ORIGINAL ARTICLE

Maternal and neonatal effects of adding morphine to low-dose bupivacaine for epidural labor analgesia

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Abstract

Aim: Labor is one of the most painful experiences a woman may face during her lifetime. One of the most effective methods used for eliminating this pain is epidural analgesia. The aim of this study to determine the impact of adding morphine to low-dose bupivacaine epidural anesthesia on labor and neonatal outcomes, and maternal side effects.

Materials and Methods: This is a prospective randomized double-blind study comparing two regimens of anesthetic agents used for epidural anesthesia in labor. A total of 120 pregnant women were randomized into two groups with 60 subjects in each study arm. A catheter was inserted, and 0.1% bupivacaine + 2 μg/mL fentanyl in 15 mL saline were given to Group bupivacaine-fentanyl (Group BF), while 0.0625% bupivacaine + 2 μg/ml fentanyl + 2 mg morphine in 15 mL saline were given to Group bupivacaine-fentanyl-morphine (Group BFM) with no test dosing from the needle. No morphine was added to the subsequent epidural injections in Group BFM.

Results: The total dose of bupivacaine was significantly lower in Group BFM relative to Group BF (P = 0.0001). The visual analogu scalescores at 15, 30, and 45 min were significantly lower in Group BF compared to thosein Group BFM (P = 0.0001, P = 0.001, and P = 0.006, respectively). The second stage of labor was significantly shorter in Group BFM relative to Group BF (P = 0.027 and P = 0.003, respectively). The satisfaction with analgesia following the first dose was higher in the nonmorphine group (P = 0.0001). However, maternal postpartum satisfaction was similar in both groups. Either nausea or vomiting was recorded in eight patients in Group BFM.

Conclusion: We believe that epidural analgesia comprised of a low-dose local anaesthetic and 2 mg morphine provides a painless labor that significantly reducesthe use of local anesthetic without changing the efficiency of the analgesic, ensuring the mother's satisfaction without leading to an adverse effect on the mother or foetus, while mildly (but significantly) shortening the second stage of labor.

Key words: Bupivacaine, epidural analgesia, fentanyl, morphine, painless labor

Date of Acceptance: 25-Jul-2013

Introduction

A variety of methods can be used to provide painless labor by reducing the pain resulting from uterine contractions during labor, with no influence on the power of the contractions. Regional analgesia has become the most common method of pain relief used during labor in many countries.[1,2] One of the most widely used methods for relief of labor pain is epidural analgesia.[3] Implementation of epidural analgesia, an epidural catheter is inserted into the epidural space and a continuous infusion or multiple injections of local anesthetic were given according to the patient's pain level.[4] Local anesthetics commonly used for epidural analgesia include bupivacaine and ropivacaine and opioids, such as morphine and fentanyl. In conventional epidural analgesia, ahigh concentration of local anesthetic is used alone, ensuring a deep motor block.[5] Epidural opioids ensure analgesia

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Access this article online	
Quick Response Code:	**Website**: www.njcponline.com
	DOI: 10.4103/1119-3077.127559
	PMID: 24553033

without a motor block; however, when they are used alone, they do not lead to a satisfactory analgesia throughout labor.[6-8] When the two drugs are combined, both the local anesthetic and opioids can be administered at low concentrations, resulting in increased maternal satisfaction and most importantly, a decrease in the incidence of adverse effects such as hypotension and drug toxicity.[9]

In the current study, our primary aim is to determine the impact of adding morphine to low-dose bupivacaine epidural anesthesia on labor and neonatal outcomes, and maternal side effects.

Materials and Methods

The current study was conducted on 120 pregnant multiparous women who presented in spontaneous labor. Written consent was obtained from all patients. The study was approved by Ataturk University Ethics Committee and was conducted in a double-blind fashion with the association of obstetricians.

