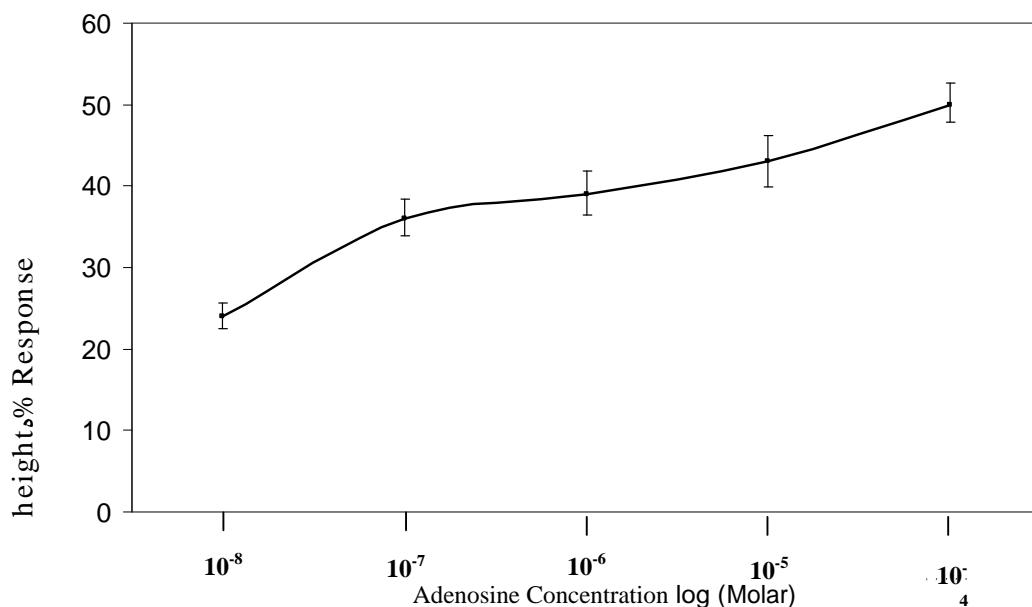
**Figure (5): The effect of adenosine upon 80 mM KCl in the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control 80mM KCl contracture. Each point represents the mean  $\pm$  SE (n=6)**



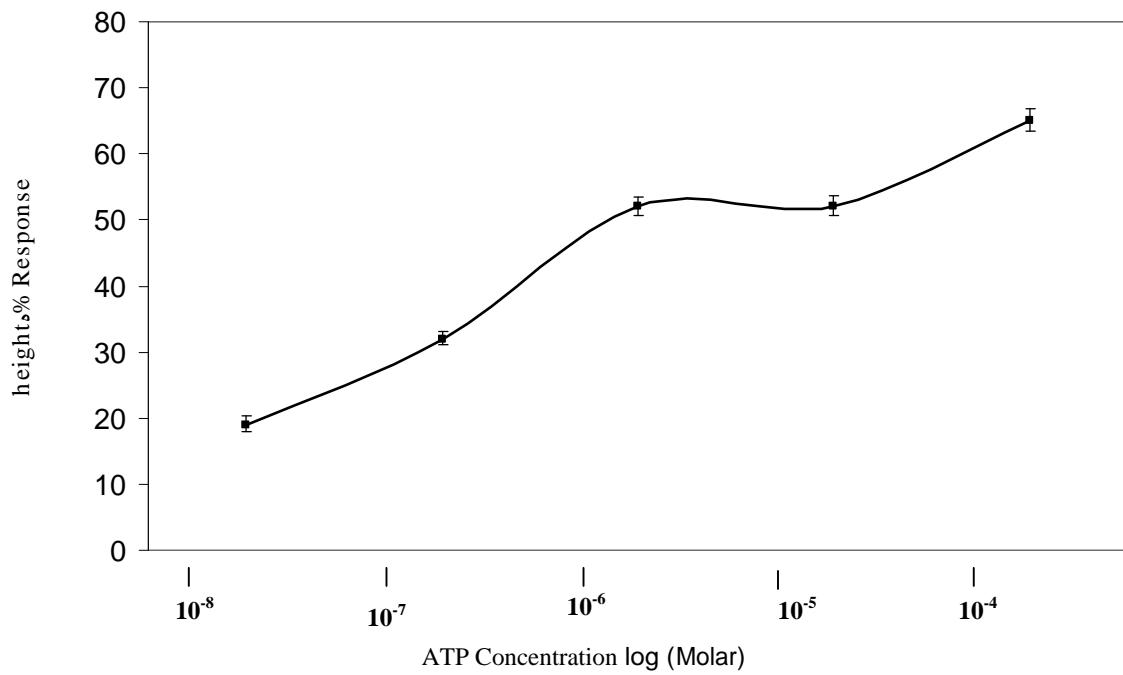
**Figure (6): The effect of adenosine upon  $10^{-5}$  M ACh in the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control  $10^{-5}$  M ACh contracture. Each point represents the mean  $\pm$  SE (n=6)**



