eISSN 2255-0569

ORIGINAL

Comparison of low-dose ketamine intravenous infusion with spinal anesthesia in pain control of mothers being a candidate for painless labor

Comparación de la infusión intravenosa de ketamina en dosis bajas con anestesia espinal en el control del dolor de madres candidatas a un trabajo de parto indoloro

Somayeh Nikfar[1], Ramin Parviz Rad[2], Saeid Soltani[3], Yousef Shah Taheri[3], Alireza Kamali[3]

1. Department of Gynecology, Arak University of Medical Sciences, Arak, Iran.
2. Department of Emergency Medicine, Arak University of Medical Sciences, Arak, Iran.
3. Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, Arak, Iran.

Correspondencia
Alireza Kamali
Department of Anesthesiology and Critical Care
Arak University of Medical Sciences, Arak, Iran
Tel.: 00989181622810
E-mail: Alirezakamali849@gmail.com

Recibido: 30 -X - 2020
Aceptado: 12 - I - 2021

doi: 10.3306/MEDICINABALEAR.36.01.50

Abstract

Objective: Relieving severe pain during labor has a positive effect on its process. Recognition of maternal and neonatal complications and the effect of reducing pain intensity in different methods of anesthesia requires consideration. Therefore, this study aimed to compare low-dose ketamine intravenous infusion with spinal analgesia in controlling labor pain.
Methods: The study was designed as a clinical trial. The number of 100 patients were randomly divided into two groups of 50. In the ketamine group, 0.2 mg/kg of Ketamine per kilogram of the mother's weight was injected simultaneously with the onset of the active phase and continued until the end of labor and the baby's removal from the cervix. Data analysis was performed based on SPSS-19 software.
Results: There was a significant difference between the two groups in terms of the mean pain scores of the patients so that the mean visual analog scale (VAS) of the patients from 10 minutes after the intervention to the end of labor in the spinal group was significantly lower than the ketamine group (P = 0.01, P = 0.02). The mean of the active gestational phase in the ketamine group was longer than the low-dose spinal group (P = 0.01), but the second gestational phase's mean was longer in the low-dose spinal group, unlike the active gestational phase (P = 0.03).
Conclusion: Considering the results obtained in this study, it seems that in the case of knowledgeable acceptance of the receiving spinal injection by the pregnant woman, this method is more effective due to its better anti-pain effect and no neonatal complications. Therefore, it is recommended that low-dose spinal be used for women to reduce pain.

Key words: Ketamine, infusions intravenous, analgesia, labor pain.

Resumen

Objetivo: El alivio del dolor intenso durante el parto tiene un efecto positivo en su proceso. Hay que tener en cuenta las complicaciones maternas y neonatales y el efecto de la reducción de la intensidad del dolor en los distintos métodos de anestesia. Por lo tanto, este estudio tuvo como objetivo comparar la infusión intravenosa de ketamina a dosis bajas con la analgesia espinal en el control del dolor del parto.
Material y métodos: El estudio se diseñó como un ensayo clínico. Se dividieron aleatoriamente 100 pacientes en dos grupos de 50. En el grupo de ketamina, se inyectaron 0,2 mg/kg de ketamina por kilogramo de peso de la madre simultáneamente con el inicio de la fase activa y se continuó hasta el final del parto y la extracción del bebé del cuello uterino. El análisis de los datos se realizó con el programa informático SPSS-19.
Resultados: Hubo una diferencia significativa entre los dos grupos en cuanto a las puntuaciones medias de dolor de las pacientes, de manera que la media de la escala visual analógica (EVA) de las pacientes desde los 10 minutos después de la intervención hasta el final del parto en el grupo de espinal fue significativamente menor que en el grupo de ketamina (p = 0,01, P = 0,02). La media de la fase gestacional activa en el grupo de ketamina fue más larga que en el grupo de dosis bajas de espinal (p = 0,01), pero la media de la segunda fase gestacional fue más larga en el grupo de dosis bajas de espinal, a diferencia de la fase gestacional activa (p = 0,03).
Conclusiones: Teniendo en cuenta los resultados obtenidos en este estudio, parece que en el caso de que la gestante acepte con conocimiento de causa recibir la inyección espinal, este método es más eficaz por su mejor efecto antidolor y sin complicaciones neonatales. Por lo tanto, se recomienda el uso de dosis bajas de espinal para las mujeres para reducir el dolor.

Palabras clave: Ketamina, infusiones intravenosas, analgesia, dolor de parto.