The study was conducted with multiparous pregnant women who were in the American Society of Anesthesiologists (ASA) physical status I-II group, at 37-42 weeks of gestation, cervical dilatation of 3.5 cm, between 16 and 30 years of age and had request for labor analgesia. All foetuses were singlewith vertex presentation and had normal heart rate pattern status. The criteria for exclusion from the study were as follows: Nulliparity, a history of sensitivity or allergy against/to amide local anesthetics, any contraindication to fentanyl or morphine, previous use of any intravenous opioid agonist or antagonist, contraindication to regional anesthesia, preeclampsia, any cardiovascular disease, a serious hypertension or hemorrhage during pregnancy, a body mass index (BMI) >30, intrauterine growth retardation, foetal distress, a multiple pregnancy, nonvertex presentation, nausea, or vomiting. Induction of labor in all women was done with artificial rupture of foetal membranes (when the cervix was 3 cm dilated) and syntocin on infusion (6 mIU/min). According to maternal or fetal indications, cesarean delivery was applied.

Randomization was performed the start of the study using computer software. The patients were randomized into two groups with 60 subjects each. Maternal oxygen saturation, heart rate, noninvasive blood pressure, and fetal heart rate were monitored during labor. All epidural catheters (Perifix® soft tip 701 Filter set, Braun, Melsungen) were inserted via the L2-3, L3-4, or L4-5 intervertebral space with an 18-gauge Tuohy needle using the hanging drop technique when the cervical dilatation was 3.5-6 cm and with the patient in a sitting position. The catheter was fixed at 3-5 cm in the epidural space. A dose of 0.1% bupivacaine + fentanyl was administered to the subjects in Group bupivacaine-fentanyl (Group BF), and the subjects in Group bupivacaine-fentanyl-morphine (Group BFM) received 0.0625% bupivacaine + fentanyl + morphine.

If the patient's visual analog scale (VAS) score ≥40, asolution of 0.1% bupivacaine + 2 μg/cc fentanyl in 15 mL saline was givenrandomly to Group BF, while a solution of 0.0625% bupivacaine + 2μg/cc fentanyl + 2 mg morphine in 15 mL saline was givenrandomly to Group BFM without any test dosing. Additional doses were administered according to scores of VAS (VAS score ≥40). In Group BFM, the additional doses did not include morphine. The study solution was prepared by an anesthesiologistwith no direct involvement in the patient's care or data collection, and the investigators and patients were blinded as to the solution type.

The pain felt by patients was evaluated using the VAS score at a 15-min interval (0 = No pain, 100 = Worst possible pain). A VAS score of 40 or above was regarded as insufficient analgesia, and 10 mL of solution was administered. AVAS score of below 40 was regarded as sufficient analgesia. The degree of motor block in the lower extremities was evaluated once every 30 min using the Bromage scale (1: No pain at the lower extremity. 2: Ankle is able to perform flexion. 3: Knee joint is able to perform flexion. 4: Flexion is present at the hip in a supine position. 5: Patient is able to stand. 6: Patient is able to stand and bend her knee).

Variables collected for each patient were age, height, weight, BMI, satisfaction from analgesia following the first dose, total dose of bupivacaine and fentanyl, Bromage score once every 30 min, incidence of instrumental vaginal delivery, duration of labor stages, total duration of delivery, patient satisfaction following delivery, total doses of oxytocin and morphine-derived side effects during labor and postpartum period (respiratory depression, nausea, vomiting, itching, sedation, whether urinary retention and neurological deficit). Postoperative urinary retention was defined as the inability to void in the presence of a full bladder.[10] After delivery of the baby, controlled cord traction was done by obstetrician, then the placental side of the divided umbilical cord was doubly clamped and then blood was drawn from the umbilical artery for the measurement of pH and an infusion of oxitocin was started (20 IU per 500 mL at rate of 60-100 mL/h). Moreover, although the VAS score was evaluated once every 15 min, recordings were only obtained once every 15 min for the 1st h, once every 30 min for the 2nd h, and once an hour for the remaining period. If the respiration rate was below 10/min, respiratory depression was to be considered. If the systolic arterial pressure was below 100 mmHg or lower than 20% of the baseline level, hypotension was to be considered. Additionally, evaluation of sedation was regarded as follows: None (alertness), mild (somnolence), moderate (sleepy), and severe. The level

of maternal satisfaction was assessed as poor, moderate, or good. The patients were monitored for 24 h for respiratory depression and sedation. The Apgar score at the1st and 5th min, the pH of the umbilical artery, and the requirements for tracheal intubation and ventilation were also recorded.