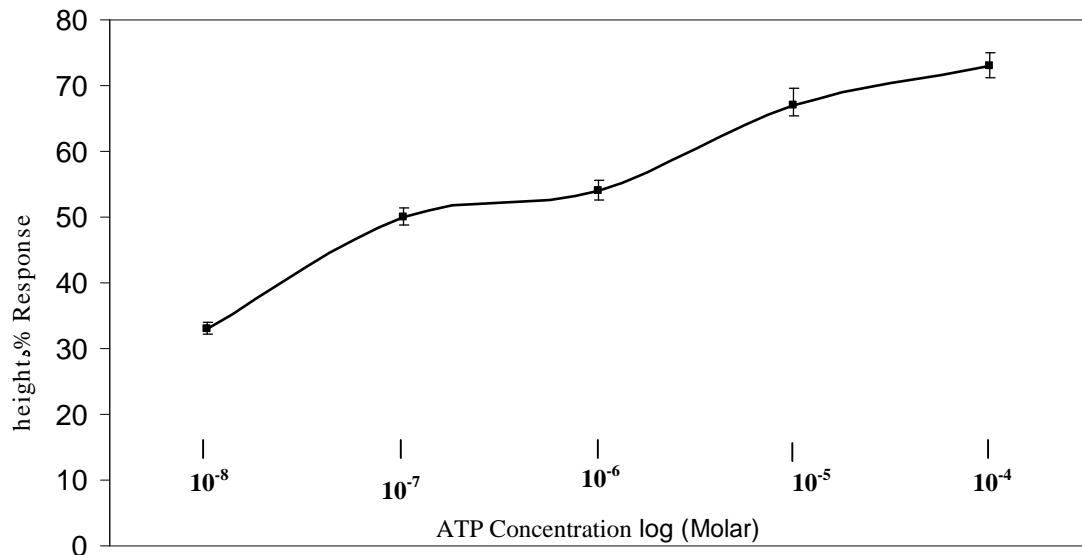
**Figure (7): The effect of theophylline and adenosine on the contraction of the rabbit jejunum smooth muscle. Responses are expressed as a percentage of SE ( $n=6$ )  $\pm$  control 80mM KCl contracture. Each point represents the mean**



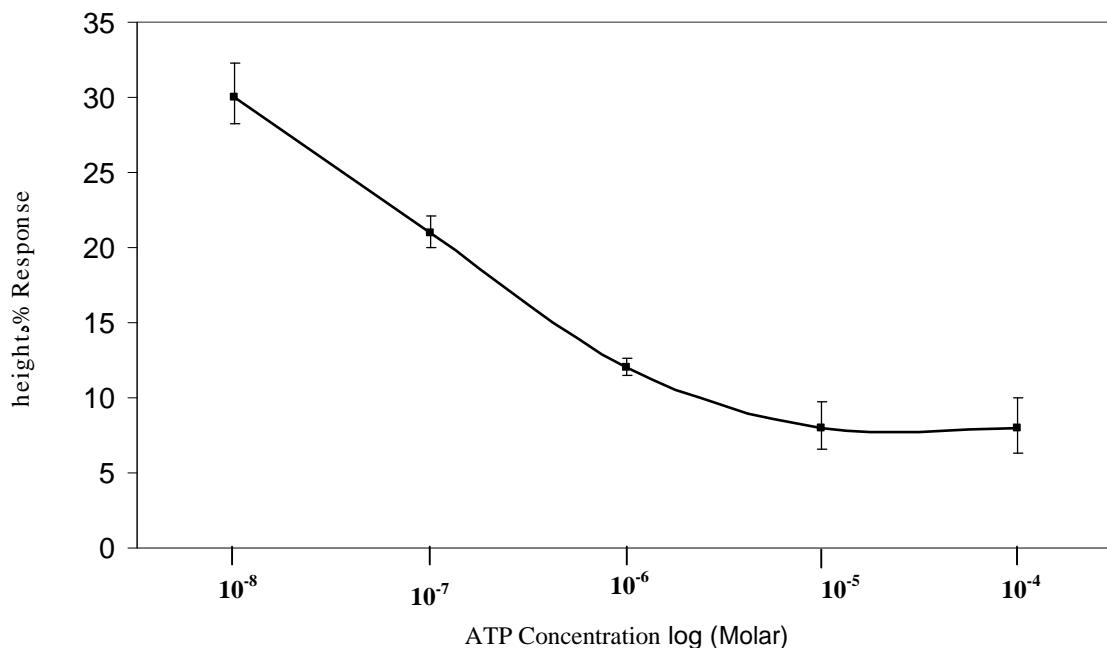
**Figure (8): The effect of theophylline and adenosine on the contraction of the rabbit jejunum smooth muscle. Responses are expressed as a percentage of SE ( $n=6$ )  $\pm$  control  $10^{-5}$  M ACh contracture. Each point represents the mean**



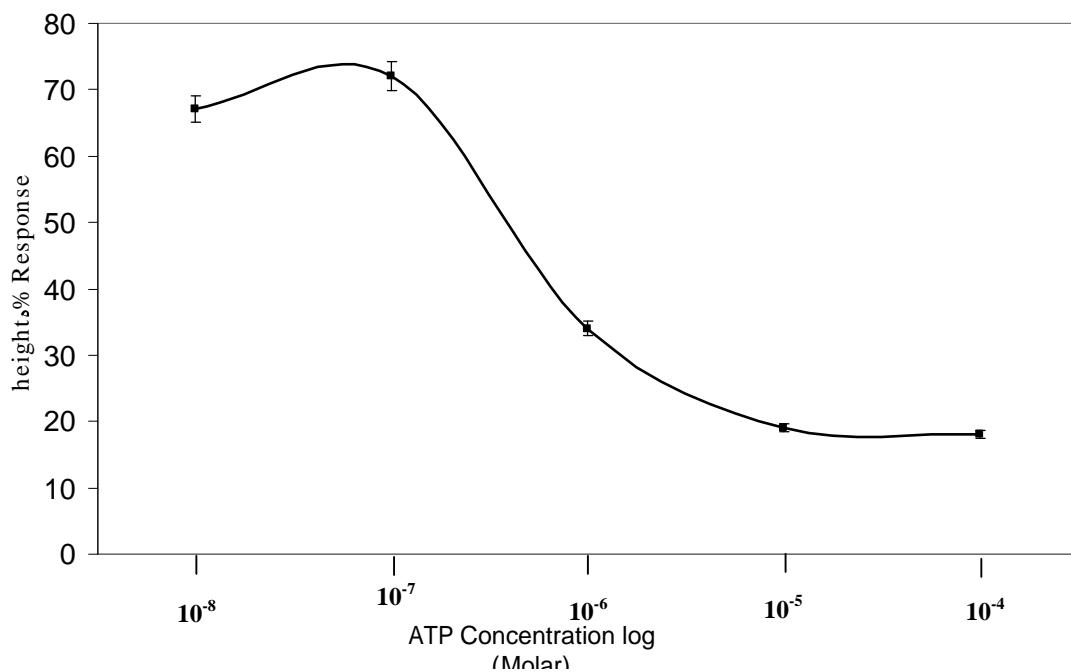
**Figure (9): The effect of ATP upon 80 mM KCl in the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control 80mM KCl contracture. Each point represents the mean ± SE (n=6)**