Introduction

Labor is one of the most critical events in a woman's life accompanied by acute pain[1]. Fear of this pain usually leads to reluctance to natural birth among women. This pain is normal and does not arise from pathological conditions[2]. Uterine contractions and cervical dilatation cause this pain through the sympathetic nerves of the visceral organs that enter the spinal cord from T10 to L1. In the later gestational phase, the elongation of the perineum transmits pain through peduncle nerves and S2 nerve to S4[3,4]. Pain is caused by significant physiological changes in cardiopulmonary function and increased oxygen consumption. It is also associated with neurodegenerative stress responses and adverse effects on uterus function and uteroplacental circulation[5]. Labor pain may have a negative effect on the relationship between the mother and the baby in the first days of pregnancy[6], and it has been shown that relieving pain during labor has positive effects on the process of labor. Also, possible increasing stress reduces catecholamine, reduces cervical dilatation, and makes labor more tolerable[2].

Painless labor is performed in two ways, pharmacologically and non-pharmacologically. Non-pharmacological methods such as acupuncture, ice massage on the hands, and hypnosis are possible. The painless pharmacological methods include both systemic and neuraxial methods. Systemic ones include inhaling methods such as nitric oxide and intravenous methods with narcotic drugs such as pethidine, sofentanethyl, and non-narcotic drugs such as ketamine non-steroidal anti-inflammatory drugs. The neuraxial method also includes spinal, epidural and, combined spinal-epidural methods [8]. Studies have shown that an ideal method for pain relief should not interfere with uterine contractions and labor progress and should not increase the chances of cesarean section. Also, it should not lead to respiratory depression for the newborn, and inappropriate effects on the mother and the genital and it should be prescribed easily[9].

Ketamine is one of the anesthetics that, in addition to its hypnotic effect, has an anti-pain effect. Ketamine in low dose does not lead to anesthesia, but it keeps its anti-pain effects, and respiratory depression could not occur in this dose[10]. Some studies have illustrated that Ketamine in low does some positive effects on pain relief in labor, and it does not increase the duration of the labor and the chance of cesarean section[2]. In several studies, Ketamine has been used in different doses, and different ways, including intravenous, oral, intramuscular, intranasal, subcutaneous, anal, and epidural, and in some cases prescribed with morphine[11,12] and in some studies have been prescribed in low doses (less than 2 mg per kilogram of body weight in intramuscular use and less than 1 mg per kilogram of body weight in intravenous use)[13]. In this case, minimal research has been done on the effect of low doses of Ketamine (0.5 mg of t per kilogram of body weight)[14,15,16]. As Ketamine is a phenol-cycledine analog, high doses can cause some side effects such as hallucinations, nightmares, increased bronchial secretions, and increased brain pressure[16]. It has been suggested that low-dose use may be associated with earlier diagnosis and fewer complications, as well as appropriate postoperative pain relief[17]. Considering the above, in this study, we intend to compare the effect of low-dose ketamine intravenous infusion with spinal anesthesia on painless labor and measure these two methods' side effects.

Materials and Methods

The present study was designed as a clinical trial. The test population was selected from the patients admitted for natural labor at Taleghani Hospital in Arak-Iran. The sampling method was convenience sampling with entry and exit criteria. The data collection tool was collected as a checklist.

Inclusion criteria

1. Singleton pregnancy.
2. Gravidity I.
3. The onset of the active gestational phase.
4. Display of cephalic embryos.
5. Pregnancy age equal to or more than 37 weeks.

Exclusion criteria

1. Gravidity equal to or more than 2.
2. Twin and multiple pregnancies.
3. Contraindications for spinal anesthesia, such as local infection of anesthesia spot.
4. Eclampsia blade.
5. Distortion.
6. Thrombocytopenia less than 80,000.
7. Midwifery contraindication for natural labor such as the presence of placenta previa, breech , transverse prosthetics, history of cesarean section .
8. Having any underlying disease such as heart disease, high blood pressure, asthma, kidney or psychiatric illness.
9. Having a drug allergy background to Ketamine or any of the drugs used to cause pain relief

How to calculate the sample size and number?
According to the formula, the sample size was estimated 40 people in each group, which with an estimated 20% decline, 50 people in each group was required.

$$n = \frac{2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (s_1{}^2 + s_2{}^2)}{d^2}$$

S1=8 S2=16 d =8 n1=n2=40

In this study, 100 patients considering entry and exit criteria and providing the necessary information about the plan who expressed their consent about painless labor were entered and randomly divided into two groups with equal numbers (50 people in each group) divided. With the onset of the active gestational phase, the patients in both groups were ready for labor. In the ketamine group, 0.2 mg/kg of Ketamine was infused per kilogram of maternal weight as an infusion simultaneous with the active phase's onset and continued until the end of labor and the baby's removal of the cervix. In the spinal group, the patients were hospitalized after receiving fluid in a sitting position from the L4-L5 or L5-S1 space through the Bibran G25 spinal needle by 100 micrograms of Ketamine, the volume of which was increased to 5 mL with distilled water.