The power calculations were based on the preliminary study, the median dose of bupivacaine was determined as 48 mg (SD 15 mg) in the group that received 2 μg/cc fentanyl with 0.1% bupivacaine. We predicted a reduction ofthe requirement for bupivacaine by 20% by reducing the dose of bupivacaine to 0.00625% and adding 2 mg morphine (a difference of 9.6 mg). On the basis of the assumption that the α error is 0.05 and the β error is 0.10, the estimated number of patients required is 52, with a power of 80%. The sample size in our study determined according to these results as 60 patients.

Statistical analysis

Data were analyzed using SPSS 10.0 statistical software. Age, height, weight, BMI, duration of the labor stages, duration of delivery, foetal outcomes, VAS scores, and administered total dose of bupivacaine and fentanyl of patients and whether the motor block, hypotension, itching, urinary retention, respiratory depression, neurological deficit, satisfaction with the analgesia, nausea, and vomiting were analyzed with appropriate statistical tests. The Komogorov-Smirnov test was used to assess the normal distribution of data. If data werenot normally distributed, comparisons were determined using Mann-Whitney U-test, Student's *t*-test was used for normally distributed continuous variables. Chi-square test was used to compare categorical variables. A "*P*" value below 0.05 is regarded as statistically significant.

Results

A total of 120 term multiparous women in spontaneous labor were included to this study (60 patients in each group). Patient details were similar for the two groups [Table 1]. The VAS scores at the 15th, 30th, and 45th min were significantly lower in Group BFthan in Group BFM ($P = 0.0001$, $P = 0.001$, $P = 0.006$, respectively) and no difference were observed between two groups in terms of VAS scores after the first 45 min [Table 2].

Satisfaction from analgesia following the first dose was significantly better in Group BF than in Group BFM ($P = 0.0001$), while no statistically significant difference was detected between Group BF and Group BFM in terms of maternal the postnatal satisfaction [Table 3]. The total dose of bupivacaine administered was significantly lower in Group BFM compared to that of Group BF ($P = 0.0001$). No statistically significant difference was detected between Group BF and Group BFM regarding motor block or foetal outcomes. There was no significant difference between the two groups regarding the duration of the 1st stage of delivery or total duration, while the second and third stages of labor were significantly shorter in Group BFM relative to Group BF ($P = 0.027$ and $P = 0.003$, respectively). Total oxytocin doses in two groups were found to be similar [Table 4]. None of the babies required ventilation or intubation. There was no hypotension, itching, respiratory depression, urinary retention, sedation, and neurological deficit in groups. None of women in Group BF had nausea and vomiting although eight women in Group BFM had nausea and vomiting. Regarding side effects, the instance of nausea and vomiting was significantly higher in Group BFM than in Group BF ($P = 0.003$). None of patients required instrumental delivery.

Table 1: Patient's details

	BF	BFM	*P* value
Age (years)	26.0±3.50	25.2±2.85	0.056
Weight (kg)	70.9±6.25	71.0±7.81	0.938
Height (cm)	160.9±2.89	61.4±5.28	0.494
BMI	27.0±2.40	26.8±2.40	0.685
Parity	2.24±0.96	2.31±0.47	0.060

All values are expressed as the mean±standard deviation; BF=Bupivacaine, fentanyl group; BFM=Bupivacaine, fentanyl, and morphine group, BMI=Body mass index

Table 2: Visual analog scale scores

Time (min)	Group BF	Group BFM	*P* value
15th	15.26±17.3	31.4±26.0	0.0001*
30th	12.8±11.7	24.5±23.0	0.001*
45th	12.6±12.4	19.6±13.9	0.006*
60th	17.1±12.5	22.7±17.7	0.06
90th	19.0±13.8	24.2±20.7	0.181
120th	24.7±15.5	25.9±15.3	0.705
180th	21.0±13.4	25.8±16.7	0.177
240th	17.5±7.6	20.0±7.2	0.190
300th	23.3±8.7	21.0±11.2	0.427
360th	30.0±18.6	28.2±11.4	0.711
420th	26.7±16.4	26.7±12.6	1.000

All values are expressed as the mean±standard deviation; BF=Bupivacaine, fentanyl group; BFM=Bupivacaine, fentanyl, and morphine group; The visual analog scale scores at the 15th, 30th, and 45th min demonstrate a significant reduction in Group bupivacaine, fentanyl compared with group bupivacaine, fentanyl, and morphine (*P*=0,0001, *P*=0.001, *P*=0.006)