**Figure (10): The effect of ATP upon  $10^{-5}$  M ACh in the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control  $10^{-5}$  M ACh contracture. Each point represents the mean ± SE (n=6)**



**Figure (11): The effect of Quinidine and ATP on the contraction of the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control 80 mM KCl contracture. Each point represents the mean  $\pm$  SE (n=6)**



**Figure (12): The effect of Quinidine and ATP on the contraction of the rabbit jejunum smooth muscle. Responses are expressed as a percentage of control  $10^{-5}$ M ACh contracture. Each point represents the mean  $\pm$  SE (n=6)**

# Effects Of The Electromagnetic Field On Mice Reproduction

## ABSTRACT

**Background and objectives.** Electromagnetic fields (EMFs) are defined as that field which is created when the electric current flows. This study included the effects of (EMFs) on mice reproduction, and they was achieved by exposing male and female mice to EMF and comparing the parameters with the control group.

**Material and method:** a prospective study which was carried on 10 couples of albino mice which were exposed to EMF & 50Hz and 70gausses. Males were exposed separately from females. The exposure was for 60 days, 24 hours/ day. Mating then occurred. 10 couples were considered as a control. All the groups were followed up for 3 months after the end of the exposure.

**Results:** The results revealed that, newborns (pups) were low in number and had reduced weight. This reduced weight and number differed significantly from the control group. The exposed group showed reduced frequency of pregnancy as compared to the control group.

### Conclusion and Recommendation:

EMFs may have effects on mice reproduction. Further studies are needed to clarify the exact mechanisms of these effects.

## Introduction

Electromagnetic fields (EMFs), either man made or naturally occurring, can be found anywhere on the earth. According to the World Health Organization (WHO), the definition of an electric field is that field which is created by differences in voltages and a magnetic field is that field which is created when electric current flows (WHO, 2006)<sup>(1)</sup>. People are exposed to electromagnetic currents on a daily basis, and with the ever increasing use of electronic technologies, electromagnetic fields are more prevalent in modern lives than most people would realize. Using electricity, listening to the radio, cooking with a microwave, even using a cell phone, all result in exposure to EMFs. A study done in United Kingdom homes looked at 226 common appliances during a six-week period<sup>(2)</sup>. The authors found that the appliances had the highest reading of magnetic fields when measured closest to the source.

One ongoing controversy that is taking place in the current science and medical world is whether high power tension lines have a connection to cancer and other health risks<sup>(3)</sup>.

There are theories that suggest that living under or near high power tension lines will cause leukemia & breast cancer<sup>(4,5,6)</sup>. Few studies have suggested EMFs may cause a reduction in infertility<sup>(7,8)</sup>.

There have been several mechanisms that have been proposed to explain how EMFs affect the targeted cells<sup>(9)</sup>. An outside source of electrical magnetic fields that is presented to the cell will cause a forced vibration in the ions that are present in and around the cell. These ions will start to move with the

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presented field and this can exert a force on the membrane channels. The voltage gates will open and the balance of the cell will be upset with the movement of ions either entering or leaving the cell<sup>(10)</sup>.

## Materials and Methods

### Animals

Twenty couples of albino mice, BALB\c mice were used (each mouse was about 8-10 weeks of age, weighing 27 gm to 30 gm).

These animals were divided randomly into two groups, the exposed group (10 couples) and the control group (10 couples).

Then we separated the males from the females in the exposed group before exposure, and each (10 males & 10 females) were put in separate cages and then exposed to low frequency 50Hz and 70 gauss of static uniform magnetic field. This was achieved by locating the two cages (male and female cages) in the middle of the static magnetic field. The exposure was for 60 days, 24 hours/day in 12L/ 12D.

Then after the end of the time of exposure, these animals were transmitted to 10 small cages with each cage containing one exposed couple. These animals were followed for three months.

The animals under control (10 couples) were put in ten 10 small cages as in the exposed group. These animals were followed for three months also.

### Examination

Numbers of the newborn (pups), and their weights beside the frequency of pregnancy were estimated in both groups.

### Statistical analysis:

Statistical analysis was carried out by using:

Mean standard deviation and standard error of the mean SEM.

T-test to find out the significant difference of the parameters in both groups.

## Results

The table below revealed the mean levels of the newborn number and their weights in these two groups i.e. control and the exposed groups. The mean levels were : 10.1+ 0.236, 5.8+ 0.34, 0.91gm+ 0.325, 0.56gm +0.12.

Regarding frequency of pregnancy in both control and exposed groups was: three (3) and two (2) respectively.

The mean levels and S.E of number of newborn and weight in both groups.

Parameters	Control	Exposed	Statistical analysis
Number of newborn	10.1 +0.236	5.8+0.34	0.05*
Weight	0.91+0.325	0.56 +0.12	0.05*
Frequency of Pregnancy	3	2	

\*significance.

By using t-test it is clear that there was a significant difference ( $p < 0.05$ ) between the two groups regarding number and weight of the newborn. It is revealed that frequency of pregnancy was affected also.

## Discussion

It had been found from this study, that prolonged exposure to EMFs may affect some parameters of mice reproduction.