The mothers underwent permanent monitoring of fetal heart rate (FHR) during labor, and the progress of labor was investigated by a female resident who did not know how to receive the combination of Spanish anesthetic but about the method of controlling complications, pain relief, anesthesia, and the movement of the cases was instructed. Cesarean section indications in this study included fetal distress and no progression of labor. In cases where the mother and embryo were indicated for a cesarean section, a cesarean section's conditions were available. Sensory level with the needle (based on the level of surface marks such as umbilical surface T10, T6 gypsum level, between the umbilicus, T8 gasified) and motor level (based on Bromage degree) by observing their muscular force (lower limb movement from leg lift and pressure resistance to its immobility) were investigated. The amount of pain based on the VAS from 0 to 100 before, during, and after the labor was determined. Maternal monitoring, including blood pressure, the duration of the second gestational phase, and the total labor duration, was recorded. 1 to 2 hours after the labor, the mother's vital signs, including heart rate, respiratory rate, pain, and blood pressure, were re-measured and recorded. Infant monitoring, including neonatal Apgar, was performed and recorded at 1 and 5 minutes after birth and FHR.

Data analysis

Data analysis was performed based on SPSS-19 software, and in the analysis of the results, average indicators, standard deviation, criterion error, frequency percentage were used. For possible analytical analysis, a covariance test, chi-square test, independent t-Test, or nonparametric equivalent were used to compare the mean.

Ethical Considerations

A written application was received from the officials of the university to be introduced to the research centers. The study's purpose was described for all the research units, and written consent was obtained. The information of all the patients was kept confidential with the project executor. At all the research stages, all ethical statements were included in the Helsinki Research center and the Ethics Research Committees of the University of Medical Sciences.

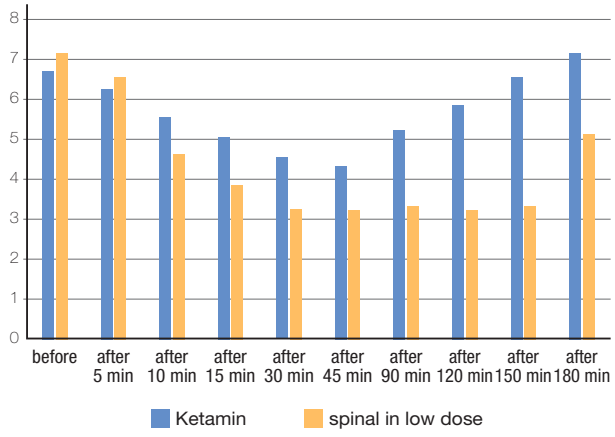
Result

The results of comparing the mean age and gestational age of the patients being a candidate for painless labor in the ketamine group were 24.6 ± 4.9 years and 38.85 ± 5.9 weeks, respectively, and in the spinal group were 23.9 ± 5.6 years, and 38.22± 6.3 weeks, and according to the results obtained between the groups, there was no significant difference between them in terms of mean age (P = 0.4) and mean gestational age (P = 0.6). The mean age of patients was approximately 24 years, and the mean gestational age was 38.5 weeks.

Comparison of mean arterial pressure (MAP) before the intervention and postpartum in the patients in the ketamine group was calculated as 80.3 ± 7.8 and 89.5 ± 8.3, respectively. The MAP before the intervention and postpartum was not significantly different between the groups, and the MAP before the intervention was 81 and for postpartum was 89 mm Hg (P = 0.4).

According to **figure 1**, there was a significant difference between the two groups in terms of mean pain scores of the patients (i.e., VAS), so that the mean VAS of the patients from 10 minutes after the intervention to the end of labor in the spinal group with a low dose, was significantly less than the ketamine group (P = 0.01, P = 0.02).

Fihure 1: Comparison of mean pain score of patients being candidates for painless labor.



According to **table I**, there was no significant difference between the two groups in terms of the mean FHR of the patients, so that the mean FHR of the patients at almost all labor times between the two groups was almost the same (P = 0.4) (P = 0.2).

Table I: Comparison of mean FHR of the patients being candidates for painless labor.

