Brief Communication

Spinal anesthesia with minidose bupivacaine-fentanyl for cesarean section in preeclamptic parturients

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Spinal anesthesia is often used for most cesarean sections, and it offers some advantages. Years ago, spinal anesthesia was considered contraindicated in patients with preeclampsia. The reason was a fear that the fast onset of anesthesia would possibly produce an undue degree of hypotension in volume-depleted, vasoconstricted patients with preeclampsia. Possible adverse effects on the fetus owing to uncontrolled hypotension were feared. However, recent studies have not found these concerns. These patients present particular hazards with general anesthesia, such as concerns for rapid airway control and cerebral blood flow alterations during induction of general anesthesia and intubation. Spinal anesthesia has only recently been recognized to have a place in operative management in preeclampsia. Therefore, the use of a single shot of spinal anesthesia is considered acceptable by some experts, and they attempt to minimize hypotension of spinal anesthesia. One approach has been to minimize hypotension by using very small doses of local anesthetics. Although the use of a single shot of low dosage local anesthetic for spinal blockade may limit hypotension, it may not provide acceptable anesthesia. Opioids and local anesthetics administered together intrathecally have a potent synergistic analgesic effect. Intrathecal opioids enhance analgesia from subtherapeutic doses of local anesthetic and make it possible to achieve successful spinal anesthesia using otherwise, inadequate doses of local anesthetic.[1-3] Yet because intrathecal fentanyl causes, neither by itself nor in combination with bupivacaine, any further depression of efferent sympathetic activity, it is possible to enhance the sensory blockade without altering the degree of sympathetic blockade. The goal of this study was to compare the hemodynamic and sensory effects of a minidose bupivacaine-fentanyl spinal anesthetic versus a conventional dose of spinal bupivacaine in preeclamptic patients undergoing cesarean section.

This study was performed from February 2005 to August 2005 in Alzahra Hospital, Tehran, Iran on 44 preeclamptic parturients with mean systolic and diastolic pressure higher than 140/90 mm Hg, chosen to have spinal anesthesia for cesarean section. Exclusion criteria were patient refusal or any other relative contraindication to spinal anesthesia, patients with cardiovascular and pulmonary disease, diabetics, and patients with CNS disorders, seizure, coagulopathy, and HELLP syndrome. Parturients were randomly assigned to 2 groups defined by the spinal injectate. This study was carried out in Alzahra Hospital during 2005, lasts one year. After obtaining written informed consent of the subjects, group A were given 6 mg bupivacaine 0.5% in glucose, plus 20 µg fentanyl, and group B, received 12 µg bupivacaine 0.5% in glucose. Bupivacaine 0.5% in glucose was prepared by adding 4 mg glucose 50% to 20 ml bupivacaine 0.5%. In both groups distilled water was added to the drug mixture to make a drug volume of 2.5 ml in total. One researcher prepared the syringe and a second anesthetist who performed subarachnoid blocks and remained blinded to its contents administered it. A blinded observer carried out patients' assessment, care, and data recording. The antepartum management included seizure prophylaxis in patients with severe preeclampsia and consisted of magnesium sulfate ($MgSO_4$) administered at a loading dose of 4 g intravenously, followed by 1 g hourly intravenously. Hydralazine was administered intravenously as a vasodilator for additional blood pressure control against a standardized protocol that was identical in both groups. Previous use of other agents (a-methyl dopa, Dexamethasone) was recorded. Before block, each patient received a rapid infusion of 8 ml/kg of ringer's solution, in the left lateral position over 15-30 minutes and the baseline blood pressure and heart rate were noted. After prep and drep of the back of the patient, subarachnoid injection was performed in the sitting position using a 25-gauge Quincke needle positioned midline at the L3-L4 interspace. After aspiration of 0.5 ml of CSF the local anesthetic drug was injected into the spinal space over 10-15 seconds (if no blood was aspirated). After completion of injection, the patients were immediately returned to the supine position and the operating bed positioned in 15-30 degree head down, with left uterine displacement. The parturients head was rested on a pillow. Each patient received 6-8 lit/min O_2 by face mask. Standard monitoring included continuous ECG, pulsoximetry, maternal blood pressure, and heart rate. The vital signs were recorded every one-minute up to the birth of the neonate, and then every 5 minutes using an automated noninvasive device. Pinprick testing in the right side of body was used to establish onset and peak level of blockade. For the purpose of the study, hypotension was defined as a systolic blood pressure decrease of more than 30% from baseline. Hypotension was treated promptly by increasing uterine displacement and the rate of fluid administration. If hypotension persisted despite these measures, ephedrine 2.5-5 mg was injected and

repeated as needed. Patients received 1500-2000 ml of ringer solution during the whole surgery. The vital signs, number of hypotension measurements, total ephedrine dose for each patient, and intraoperative patient complaints of pain, nausea, and vomiting were recorded. Metoclopramide 5-10 mg was used to treat nausea or vomiting. The condition of the neonates was assessed by Apgar score at one and 5 minutes after delivery. All mothers received oxytocin by continuous infusion after delivery. Return of sensory and motor function was assessed at 15-minute intervals until complete recovery from anesthesia. Statistical analysis was performed using SPSS. Analyzes of variance was used to analyze demographic data. The non-depended T- test and Chi-square test were used to analyze data. Results were considered significant at $p<0.05$. The type of study was an interventional comparison.