Conflicting observations have been reported regarding the potential toxic effects of EMFs on spermatogenesis and reproduction in experimental animals and humans.

In a study by Chung et. al., (2003)<sup>(11)</sup>, the authors found that there were no notable and significant differences in the number of corpora lutea implantations, dead fetuses and placental weight in the fetuses in both exposed and sham groups.

A study by Chung et. al., (2004)<sup>(12)</sup> revealed that there was no significant difference in the sperm examination which looked at morphology, number of spermatids present and motility. There was also no difference in copulation, fertility and pregnancy frequency.

Multi-generational reproductive toxicity study showed that continuous exposure of Sprague-Dawley rats to 60 Hz magnetic field has no significant adverse effects on adults' reproductive capacity, developing fetus and neonatal development in rats. (Ryan BM et.al., (1999)<sup>(13)</sup> Lundeberg et. Al., (1995)<sup>(14)</sup>, reported that human sub fertility was not associated with occupational 0.3mT exposure on morphology, motility and sperm concentration among males. Kowalcuk et.al., (1995)<sup>(15)</sup> also did not find dominant lethal mutation in the male germ cells of mice when they were exposed to power frequency magnetic fields at 10mT for the approximate period of spermatogenesis. A study by Heredia - Rojas et.al., (2004)<sup>(16)</sup>, reported that 60Hz and 2mT magnetic field exposure did not affect meiotic chromosomes and morphological characteristics of male germ cells in mice.

On the contrary, De vita et.al., (1995)<sup>(8)</sup>, reported that exposure to 50Hz and 6.7mT for 4 hours caused a significant decrease in the number of elongated spermatids on day 28 after treatment. A study by Al-Akhras et.al., (2006)<sup>(17)</sup>, reported that there was a difference in the weight of the seminal vesicles, and testicular sperm count beside the increase in the serum level of lutinizing hormone, in the exposed rats compared to the control group. Another study by Al-Akhras et.al., (2002)<sup>(18)</sup>

reported that exposure of adult male rats to 50Hz magnetic fields for 90 days had a significant effect on the fertility of females impregnated by the exposed males.

Furuya et.al., (1998)<sup>(19)</sup> suggested that long term exposure to EMF magnetic fields (1.0mT) had a possible effect on the proliferation and differentiation of spermatogonia. Ramadan et.al., (2002)<sup>(20)</sup> also reported that exposure of fractionated doses of magnetic fields (20mT) caused a significant decrease in sperm count, motility and daily sperm production in mice.

There are many studies which delineate the effect of EMFs on the histological pattern of the testis and consequently may lead to fertility or sub-fertility.

Lee et .al., (2004)<sup>(21)</sup> reported that continuous exposure to EMF (60Hz, 0.5 mT) for 8 weeks caused an increased incidence of testicular germ cell death and this finding resulted from an increased incidence of germ cell apoptosis in mice. Hong R. et.al., (2005)<sup>(22)</sup> suggested that, 50Hz EMFs may have the potential to induce DNA strand breakage in testicular cells and sperm chromatin condensation in mice. Khaki AA et.al., (2006)<sup>(23)</sup> suggested that EMF exposure may cause profound changes in the boundary tissue of the rat's seminiferous tubules, therefore this exposure may result in pathological changes that lead to sub fertility and infertility. Lokhmatova SA (1993)<sup>(24)</sup>, (1993)<sup>(25)</sup>, found in two separate studies that exposure of mice to EMF may lead to: increase in the destructive process in both spermatogenous epithelium and indicate that exposure to EMF gave rise to desquamation of spermatogenous epithelial layers in the seminiferous tubes, reduction of the number of testosterone-producing cells, microcirculatory changes, metabolic rearrangements.

Most recently, Wdowiak A (2007)<sup>(26)</sup>, indicate in a study to evaluate the effect of using mobile phones on male fertility, it was noted that an increase in the percentage of sperm cells of abnormal morphology is associated with the GSM phones. It was also confirmed that a decrease in the percentage of sperm cells in vital progressing motility in the semen is correlated with the frequency of using mobile phones.

The apparent discrepancy among the above studies might be due to differences in animals used, exposure period and intensity, environmental conditions, as Junttilainen J (1997)<sup>(27)</sup> indicated that the animal strain is an important variable in bioelectromagnetics research, as even closely related strains may show different response to magnetic field exposure.

In view of our findings and the contradictory reports above, it is necessary to conduct much wider studies under different experimental conditions and using different parameters (sperm analysis, hormonal assays, histology) to help clarify the controversy concerning the possible spermatotoxic risk associated with magnetic field exposure.

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# Cecum Cancer Presenting with Abdominal Wall Abscess and Gas Gangrene

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## ABSTRACT

Colorectal cancer is common in developed countries. Bleeding, constipation, and obstruction are the usual presentation. Fever or pain caused by abscess formation has been less frequently reported as the initial symptom of colorectal cancer.

We report a case in which abdominal wall abscess and gas gangrene were an initial presentation of cecum cancer.

**Key Words:** colorectal cancer, abdominal wall abscess, gas gangrene, cecum cancer.

## Introduction

Colorectal cancer is common in developed countries, carrying a high incidence of both morbidity and mortality. Bleeding, constipation and obstruction are the usual presenting symptoms<sup>[1]</sup>.

Fever or pain caused by abdominal wall abscess formation and gas gangrene has been less frequently reported as the initial presenting symptom of colorectal cancer. Invasion towards adjacent organs is often found in advanced colorectal cancers, but concomitant invasion as an abdominal wall abscess is relatively rare<sup>[2]</sup>.

## Case study

A 65-year-old woman was admitted through the emergency room to surgical ward with fever and right lower quadrant abdominal wall abscess, and signs of gas gangrene, a leukocytes level of 25,000 cells\mm<sup>3</sup>.