Table 3: Characteristics of epidural procedure

	BF	BFM	*P* value
Satisfaction from analgesia following the first dose			
Good	56*	36	0.0001*
Moderate	2	0	
Poor	2	24*	
Postpartum maternal satisfaction			
Good	60	56	
Moderate	0	2	
Poor	0	2	

BF=Bupivacaine, fentanyl group; BFM=Bupivacaine, fentanyl, and morphine group; There is a significant difference in group bupivacaine, fentanyl relative to group bupivacaine, fentanyl, and morphine in terms of patient satisfaction following the first dose, *P*=0.0001

Table 4: Conduct of labor and foetal outcomes

	BF	BFM	*P* value
Total dose of bupivacaine (mg)	47.4±14.28	34.4±17.05	0.0001**
Total dose of fentanyl (mg)	94.8±28.55	105.9±51.95	0.150
Motor block	-	-	
First stage of labour (min)	741.8±383.9	810.2±352.6	0.311
Secondstage of labour (min)	25.8±12.5	20.5±12.5	0.027*
Thirdstage of labour (min)	7.7±2.8	6.1±3.0	0.003**
Duration of labour (min)	758.07±382.1	852.86±342.2	0.168
Apgar score			
1 min	8.8±0.62	8.7±0.91	0.485
5 min	10.0±0.00	10.0±0.18	0.156
Umbilical artery pH	7.37±0.07	7.35±0.08	0.249
Maximal oxytocin dose mIU/min	15.50±2.30	14.80±2.15	0.06

All values are expressed as the mean±standard deviation. BF=Bupivacaine, fentanyl group; BFM=Bupivacaine, fentanyl, and morphine group; There is a significant reduction in the total dose of bupivacaine in group bupivacaine, fentanyl, and morphine, *P*=0.0001; The second and third stages of labor were significantly shorter in Group bupivacaine, fentanyl, and morphine (P=0.027 and *P*=0.003)

Discussion

This prospective, randomized, and double-blind study comparing 0.1% bupivacaine + 2 μg/cc fentanyl with 0.0625% bupivacaine + 2 μg/cc fentanyl + 2 mg morphine demonstrated a significantly lower total dose of the local anesthetic administered to the morphine group without a change to the analgesic efficiency. Studies conducted on the delivery analgesia have focused on reducing the dose of local anaesthetic to minimize the motor block. Opioids were added to the low-dose local anesthetic in an effort to reduce the motor block. Minimizing the motor block enables a pregnant woman to move independently during delivery, and contractions are maintained without pain.[9-12] Although contradictory, it is believed that walking contributes to the progression of labor.[13,14] Moreover, epidural anesthetics reduce uterine contractility by suppressing the production of endogenous oxytocin and administration of low doses of such drugs may also minimize this risk.[15,16]

In the current study, the dose of bupivacaine was reduced to 0.0625% for the reasons defined above and for preventing motor block. One of our concerns was whether this dose would ensure analgesia. Therefore, we added 2 mg morphine to this group to increase analgesic efficiency.

In the current study, although the VAS score in the first 45 min was significantly lower in Group BF compared with Group BFM, the VAS score was not significantly lower toward the end of labor in the morphine-administered group. Moreover, although analgesia satisfaction in the morphine administered group was notably poor after the first dose, it was high atthe postpartum visit. We believe these outcomes result from the long-term effects of morphine.

We administered that bolus doses more frequently in the morphine group to ensure sufficient analgesia during the first hours of labor because analgesic satisfaction following the first dose was poorer in this group; however, despite frequent administration of the drug, the total dose of the local anesthetic administered was significantly lower in this group and no motor block was observed.