There were 22 patients in each of the 2 groups. There were no differences between the demographic characteristics of the 2 groups. Though baseline systemic blood pressure was slightly higher in group B, this was not a significant difference. (157.91±16.920 in group B versus 155.23±13.73 in group A). No patients in either group complained of intraoperative pain or required supplemental analgesics intraoperatively. Peak sensory block level was similar in both groups. The lowest recorded systolic and diastolic blood pressures are reported in **Table 1** as well as their percentages of the baseline pressures. In group A, 5 of 22 patients, and in group B, 17 of 22 patients experienced hypotension according to the protocol definition of hypotension. Seventeen patients in group B and 5 patients in group A required treatment with ephedrine. However, numbers of ephedrine administration in incremental doses were 19 times in group B versus 5 times in group A and this difference is significant ($p=0.0001$). Nausea was seen in 12 patients of group B and 3 patients of group A. Also 8 patients in group B and no patient in group A had vomiting. Postoperative follow-up revealed uneventful recovery in all patients expect for 3 patients of group A that complained of pruritus and were treated with antihistamine.

Table 1 - Study data in the 2 groups.

Patient data	Group A	Group B	*P*-value
Peak level of block	T(5.7 ± 1.146)	T(5.7 ± 1.225)	0.058
Patients having pain during surgery	0	0	
Patients experienced hypotension	6	14	0.34
Lowest systolic pressure	109.8 ± 14.5	100.8 ± 13.0	0.037
Lowest/baseline systolic pressure			0.042
Mean ± SD	0.712 ± 0.113	0.645 ± 0.100	
(%)	(71.2)	(64.5)	
Lowest diastolic pressure	57.1 ± 12.2	52.2 ± 7.6	0.117
Lowest/baseline diastolic pressure			0.072
Mean ± SD	0.599 ± 0.127	0.535 ± 0.101	
(%)	(60)	(55.5)	
Number of patients treated for hypotension	6	11	0.597
Number of ephedrine injection	5	19	0.0001

Data are mean ± SD unless other wise indicated. *P*<0.05 was significant
Group A - spinal anesthesia with bupivacaine 6 mg plus fentanyl 20 µg
Group B - spinal anesthesia with bupivacaine 12 mg, T - thoracic level.

This study demonstrates, that the use of minidose bupivacaine plus fentanyl spinal anesthetic (6 mg bupivacaine plus 20 µg fentanyl) for cesarean section in preeclamptic parturients provides successful anesthesia and incurs a minimum of hypotension. In the minidose group, 5 of 22 patients experienced hypotension, and in these patients a single dose of 5 mg ephedrine sufficed. This stood in contrast to the marked reduction in blood pressure, and the significant vasopressor requirements seen in the group receiving spinal anesthetic of bupivacaine 12 mg (17 of 22 patients in group B). Numbers of ephedrine administration showed a significant difference ($p=0.0001$) between the 2 groups (5 times in group A versus 19 in group B) and meant that the incidence of blood pressure drop in group B was higher, more severe, and required more ephedrine injection in incremental doses than patients of group A. Ben-David et al[4] showed that minidoses of spinal bupivacaine-fentanyl caused dramatically less hypotension anesthesia than 10 mg bupivacaine, and nearly eliminated the need for vasopressor support of blood pressure for surgical repair of hip fracture in the aged. The intravenous fluid preload of 8 ml/kg of Ringer's solution was used in this study. Fluid administration may prevent a decrease in central venous pressure and may diminish or even reverse the decrease in cardiac index, however, blood pressure falls nevertheless because of a substantial decrease in systemic vascular resistance. However, an excessive administration of crystalloid or colloid may also result in pulmonary or cerebral edema in preeclamptic patients, and is therefore, to be avoided.[1] Pouta et al[5] demonstrated that an intravenous fluid bolus resulted in a greater increase in central venous pressure in preeclamptic woman than in normotensive controls undergoing spinal anesthesia.[1]

Ephedrine is probably the most commonly used vasopressor drug of choice in cesarean section. It does not have a detrimental effect on uterine blood flow, thus, it is widely used as pressor for hypotension of spinal anesthesia in the parturients,[1] however, systemic vasoconstriction and accelerated response to

vasopressors in preeclamptic parturients limited it to use in large doses in these patients. In this study, ephedrine was used in incremental doses and started with 5 mg. Nausea and vomiting during spinal anesthesia may be related to a postural hypotension and hypoxemia of the vomiting center. Excessively risen blood pressure following administration of a vasopressor may also produce nausea. This problem is unpleasant during surgery. In this study, the incidence of nausea and vomiting in group A (mini dose group) was 3 and 0, and in group B was 12 and 5, and the differences were significant ($p<0.05$). This difference showed that nausea and vomiting were higher in group B than group A, which were more hypotensive following administration of spinal anesthesia. We conclude that the more possible cause of nausea and vomiting is hypotension than other causes such as intrathecal fentanyl, especially in these lower doses.