Drainage of the abscess and debridement were performed in the same day of admission.

On the following day of hospitalization computed tomography revealed severe gas forming infection in the right abdominal wall and retroperitoneal area, psoas abscess with the possibility of complicated appendicitis as the primary pathology.

The patient underwent a second operation in which she was found to have a large retroperitoneal abscess, necrotic appendix, with severely inflamed perforated cecum.

A decision was taken at that time to do right hemicolectomy with nodal dissection, taking into concern the age of the patient, the severity of the pathology, and the high possibility of malignancy as the primary pathology.

After drainage of pus and all necrotic tissues, Right hemicolectomy with nodal dissection and primary anastomosis were performed. Also proximal diverting ileostomy was done to clean the area of infection and to protect the at high risk distal anastomosis. Tound was left open and surgical drains were applied.

The patient had a smooth post operative course with dramatic improvement, underwent frequent dressing and debridement to the abdominal wall infection, her wound became clean, infection was cleared, and wound was closed by the plastic surgeons.

The final histopathology report showed moderately differentiated adenocarcinoma of the cecum, with negative lymph nodes and free resection margins. Patient underwent operation for closure of her ileostomy and was referred to the oncology department to continue her management and follow up.

## Discussion

Colorectal cancer is common in developed countries, carrying a high incidence of both morbidity and mortality. Bleeding, constipation and obstruction are the usual presenting symptoms<sup>[1]</sup>.

Fever or pain caused by abdominal wall abscess formation and gas gangrene has been less frequently reported as the initial presenting symptom of colorectal cancer. Invasion towards adjacent organs is often found in advanced colorectal cancers, but concomitant invasion as an abdominal wall abscess is relatively rare<sup>[2]</sup>.

One of the common routes of colon cancer spread is local invasion to adjacent structures and dissemination through the peritoneal cavity. The direct invasion is most commonly seen with advanced tumors. The incidence of abscess formation has been reported to occur in 0.3 to 0.4%. This figure is decreasing due to recent advances in diagnostic and radiological technique<sup>[3,4]</sup>.

Colonic tumors' perforation usually occurs inside the

peritoneal cavity. Abdominal wall abscess secondary to perforated colonic tumors is rare<sup>[5]</sup>.

Most of colon tumors presenting with abdominal wall abscess are of the mucinous histopathological type. Mucinous carcinomas are slowly growing tumors that usually spread by direct extension; psoas abscess associated with colonic tumors is extremely rare<sup>[6]</sup>.

The drainage of an abscess caused by perforated colonic tumor is a potential cause of regional spreading of cancer cells.

En bloc resection of the cancer with fistula and abscess wall is advised<sup>[3,5]</sup>.

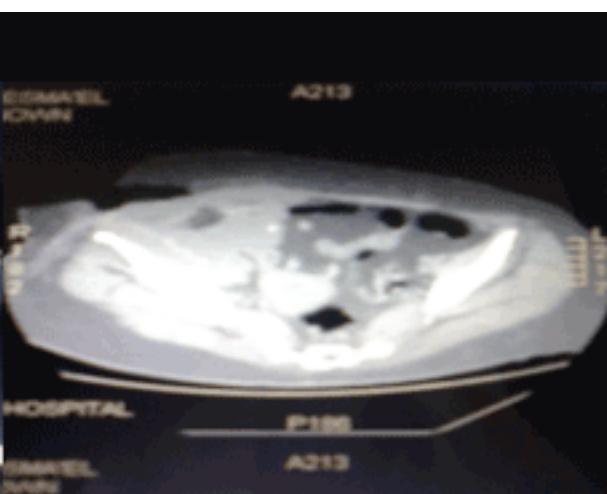
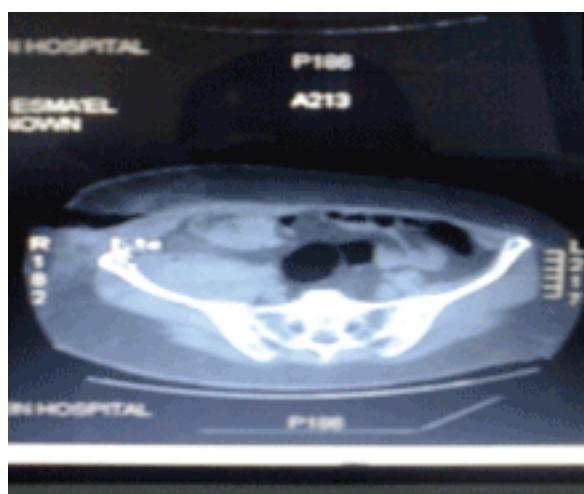
In summary most of the colonic tumors presented with perforation perforate intraperitoneally; extraperitoneal perforation is rare, and most of perforated colonic tumors are mucinous carcinomas; abdominal wall abscess and psoas abscess secondary to perforated colonic tumor are rare.