Studies have demonstrated that continuous epidural infusion of local anesthetic and frequently repeated bolus doses may increase the total dose of the local anesthetic, resulting in motor block.[16,17]

In a study comparing continuous epidural infusions of 0.0625% bupivacaine/0.0002% fentanyl and 0.0125% bupivacaine,[18] the total dose of bupivacaine in the low-dose group was higher than in the group receiving a similar treatment in our study (67 ± 32 mg vs. 34.4 ± 17.05 mg in our study). Moreover, a high level of satisfaction with the analgesia was reported by 88% of the patients during the first stage of the labor and in 59% of the patients during the second stage. In this study, all solutions were administered as continuous infusions, and bupivacaine was also administered as a bolus if sufficient analgesia could not be achieved. This approach increased the volume of the local anesthetic and also resulted in motor weakness. Despite poor analgesia satisfaction in the low-dose group and the resultant increased frequency of bolus administration in the current study, the total dose of bupivacaine was lower, no motor block was observed, and sufficient analgesia was ensured for the first and second stages of labor. The reason for administering alower dose of the local anaesthetic was due to the administration of bupivacaine via an intermittent bolus approach. Epidural bolus doses were administered whenever required without a time limitation, and the required dose of bupivacaine, which was significantly reduced due to analgesic efficiency, increased with morphine.

Morphine is one of the primary opioids used in labor analgesia. It was demonstrated in humans that morphine administered via an epidural route enables efficient and long-term relief for chronic and postoperative pain without leading to a sympathetic or neuromuscular blockade.[19] Such characteristics of morphine can be advantageous for labor analgesia. The reasons for selecting the opioids fentanyl and morphine are the rapid onset of the effect of fentanyl and the long-term effect of morphine.

In the current study, we demonstrated that low-dose morphine added to low-dose bupivacaine together with the local anesthetic ensures efficient analgesia, and it can be used for labor analgesia without leading to any adverse neonatal or maternal effects. In recent years, there are no studies using epidural morphine as regional analgesic method in vaginal deliveries. In a study conducted by Hughes *et al.*,[20] sufficient analgesia was not achieved in

any patients who were administered 2 mg and 5 mg of epidural morphine. In 7 of 11 patients in the morphine group (7.5 mg), analgesia was achieved until the end of the first stage of labor and all patients were given bupivacaine to provide sufficient analgesia. In the group that received 7.5 mg morphine, pain relief began 20-45 min after the administration of the drug. This may be perceived as a long time by pregnant women experiencing acute pain. However, it was reported that 5 mg morphine administered via an epidural route ensured long-term analgesia in the postoperative period.[21] This is due to the difficulty of blocking the afferent nerves responsible for acute pain and the delay of this blockade. Such problems can be overcome by ensuring more intense analgesia based on concurrent use of morphine with the local anesthetic.

In a study that focused on this problem,[22] 2 mg epidural morphine combined with 0.25% bupivacaine was reported to result in effective analgesia, and when compared with 0.25% bupivacaine alone, the duration of analgesia was longer and the quality was higher. Our results were similar to those of the mentioned study; however, we achieved efficient analgesia even with a lower dose of bupivacaine. However, we were unable to find any information regarding the total dose of bupivacaine in the mentioned study.

Morphine ensures effective analgesia by stimulating Mu receptors, but it is also associated with undesirable side effects. The use of epidural or intrathecal morphine for labor analgesia is limited due to concerns regarding such side effects (nausea, vomiting, pruritus, and urinary retention), particularly respiratory depression.[23,24] It has been suggested that epidural morphine results in emetic effects by activating opioid receptors in the chemoreceptor trigger zone.[24] Moreover, the pregnancy status and the further intensification ofthe delay of gastric passage caused by opioids in pregnant women may lead to nausea and vomiting.

In our study, we observed nausea and vomiting as side effects in eight patients in the group that received morphine. Neither side effect persisted nor these women require any therapy.

Respiratory depression is one of the most significant problems observed after opioids such as hydrophilic morphine are administered via a neuraxial route, and it is dependent onthe dose of the opioid.[25] This effect may occur at 6-18 h following administration due to the slow rostral diffusion and absorption of morphine in the respiration centers.[25] The incidence of respiratory depression in obstetric patients who received morphine via a neuraxial route was lower than that in nonobstetric patients.[19] Although the incidence of respiratory depression is low in pregnant women, it is a serious risk. Therefore, the respiration, oxygenation, and sedation levels of the mother should be closely monitored throughout the labor and the postpartum period. We also monitored the patients' respiratory rates and sedation levels for 24 h. No evidence of respiratory depression was observed. A possible benefit of using a low-dose local anesthetic in combination with narcotics is the minimization of the side effects and toxic effects of those drugs on the mother and foetus that may occur secondarily to their intravascular and intrathecal administration.