In the study of Vercauteren et al,[6] which used small-dose bupivacaine versus plain bupivacaine spinal anesthesia for cesarean section, a low incidence of hypotension and nausea was seen. Thus, intrathecal fentanyl in combination with bupivacaine causes further depression of efferent sympathetic blockade and increases the efficacy of intraoperative analgesia, and therefore decreases the incidence of nausea and vomiting. In this study none of the patients complained of pain intraoperatively. Pregnant patients require less local anesthetic because of the increase sensitivity of nerve fibers for local anesthetics, the reduced amount of CSF and the effect of the gravid uterus on cephalad spread of intrathecally injected substances.[1-4,6] However, the use of single shot low dosage local anesthetic (lower than 10 mg bupivacaine) for spinal blockade although can limit hypotension, may not be possible to develop a reliable anesthesia even in parturients. However, the addition of an opioid intrathecally to the local anesthetic reduces the dose requirements, because of the potent synergistic analgesic effect of it and local anesthetic, and provides satisfactory anesthesia.

The minidose of 6 mg bupivacaine in combination with 20 µg fentanyl provides acceptable spinal anesthesia for cesarean section in preeclamptic patients. The minidose of bupivacaine-fentanyl caused less hypotension than 12 mg bupivacaine and nearly eliminated the need for vasopressor supports of blood pressure, and decreases the incidence of nausea and vomiting.

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Our experiences in surgical repair of secundum atrial septal defect in adults: early and mid-term results

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Atrial septal defect (ASD) is the most common congenital heart disease in adults. Although the secundum type is the most common lesion, sinus venosus defect of both the superior and inferior vena caval types and ostium primum ASDs are seen as well. Although most patients with an ASD are asymptomatic, atrial fibrillation, reduction in exercise tolerance, heart failure, pulmonary or systemic emboli may develop with age. Thus, before the development of these sequels, it is important that the defect is closed when the diagnosis is made. In patients with a Qp/Qs (pulmonary flow / systemic flow) ratio greater than 1.5, and pulmonary vascular resistance less than 6-8 Wood units/m^2, defect closure is usually indicated.[1] However, it is debatable that the defect must be closed in adults. In this study, we tried to investigate the risk factors affecting the short and long-term mortality and morbidity in patients with secundum ASDs treated surgically. The study design was reviewed and approved by the institutional ethics committee.

Between September 1991 and December 2005, 532 patients underwent surgical repair due to the secundum ASD. In this study, the primum types of atrial septal defects were excluded. There were 479 men (90%) and 53 women (10%). The mean age of patients at the time of operation was 19 ± 2 years. Of these patients, 235 were class I, 285 were class II, and 12 were class III, according to, New York Heart Association (NYHA) functional classification. Diagnoses were achieved by echo cardiography in all patients. The mean weight at the time of surgical intervention was 68 ± 16 kg (range 50-89 kg). The mean follow-up time was 48 ± 11 months. All patients were followed at Gulhane Military Medical School once in every 6-month interval for a detailed physical examination combined with echo cardiographic assessment. Preoperative and intraoperative data including age, gender, NYHA functional class, pulmonary artery pressure, pulmonary vascular resistance, indication for operation, cardiac rhythm, cerebrovascular accident, left ventricular ejection fraction, right and left chamber's diameters (left and right ventricle, and atrium), cardiopulmonary bypass, and aortic cross clamp times were analyzed retrospectively.

Although median sternotomy was the standard surgical approach, in 4 female patients, operations were performed through right anterolateral thoracotomy for cosmetic purposes due to the patients' own will. Cardiopulmonary bypass was achieved by cannulating the ascending aorta and both vena cava through the right atrium, whereas in patients to whom right thoracotomy were applied, femoral artery cannulation was used. Myocardial protection was performed by moderate hypothermia at 28°C and cardioplegic arrest was obtained by administering antegrade cold crystalloid cardioplegia solution into the aortic root. Our preferred closure technique of the defect has been direct suture closure. If there was an adequate useful septum primum tissue, we expected less tension on the suture line and hence we used direct suturing. In the remaining patients and in patients with defects larger than 3 cm^2, the defects were closed with autologous pericardial patches, which we harvested at the beginning of the operations and kept in sterile saline solution until the time of closure. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percents. To evaluate independent risk factors for hospital mortality, preoperative, and intraoperative variables were examined by multivariate analysis by forward stepwise logistic regression. A *p*-value below 0.05 was considered significant.