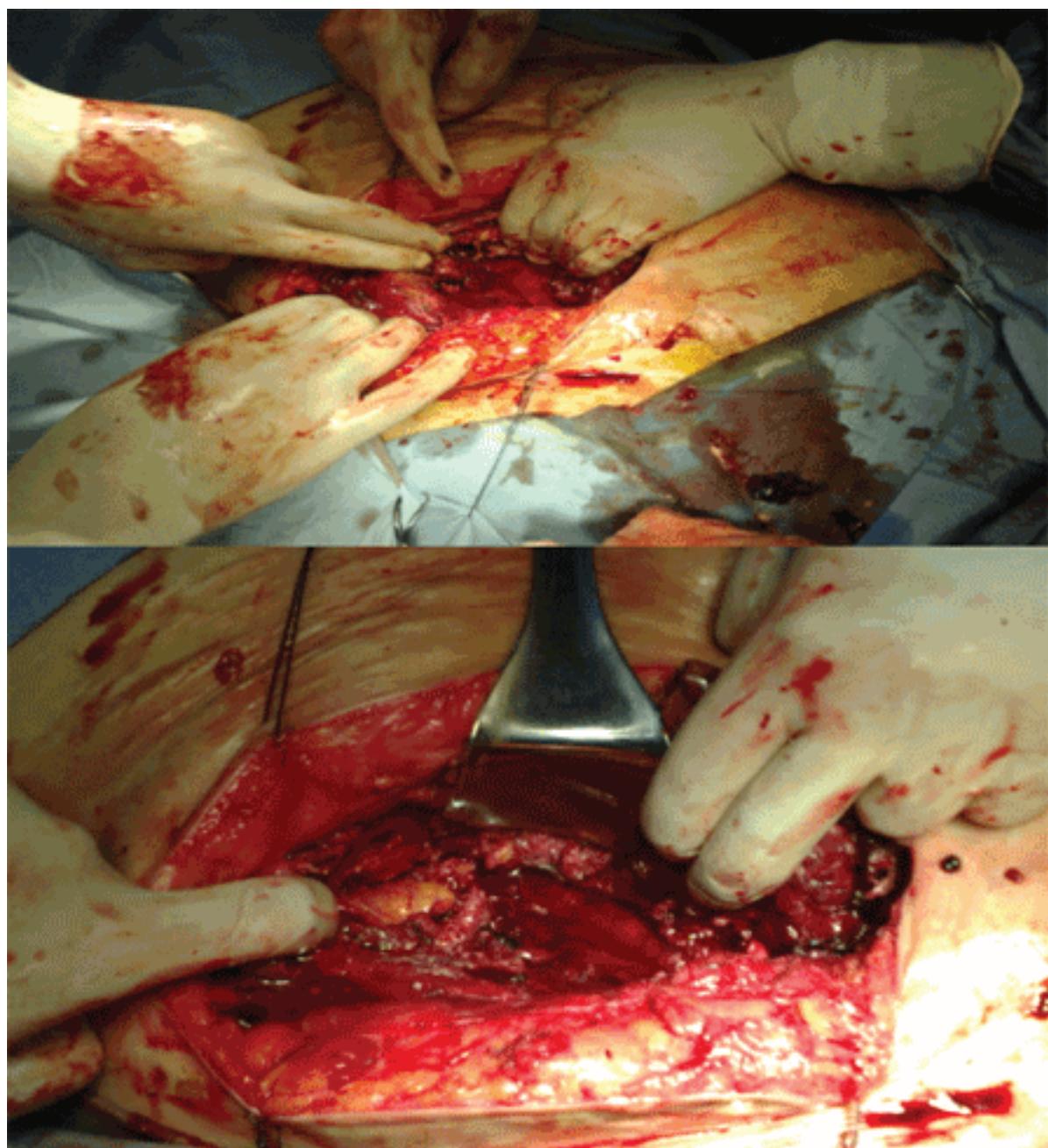
We report a rare presentation of colonic tumors, a case of a perforated adenocarcinoma of the cecum which presented with psoas abscess complicated by abdominal wall abscess and gas gangrene, which was successfully diagnosed and treated.

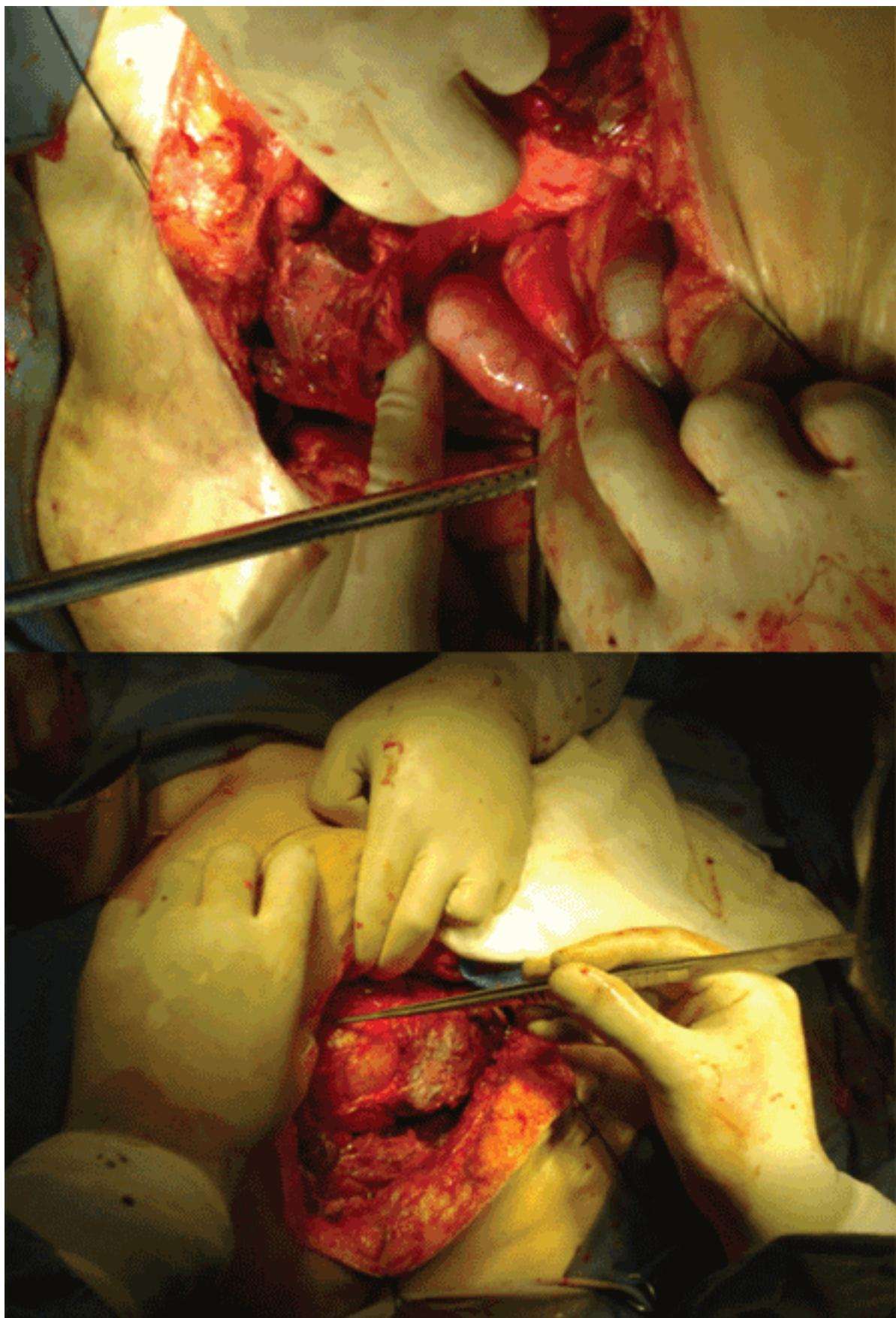
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# Familial Atrial Septal Defect with Atrioventricular Conduction Defect and Mitral Valve Prolapse