Maternal effects of neuraxial opioids also have direct and indirect influences on the foetus. If the mother develops respiratory depression, the foetus will also indirectly develop respiratory depression, and epidural morphine has been demonstrated to cross the placental barrier.[26] Although very rare previous studies have suggested that a continuousepidural infusion of opioids may result in an accumulation of the drug and neonatal respiratory depression.[27]

In our study, we observed that adding low-dose morphine to bupivacaine had no adverse effect on the foetus. The dose of morphine administered in the current study was low, and it was only added to the baseline bolus dose. The Apgar scores of neonates at the 1st and 5th min were high, and the values obtained from umbilical artery blood gas analysis were normal. These results correspond to the results of the study conducted by Abboud *et al.*[22] They also added 2 mg morphine to bupivacaine, and they observedno adverse effect on the foetus.

One contradictory issue associated with labor analgesia is related to the effects of neuraxial analgesia on the second stage of the labor and the incidence of instrumental delivery. The American College of Obstetricians and Gynecologists defines a prolonged second stage in nulliparous women as lasting more than 3 h with neuraxial analgesia; for parous women with neuraxial analgesia, a prolonged second stage is defined as more than 2 h. The use of a local anesthetic at a high concentration may result in relaxation of the pelvic floor muscles. Straining movements are accomplished by the pelvic floor muscles, which plays an important role in labor. Reducing the motor blockade of these muscles facilitates the descent of the foetal head into the pelvis and rotation of the foetal head; but it also enables coordinated push strength on the foetus throughout the second stage of labor.[28]

Prolongation of the second stage and the need for instrumental delivery may cause morbidity ofthe mother, and it may also have a negative effect on maternal satisfaction during labor.[29] Although it has been speculated that despitethe possible correlation between epidural labor analgesia and the increase in incidence of instrumental delivery, it is difficult to discern whether these instrumental deliveries were elective. For the most part, obstetricians prefer elective instrumental delivery in women with analgesia.[29] No instrumental deliveries were observed in our study.

Certain studies suggest that epidural analgesia mayshorten the second stage of delivery, while other studies demonstrate no change.

Although the difference was minor, the duration of the second stage of delivery was significantly shorter in the low-dose group compared with the other group in our study.

In another study,[28] patients given 0.25% bupivacaine and 2 μg/mL fentanyl + 0.1% bupivacaine demonstrated a reduction in the duration of the second stage. In our study, the duration of the second stage of labor was shorter despite the similarity of the administered volume of bupivacaine at the same dose [45 (35-50) mg in the study mentioned and 47.4 ± 14.28 mg in our study].

In another study,[30] analgesia during the second stage was ensured with the continuous epidural infusion of 0.0625% bupivacaine and 2 μg/mLfentanyl. There was no statistically significant difference between the two groups in terms of the duration of the second stage of labor. In the study mentioned, the duration of the second stage was 53 min in the treatment group.

In our study, the duration of the second stage of labor was 25.8 ± 12.5 min in Group BF and 20.5 ± 12.5 min in Group BFM, and the recorded durations were shorter than the duration of the second stage in the study mentioned above. This may result from the continuous infusions of the solutions in our study or from the lower dose of bupivacaine administered compared with the bupivacaine dose administered in the other study (47 and 34 mg in our study vs. 63 and 44 mg in the study mentioned above).

If morphine had been added while the dose of the local anesthetic was kept constant in one of the two groups in our study, the need to reduce the local anesthetic could have been determined more objectively. However, we surmised in our preliminary studies that the local anesthetic used at this dose may have provided sufficient analgesia.

Conclusion

We believe epidural analgesia comprised of a low-dose local anesthetic and 2 mg morphine can provide a painless labor with efficient analgesia despite the reduction the useof local anesthetic. Furthermore, this method of analgesia ensures good maternal satisfaction without leading to adverse effects on the mother or the foetus, and it slightly (but significantly) shortens the second stage of labor.

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How to cite this article: Dostbil A, Celik M, Alici HA, Erdem AF, Aksoy M, Ahiskalioglu A. Maternal and neonatal effects of adding morphine to low-dose bupivacaine for epidural labor analgesia. Niger J Clin Pract 2014;17:205-11.
Source of Support: Nil, **Conflict of Interest:** None declared.