None of the patients had congestive heart failure at the time of admission. All patients had normal sinus rhythm. In 96 (18%) patients, defects were closed with pericardial patch, and defects were closed primarily in remaining patients. Twenty-four patients had pulmonary hypertension, which was defined as a mean pulmonary artery pressure of greater than 30 mm Hg. None of these patients had increased pulmonary vascular resistance calculated from the mean pressure gradient over the pulmonary vascular bed and pulmonary blood flow values, which were obtained from oximetry by using the Fick principle. Mean value of Qp/Qs was 1.6 ± 0.9. Characteristics of the patients are summarized in **Table 1**. There was no operative mortality, which was defined as the mortality seen in the first postoperative 30 days. Hospital stay time was 5 ± 3 days and intensive care unit stay time was 24 ± 8 hours. The majority of the complications were rhythm disturbances in the postoperative period. Atrial fibrillation was present in 7 patients (1.3%) who had large right atrium and right ventricle (p=0.04). Normal sinus rhythm was maintained in these patients by the administration of anti-arrhythmic agents and cardioversion. In the postoperative echo cardiographic assessments, there were no residual shunts. Significant decrease in right ventricular end diastolic (44.1 ± 3 versus 39 ± 2.1, p=0.034) and end systolic diameters were observed (33.3 ± 2.1 versus 30.6 ± 7.2 p=0.044). Slight decrease in the right atrial diameter was observed

Table 1 - Characteristics of patients

Characteristics	n (%)
Gender	
Women	53 (10)
Men	479 (90)
Operation technique	
Pericardial patch	96 (18)
Primary	436 (82)
Patient conditions according to NYHA	
Class I	235 (44)
Class II	285 (54)
Class III	12 (2)
Hemodynamic and echocardiographic features	
Qp/Qs	1.6 ± 0.9
Pulmonary artery pressure (mm Hg)	25 ± 11
Pulmonary vascular resistance (Woods unit)	3 ± 1.2
RVDd (mm)	44 ± 3
RVDs (mm)	33 ± 2.1
RA (mm)	42 ± 3
Operative features	
Aortic clamp time (minutes)	14 ± 5
Cardiopulmonary by pass time (minutes)	39.4 ± 9

NYHA - New York Heart Association, Qp/Qs - ratio of pulmonary flow to systemic flow, RVDd - right ventricular diameter in diastole, RVDs - right ventricular diameter in systole, RA - right atrial diameter

when compared with preoperative calculations, however, that was not statistically significant (p=0.57). All patients were in NYHA functional class I and had normal sinus rhythm at their last visits.

The closures of atrial septal defects have been performed successfully worldwide. However, there are many questions about ASD closure such as: When should it be closed? How should it be closed? What is the cost effectiveness of these techniques? What are the long-term results of trans catheter techniques? Typically, closure of isolated secundum ASD is undertaken in the 4th or 5th year of life. However, there is a group of patients who undergo ASD closure much earlier in life. These patients present with severe problems during infancy, such as recurrent respiratory infections, failure to thrive, heart failure, and respiratory insufficiency necessitating artificial ventilation.[2] Results of our study indicated that operation can be performed successfully without mortality in patients with older age. Although there are several reports about the successful closure of ASDs with devices, there are some unfavorable results such as cardiac perforation[3] and thrombus formation in the left atrium, right atrium or both.[4]

The most common complications occurring in the postoperative period is the rhythm disturbances, namely atrial fibrillation and sinus node dysfunction such as bradyarrhythmia and tachyarrhythmia. The sinus node dysfunction is seen more commonly in sinus venosus ASD, especially high venosum ASD, which have close relation with the sinus node.[5] In these patients, sinus node dysfunction can be avoided by selective superior vena cava cannulation. The main reason of atrial fibrillation is that the operation is fully atrial surgery. On the other hand, according to the results of our study, there is increased risk of atrial fibrillation in patients who have large atria and ventricles preoperatively. Thus, it is important that the operation should be performed before enlargement of the right chambers. On the last visit of the patients, there was no atrial fibrillation in any patient and at the echo cardiographic evaluation, in patients who had enlarged right chambers preoperatively, postoperative right ventricular and right atrial diameters were found to be reduced. All patients were class I according to NYHA classification at the last follow-up.

The ASD with associated pulmonary hypertension and increased pulmonary vascular resistance is occasionally seen in infancy and is not solely a result of atrial left-to-right shunting. This suggests presence of other factors leading to pulmonary hypertension. In our study, except for the 24 patients, there was no pulmonary hypertension and associated lesions. Thus, it was clear that hospital stay time were 5 ± 3 days and intensive care unit stay times were 24 ± 8 hours due to the fact that there were no pulmonary hypertensive events in the postoperative period.