## ABSTRACT

**Objective:** Atrial septal defect of the ostium secundum type (ASD) is usually sporadic. Familial occurrence is rare and may present as an isolated lesion or with conduction and /or skeletal abnormalities.

**Subject and Method:** We describe a family including a mother and her three daughters who all had ASD, severe mitral regurgitation (MR) due to mitral valve prolapse (MVP), and also prolonged atrioventricular conduction. Surgical closures of ASD and mitral valve repair or replacement were performed for patients. The elder daughter required pacemaker implantation. The younger daughter experienced sudden death.

**Conclusion:** The importance of this syndrome is the occurrence of progressive disease of conduction tissue and the risk of sudden death. Therefore when the conduction abnormality is found in association with ASD all available relatives should be examined.

**Key words:** Atrial septal defect, Familial, Heart block, Mitral valve prolapse.

## Introduction

Secundum atrial septal defect (ASD) is a common congenital heart malformation that occurs as an isolated anomaly in 10% of individuals with congenital heart disease (CHD). Some individuals with (ASD) have a family history of this defect or other CHD. Coexisting heart block has been observed in some families<sup>[1]</sup>. Clinical evaluation revealed three types of familial ASD: 1) Holt-Oram syndrome (heart -hand syndrome type 1) which is inherited by autosomal dominant pattern. All patients exhibited upper arm skeletal anomalies. Cardiac manifestations when present, included ASD and /or VSD, atrioventricular canal defect, and various degrees of atrioventricular block (AV block). 2) Heart - hand syndrome type III is inherited as an autosomal dominant trait.

Each affected individual also had cardiac conduction system disease. None had any evidence of cardiac septation defects. 3) ASD with AV block is inherited in some families in an autosomal dominant pattern. There were neither gross nor radiographic skeletal abnormalities in any individuals in these families. It has been demonstrated that two disorders, heart -hand syndrome type III and familial ASD accompanied by AV conduction abnormalities are genetically distinct from the Holt-Oram syndrome. While clinically these disorders appear to be partial phenocopies of Holt-Oram syndrome, neither is genetically linked to chromosome 12q2<sup>[2]</sup>. Structural heart lesions that have been associated with specific chromosomal abnormalities included familial ASDs associated with heart block (the transcription factor NKX 2.5 on chromosome 5q35), and familial ASD without heart block (the transcription factor GATA4)<sup>[3]</sup>. NKX 2.5 has a critical role not only in

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the morphogenesis of the heart but also in the physiological function of the cardiac conduction system. It has been reported that all the affected patients with NKX 2.5 mutations have AV conduction abnormalities. They exhibit progressive electrophysiological abnormalities and a high incidence of sudden death or pacemaker implantation even after surgical correction of the ASD<sup>[4]</sup>.

Here we report a family with 4 affected members (a mother with her three daughters) with ASD, severe mitral regurgitation due to mitral valve prolapse and AV conduction defect that resulted in one of them having sudden cardiac death.

### Clinical presentation

A 48 - year old woman was admitted due to fatigability. Physical examination revealed a grade ejection systolic murmur at upper left sternal border accompanied by wide and fixed splitting of second heart sound. Chest X ray showed moderate cardiomegaly, right atrial enlargement, increased pulmonary blood flow (PBF). ECG showed right axis deviation (RAD), rsR', first degree heart block. Echocardiography revealed Scundum type ASD, MVP; severe MR. Cardiac catheterization confirmed the above findings. The patient underwent cardiac operation. ASD was closed by synthetic patch and mitral valve was replaced with a prosthetic valve.

The postoperative course was uneventful and the patient was discharged in good condition. Because of association of ASD with conduction abnormality other family members of the patient were examined. She had three daughters. The elder daughter was a 25 - year old. She suffered from frequent attacks of arrhythmia and syncope. ECG showed first degree AV block. Holter monitoring and electrophysiologic study showed frequent episodes of supraventricular tachycardia. Echocardiography revealed secundum ASD, MVP, mild MR.

Catheterization confirmed the above findings. Cardiac surgery was performed. ASD was closed with a pericardial patch, and a VVIR (ventricular demand mode) pacemaker was implanted in the heart. The postoperative course was

uneventful. At her last out - patient department (OPD) follow - up the patient was married and was 3 months pregnant. The second daughter was 20 years old. She was asymptomatic.