The major limitation of this study was the retrospective nature of the study, and operations were carried out by different surgical teams. This study suggests that ASD closure can be performed safely without preoperative mortality, even in patients with older age. This favorable result has encouraged us to operate on the secundum type ASD in the second decade of life. Morbidity such as arrhythmia significantly decreases if surgery is performed before right atrial and ventricular enlargement.

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Osteogenic activity of Sadat-Habdan mesenchymal stimulating peptide in diaphyseal segmental defects

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Fracture healing is a complex process that occurs naturally without major complications, however, sometimes it takes a bizarre path from delayed union to non-union. The incidence of impaired fracture healing occurs between 5-20%,[1] but in patients with bone loss

the incidence increases dramatically. Bone harvested from iliac crest, however has its own limitations of quantity and its complications associated with increased site morbidity. This has prompted many surgeons to look for alternatives to autologous graft. Allografts free availability, cannot be compared to autologous graft as the former has least osteo-inductive properties, and secondly the allograft is inconsistent in incorporating into the host bone. In the last few decades, different growth factors have been tried for the enhancement of fracture healing in experimental animals,[2] and Sadat-Habdan mesenchymal stimulating peptide (SHMSP) was tried with good results in the enhancement of fracture healing. Segmental bone loss occurs in 11.4% of open fractures and defects of more than 2 cm fails to heal spontaneously. Trials are in progress to assess the affect of growth factors in segmental bone loss, and as SHMSP enhances fracture healing, this study was undertaken to test its effect on critical size segmental bone defect.

This study was carried out at the College of Medicine, King Faisal University, Dammam, Kingdom of Saudi Arabia between 1st May and 31st August 2006. Thirty skeletally mature 3-month-old rabbits were obtained. Under aseptic condition, the rabbits were anesthetized with an intramuscular injection of 35 mg/kg of Ketamine mixed with Xylazine 5 mg/kg body weight. The eyes of the rabbits were protected with saline drops to prevent dryness. The right forelimbs of the animals were shaved using an electric clipper. The area was scrubbed using hibiscrub and draped in a sterile fashion. A 2 cm diaphyseal segment of ulna was removed. The animals were divided in 3 groups. In group I, after irrigation 5 milligrams/kg body weight of SHMSP was added to the bone gap and the wound closed using 3/0 Dermilon. In animals of group II, SHMSP + 100 milligrams of Bovine Collagen Type I was added, and in group III the wound was closed after irrigation. The animals were allowed unrestricted weight bearing in the cages with free access to the potable water and a standard pellet diet. The cages were housed in the animal house at standard room temperature of 25°C and 12 hours of day/night light control. Animals were sacrificed at 8 weeks and 12 weeks, and the forelimbs were removed from mid-humerus, stored in protein buffer solution and frozen. All limbs were evaluated for healing of the segment on the basis of radiology, mechanical properties, and bone mineral density with dual energy x-ray absorptiometry.

During the study period, there were no complications. At 8 weeks, healing of the defects in group I was superior to groups II and III on the basis of radiographic evaluation, mechanical testing, and histopathological healing. At 12 weeks, the picture was better than at 8 weeks. The radiological assessment in group I was 3.2 as compared to 1.0 at 8 weeks, and at 12 weeks it was 1.6 versus 0.7 (**Figure 1**). Bone mineral content and bone mineral density were higher in group I versus group III (0.01 versus 0.003g/cm and 0.016 versus 0.04 g/ cm^2). Mechanical testing showed that the 8 weeks torque to failure in group I was 293.53 Nmm versus 131.40 in group III, while at 12 weeks it was 541.53 versus 294.06 Nmm (**Figure 2**).

0pen fractures with segmental bone loss require large amounts of bone graft and in the event of its absence healing at the fracture site is fraught with complications and failure of fracture union. The introduction of bone substitutes, growth factors, like bone morphogenetic protein (BMPs), transforming growth factor, insulin-like growth factor, fibroblast growth factor, platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) has been identified to stimulate fracture healing and some of these are under trials.[2] In this study, SHMSP was used to heal segmental defects in the rabbits and the ulna showed that the polypeptide was able to stimulate new bone formation superior to the control group. The quantitative CT measurement showed that at 12 weeks in the study and the carrier group the bone formation was superior, indicating a probably higher dose initially and the necessity of a

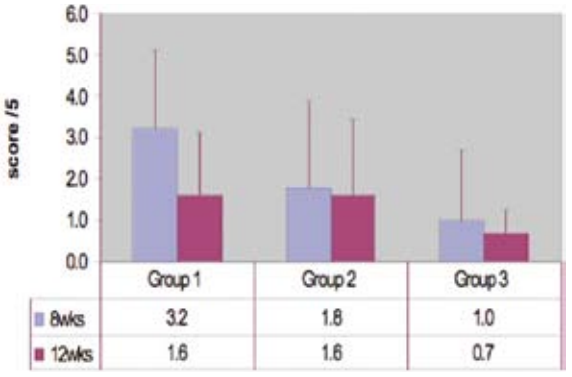

Figure - 1 Radiographic grading in the 3 groups at 8th and 12th weeks.