Physical examination revealed a grade ejection systolic murmur at left sternal border. Chest X - ray showed mild cardiomegaly, prominent pulmonary artery segment and increased PBF. ECG showed RAD, rsR' in V1, 1st degree AV block. Echocardiography revealed a large ASD, MVP, and mild MR. Catheterization confirmed the above findings. The patient underwent cardiac surgery and ASD was closed with a pericardial patch. The postoperative course was uneventful. The younger daughter (The third daughter) was 15-years old at the time of diagnosis. She was symptomatic and ECG showed first degree heart block. Echocardiography revealed secundum ASD, MVP, and severe MR. Cardiac catheterization confirmed the above findings. The patient underwent cardiac surgery. ASD was closed and mitral valve was replaced.

The postoperative course was complicated by pericardial effusion. The pericardial effusion was drained by sub - costal window. The patient was discharged in good condition. Two years later the patient experienced a sudden episode of cardiac arrhythmia during a journey and died. The father was examined and had not congenital heart disease. The parents had no son. They did not report similar disease in other family members.

## Discussion

Our proband and her three daughters showed AV conduction abnormalities associated with ASD and mitral valve prolapse. Nora and Nora reported that the recurrence risk of CHD in offspring, when one parent was affected was 3.5%, and the recurrence risk of CHD in offspring of mothers with ASDs was (4.6 %)<sup>[5]</sup>. The familial recurrence risk of isolated ASD in family members of patients with isolated ASD was higher in siblings, especially in sisters (33.3%). Moreover, a higher recurrence risk of isolated ASD was observed in mothers of patients with isolated ASD<sup>[6]</sup>. A family was described that among their members a mother, her two children and another two relatives all had ASDs. The index case and her mother also had prolonged atrioventricular conduction. It is considered that the defect is the familial type and inherited as a Mendelian dominant trait<sup>[7]</sup>.

Hosoda et al reported the first case of familial ASD with AV conduction disturbance associated with a mutation in CSX/NKX2-5 in a Japanese father and his son [4]. A large pedigree with familial ASD has been studied by Lynch et al. The pedigree showed vertical transmission of ASD through four generations. They found the existence of at least two distinct hereditary varieties of ASD, one with, and one without a prolonged P-R interval<sup>[8]</sup>. Research from Israel showed a high prevalence of familial occurrence of ASD (10% of all ASD patients).

They recommended screening all first degree relatives of ASD patients for cardiac conduction and skeletal anomalies. Conduction anomalies may be present or may develop through life, and thus should be periodically screened<sup>[9]</sup>. In a study by Mandorla et al ten families of four generations have been reported They had ASD and atrioventricular conduction defects with dominant inheritance<sup>[10]</sup>. The vertical transmission of disease in our patients and the absence of CHD in the father of

family are compatible with dominant inheritance. The facility for chromosomal study was not available for our patients. None of them had clinical or radiographic anomaly of upper limbs but all of them suffered from severe mitral regurgitation due to mitral valve prolapse. The association of ASD with mitral valve prolapse has been reported previously. Dijiovanna reported a cluster of 11 diagnosed cases of ASD within a 32-member family group. Echocardiographic examination also revealed mitral valve prolapse, thin atrial septal wall with aneurysm in some cases, and regurgitation of mitral or tricuspid valves in several individuals<sup>[11]</sup>. A genetic analysis was performed in 10 families. In these families the proband cases had ASD associated with abnormal atrioventricular conduction (First, second, or third degree heart block) or unexplained left axis deviation or a combination of these conduction disturbances. Disease of the conduction tissue in some cases was progressive with unexpected death<sup>[12]</sup>.

In conclusion: familial ASD is associated with progressive disease of the conduction pathways and the risk of sudden death. When therefore, prolonged atrioventricular conduction is found in association with a secundum ASD all available relatives should be examined.

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# Gestational Diabetes Insipidus

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**Key words:** Pregnancy, Diabetes insipidus, DDAVP

Medical problems during pregnancy carry lots of challenges for the treating physician, and we have been challenged with a case of a 23 year old female, who is 24 weeks pregnant, coming to the hospital complaining of excessive thirst, excessive urination and postural symptoms. The patient indicated that she was totally normal in her early pregnancy, but as pregnancy progressed, she noticed excessive thirst, and that she goes to the bathroom frequently. The patient was seen by her obsettrician who told her that this is part of her normal pregnancy. The patients' symptoms persisted, and she came to the emergency room because of severe dehydration. The patient's serum sodium was elevated, and she had elevated serum osmolality. Urine output was about seven to eight liters a day, with low urine specific gravity. Diabetes insipidus was suspected, and a water deprivation test was planned, but because of severe postural symptoms, the test was cancelled. A trial of DDAVP was given, with dramatic improvement in the patients' symptoms, and normalization of serum sodium and osmolality. MRI of the brain was done, which showed no abnormalities. The patient was kept on DDAVP throughout her pregnancy. After delivery, the patients' symptoms disappeared, with tapering off the DDAVP, which was eventually stopped.

Diabetes insipidus is a rare endocrine problem that occurs during pregnancy, with an incidence of 4 cases for every 100,000 pregnancies<sup>(1,2)</sup>. An increased secretion of vasopressinase with increased degradation of vasopressin, and poor response of kidneys to vasopressin, are possible physiological changes that are responsible for the development of gestational diabetes insipidus<sup>(2,3,4)</sup>.

The patient will be complaining of polyuria and polydipsia, but diagnosing this condition could be difficult during pregnancy because of the changes in water metabolism that accompany pregnancy.

Measuring serum sodium, plasma osmolality, and plasma vasopressin help in making the diagnosis. MRI might be needed to rule out central pathology<sup>(5)</sup>.

Since DDAVP is safe during pregnancy, and it is not broken down by placental vasopressinase, it is considered the treatment

of choice in treating gestational diabetes insipidus<sup>(5,6,7)</sup>.

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