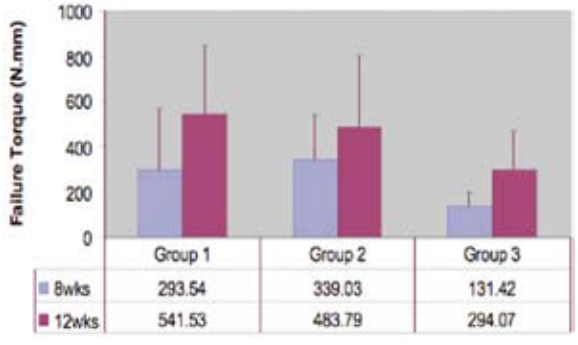

Figure 2 - Shows the results of mechanical test in torsion to failure of the 3 groups.

carrier. There was incomplete bone formation in the defect site in each group at 8 weeks and in the control group 2/5 showed signs of no growth at the fracture end.

The precise mode of action of SHMSP is still to be ascertained, however, the probable action, as reported earlier, is by promoting angiogenesis.[3] It was well established that vascular impairment leads to delayed fracture healing and angiogenesis precedes osteogenesis.[4] Growth factors like BMPs, VEGF, and PDGF are proved to be angiogenic, which helps in the fracture repair.[5] Evidence of the relationship of angiogenesis to enhancement of fracture healing is abundant, but the precise role of how angiogenesis does this has eluded researchers. At this time, we support the view that angiogenesis plays by far a major role in fracture healing and SHMSP stimulates angiogenesis, thus enhancing fracture union.

Even though this study shows that SHMSP helps in bridging the bone in the segmental bone loss in rabbits, there are a few limitations that need to be corrected in future studies. Firstly, the study was conducted in a smaller size of the animal population and in a smaller animal model, secondly, the dosing regimens still need to be adjusted, and lastly a comparison between the SHMSP group, autogenous and allograft groups need to be carried out. Further studies are being undertaken in a larger animal. Toxicology and pharmacokinetics studies will become an essential part of future studies.

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Renal failure in patients with multiple myeloma: a single center experience

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Multiple myeloma (MM) is a rare hematological malignancy. It is characterized by uncontrolled proliferation of plasma cells in the bone marrow. Common presenting features of MM include bone pain, anemia, increased susceptibility to infections, hypercalcemia, neurological manifestations, hyperviscosity syndrome, and renal failure.[1] Renal failure is a fairly common finding in patients presenting with MM, occurring in approximately 20-25% of patients.[1-3] The most common renal lesion is myeloma cast nephropathy, characterized by the presence of large tubular casts. Rarer varieties of renal lesions include light chain deposition disease and primary amyloidosis. Several factors may predispose MM patients to develop renal failure such as volume depletion, hypotension, sepsis, hypercalcemia, hyperuricemia, and exposure to intravenous radiocontrast material or other potentially nephrotoxic agents such as nonsteroidal anti inflammatory drugs.[4] Renal failure in MM patients is associated with higher mortality, partly because it limits some treatment options. Renal failure is often reversible with simple measures such as rehydration, removal of offending drugs, and correction of hypercalcemia. The reversibility of renal failure has a positive impact on the prognosis.[2,4] The aim of this study is to evaluate patients with MM with respect to the presence of renal failure at time of diagnosis, association of renal failure with other laboratory and clinical correlates and its impact on early survival.

The medical records of all patients with the diagnosis of MM admitted to King Fahd Hospital of the University (KFHU), Alkhobar, Kingdom of Saudi Arabia during the period January 1992 to December 2005 were analyzed. The inclusion criterion was a diagnosis of MM as based on the presence of 2 of the following findings: bone marrow plasma cells more than 30%, serum or urinary monoclonal protein, and osteolytic bone lesions on skeletal radiological survey. Patients with prior diagnosis of chronic renal failure were excluded. Plasma cell tumor load was determined as low, moderate, or high according to criteria proposed by Durie and Salmon.[5] Demographic, clinical, and laboratory data were reviewed with respect to age, gender, nationality, presenting symptoms and signs, hematological and chemical parameters, and the level of monoclonal protein in the serum and urine. Abnormal renal function was defined as a serum creatinine concentration ≥133 umol/l (1.5 mg/dl) at

the time of diagnosis whereas renal failure was defined as a serum creatinine ≥177 umol/l (2mg/dl) at the time of presentation. When possible, the precipitating factor of renal failure was determined from the clinical and laboratory information available. The course of the patient was monitored with respect to renal function recovery, need of dialysis support, and early mortality. Early mortality is defined as death within 3 months from time of diagnosis. Data were expressed as mean values with standard deviation. Comparison between patients with and without renal failure was performed by unpaired Student's test for numerical variables. Chi-square test was used for comparing nominal variables. Value of $p<0.05$ was considered statistically significant.

During the study period, a total of 43 patients with the diagnosis of MM were admitted to KFHU. Thirty-three patients (76.7%) were males. Mean (+ SD) age of patients was 61.1+11.4 years, range 36-83 years. Thirty-one (72.1%) were Saudi nationals. The most common presenting symptoms were bone pain (65.1%) and fatigue (25.6%). Weight loss was present in 18.6%. Anemia (Hb <100 g/l or 10 gm/dl) was seen in 58.1%. Osteolytic bone lesions were observed in 20.9%, and plasmacytoma in 18.6%. Abnormal renal function as defined by serum creatinine >133 umol/l (1.5 mg/dl) was seen in 16 patients (37.2%) at the time of diagnosis. Eleven (25.6%) patients had renal failure as defined by a serum creatinine >177 umol/l (2 mg/dl). Of these 7 (63.6%) patients had serum creatinine <265 umol/l (3mg/dl). **Table 1** compares patients with and without renal failure with respect to several clinical and laboratory variables. The two groups were similar in age, gender distribution, platelet count, serum calcium, lactic dehydrogenase (LDH) and serum albumin levels. There was a tendency for lower hemoglobin level in patients with renal failure, but did not reach statistical significance. Nine of 11 patients (81.8%) with renal failure at presentation had a Stage III myeloma as compared to 14 of 32 patients (43.8%) without renal failure ($p=0.026$). Urine Bence-Jones protein was significantly associated with renal failure at presentation. It was positive in 6 patients (54.5%) with renal failure at presentation as opposed to 7 patients (21.9%) without renal failure ($p=0.04$). Potential precipitating factors of renal failure were determined in 5 patients. These were hypercalcemia in one patient, hypercalcemia and radiocontrast exposure in one patient, sepsis in 2 patients, dehydration and intake of nonsteroidal anti-inflammatory drugs in one patient. No precipitating factor could be ascertained in 6 (54.4%) patients. Renal function normalized in 7 patients by simple measures such as intravenous hydration, treatment of infections and removal of potential offending drugs. Renal function remained abnormal, but stable in 3 patients. Three patients required hemodialysis treatments for control of uremic manifestation. One of these 3 patients remained dialysis dependent until time of death 4 months after the diagnosis of MM. Kidney biopsy was performed in 2 patients. In both cases, the histological findings were consistent with myeloma cast nephropathy. Early mortality, defined as death within 3 months from diagnosis, occurred in 3 (27.3%) patients with renal failure as compared to one patient (3.1%) in the group without renal failure at presentation ($p=0.017$).

Table 1 - Comparison of clinical and laboratory findings in patients with and without renal failure at presentation.

Variable	With renal failure (n=11) n= (%)	Without renal failure (n=32) n= (%)	*P*-value
Age (years±SD)	62.8 ± 9.8	60.5 ± 11.9	0.52
Gender: Males (%)	9 (81.8)	24 (75)	0.64
Hb (g/dl±SD)	8.5 ± 1.9	9.9 ± 2.4	0.07
Hb <100 g/l	8 (72.7)	15 (46.9)	0.12
Platelet count ($10^3/mm^3$±SD)	175 ± 107.6	253.1 ± 116.7	0.06
Serum Ca (mmol/l±SD)	2.3 ± 0.65	2.2 ± 0.18	0.67
LDH (IU/l±SD)	210 ± 108.4	171 ± 79.5	0.24
Serum albumin (g/l±SD)	2.7 ± 0.64	2.76 ± 0.63	0.73
Bone pain (n, %)	8 (72.7)	17 (53.1)	0.26
Durie-salmon stage I	1 (9.1)	8 (25.0)	0.26
Durie-salmon stage II	1 (9.1)	10 (31.3)	0.15
Durie-salmon stage III	9 (81.8)	14 (43.8)	0.026
Early mortality	3 (27.3)	1 (3.1)	0.017
M protein serum level (g/l±SD)	42 ± 28.2	50 ± 23.3	0.47
Bence-jones proteinuria	6 (54.5)	7 (21.9)	0.04

LDH - lactic dehydrogenase, Hb - hemoglobin, M - monoclonal, Ca - calcium

The study has demonstrated that patients with renal failure tended to have a higher tumor burden as demonstrated by a greater proportion with Stage III myeloma (81.8% verus 43.8%) and association with Bence-Jones proteinuria. There was a tendency for higher early mortality in MM with renal failure. The finding in our sample of MM with respect to the occurrence of renal failure at the time of diagnosis approximates what has been published internationally.[1,2,6] In our study, renal failure was reversible in 63.6%, dialysis was required in 27.3% and one patient (9.1%) remained dialysis dependent until death. Reversibility of renal failure is associated with improved survival.[6] The standard treatment of myeloma often consists of high dose chemotherapy with autologous peripheral stem cell transplantation in patients younger than 70 years. However, in many cases the presence of severe renal failure precludes such an approach. Treatment utilized in our patients included standard dose of prednisolone and melphalan, and a combination of

vincristine, Adriamycin and dexamethasone. Four patients required radiation therapy for localized severe pain due to osteolytic lesions. Two patients were treated with Thalidomide. One patient was referred for stem cell transplantation. Limitations of our study include its small size, and lack of long-term follow up. The data available, however, lead us to conclude that renal failure is present in approximately 25% of patients with MM at time of diagnosis. A precipitating event is present in approximately half of the patients. Renal failure is associated with a higher tumor burden and Bence-Jones proteinuria. It is reversible in the majority of patients. Early mortality is higher in patients with MM and renal failure.

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Pain status in Saudi governmental hospitals

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We conducted a study to evaluate the existing number of pain clinics operating among governmental hospitals in Saudi Arabia in 2006, and to describe their characteristics and care approach to pain patients. A telephone call was conducted to various governmental health facilities in Saudi. Ten pain clinics were found, 5 in the capital Riyadh, 4 in Jeddah, and one in Dhahran. The head of each clinic was contacted, and a questionnaire was completed. The profile of each pain clinic was reported. Nine clinics (90%) were found in governmental facilities, and one was in a semi-governmental center. All the hospitals were tertiary care centers located in major cities in Saudi. One clinic was affiliated with a medical school, 4 clinics in Military and National Guard centers, 2 in King Faisal Specialist Hospitals and Research Centers, one affiliated with the Ministry of Health and 2 in other governmental sectors. All clinics were unidisciplinary units ran by the anesthesia departments. Their main service was providing out-patient consultation with limited in-patient service. Input to the clinics was mainly from other relevant disciplines such as orthopedic, neurosurgery, neurology, oncology, rheumatology, general practitioners, and others. Both acute and chronic pain was treated by 60% of the respondents. Anesthesiology departments supervised 95.8% of the clinics, while 4.2% were run by neurology and palliative care doctors. None of the clinics had permanently assigned staff. All of the staff covered the clinic once or twice a week for 4-8 hours. Thirty percent of the covering staff was interested in pain management without any previous pain education (6 doctors), and 70% had special postgraduate pain training (14 certified pain specialists). An average of 2.1±1.08 SD (range 1-3/week) clinics were conducted per week and a mean of 10.1±5.6 (range 5-25/clinic) patients were managed in each clinic. Musculoskeletal pain especially low back pain (LBP) was the most frequently encountered type of pain and prescribed medications was the most commonly applied treatment modality, followed by epidural techniques, nerve blocks, and others. Implantable systems were less frequently used (6 clinics, 60%). Radio frequency ablation therapy was available in 7 clinics (70%). Psychiatric, psychophysiological methods, and neurosurgical procedures were available on limited basis as a consultation or referral. Despite the high prevalence of chronic pain among adults in various countries (a median prevalence of 15%, range 2-40%),[1] it is probably one of the most under-treated conditions in our country. The Saudi population is approximately 25 million, and the number of pain clinics available is 10 clinics only. Brena in 1985 analyzed the density of pain clinics per 1 million of population and noted that it was ranged from 1.28 in the United States of America, to 0.01 for Brazil.[2] In comparison to that, the density of pain clinic per one million Saudi populations was 0.0000004, which reflected a marked deficiency in such service.

Affiliation with a medical school was limited to one clinic and this will limit the teaching process of pain

medicine. The complexity of pain conditions necessitates a multidisciplinary approach with complement of various medical providers,[3] opposite to the current situation, in which all the clinics were unidisciplinary ones covered by part time physicians. Anesthesia departments were responsible for pain clinics in most of the facilities, and this was similar to international findings in the late 80's of the last century.[2,4] Low back pain was the most commonly encountered pain condition in all pain clinics similar to previous reports.[5] Medication was the most commonly prescribed modality in all clinics followed by epidural injection, and blocks, while implantable devices and thermal therapy were less commonly used as a result of the limited financial support. Psychological therapy was not part of any clinic, except on a consultation basis.

Although the study was limited in many aspects, it is an attempt to reveal the deficiency in the management of pain in Saudi Arabia, and to promote an initiative for a better establishment of pain management programs.

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