FHR score/ group	Ketamine group low dose	Spinal group	P-value
FHR before intervention	135.2±10.1	133.6±9.8	P=0.2 No significant
FHR 5 min after intervention	136.8±9.8	135.3±8.7	P=0.4 No significant
FHR 10 min after intervention	135.2±9.9	136.3±9.3	P=0.4 No significant
FHR 15 min after intervention	134.1±10.3	134.6±9.8	P=0.6 No significant
FHR 30 min after intervention	134.7±8.8	135.5±9.7	P=0.4 No significant
FHR 45 min after intervention	133.6±8.9	132.9±9.9	P=0.4 No significant
FHR 90 min after intervention	128.8±10.1	130.4±8.9	P=0.2 No significant
FHR 120 min after intervention	128.6±8.9	131.3±8.6	P=0.2 No significant
FHR 150 min after intervention	129.2±8.8	130.6±9.2	P=0.4 No significant
FHR 180 min after intervention	128.9±9.3	130.1±7.9	P=0.4 No significant

Comparison of the mean active gestational phase and the second gestational phase in the patients being candidates for painless labor in two infusion groups of low-dose Ketamine and spinal was investigated based on the minute, and according to the results, the mean of active gestational phase in the ketamine group was 102.91 ± 9.4 longer than the spinal group 87.5. ± 7.9 (P = 0.01) but the mean of the second gestational phase, unlike the active gestational phase in the spinal group 28.7 ± 6.2, was longer than the ketamine group 20.4 ± 4.8 (P = 0.03) and was statistically significant in both cases.

Comparison of the mean score of the satisfaction of the patients being candidates for painless labor in the two infusion groups of low-dose Ketamine and spinal was investigated in terms of minutes, and a significant difference was observed between the two groups and the mean satisfaction score in the spinal group was 2.4 ± 0.89 significantly higher than in the 0.91 ± 0.68 the ketamine group (P = 0.01).

In **table II**, the comparison of the mean Apgar minute at minuets 1 and 5 in infants, the patients being candidates for painless labor in the two infusion groups of low-dose Ketamine and spinal was investigated per minute, and according to the table, there was not a significant difference between the two groups' infants in terms of Apgar at minutes 1 and 5 in infants (P = 0.4).

Table II: Comparison of the mean Apgar minutes 1 and 5 of infants, patients being candidates for painless labor.

Mean gestational phase/ group	Ketamine group low dose	Spinal group	P-value
Mean Apgar min 1	9.1±1.2	9.3±1.1	P=0.4 No significant
Mean Apgar min 5	9.9±1.85	9.8±1.2	P=0.4 No significant

Discussion

Labor pain is one of the most common problems and is an essential factor in maternal dissatisfaction[18, 19]. The severity of pain depends on several factors such as the type and duration of labor, the type of used anesthesia used, and the applied painless method[20, 21]. As a result, the present study aimed to compare low-dose ketamine intravenous infusion with spinal analgesia in controlling labor pain among the mothers being candidates for painless labor.

During this study, it was found that there was no significant difference between the two groups in terms of mean age and mean gestational age and the mean age of the patients was approximately 24 years, and the mean gestational age was 38.5 weeks (P = 0.6, P = 0.4). One of the essential factors in selecting the type of pain-relieving method for pregnant women is its safety for the mother in hemodynamics. According to the obtained results between the two groups, the comparison of the MAP before intervention and postpartum in the patients did not show a significant difference (P = 0.4). According to the results, our study has similar results to the results of Krishna Jagatia et al. It should be noted that the increase in blood pressure in the ketamine group with cardiovascular effects, which is due to the increase in blood pressure without contact with the dose of the drug, is justifiable[10].

In general, the changes in the pregnant woman's hemodynamic status in the normal range in both groups indicate that the ability to perform both methods is not dangerous for the mother. Another significant point in choosing the type of painless natural labor method is to maintain the embryo and newborn's health. Our study showed that no significant difference was observed between the two groups in terms of FHR changes so that the mean FHR of the patients at almost all labor time was almost the same (P = 0.4, P = 0.2). These findings show that the effects of Ketamine are low and safe on the FHR. Our paper's results are similar to previous articles by Maroof, Khoshraftar, and colleagues[22, 23].

The mean of the active gestational phase in the ketamine group 102.91 ± 9.4 was longer than the spinal group 87.5 ± 7.9 (P = 0.01), but the mean of the second gestational phase, unlike the active gestational phase in the spinal group 28.7 ± 6.2 was longer than the ketamine group 20.4 ± 4.8 (P = 0.03), as the article by Jagatia Krishna et al., who used low doses of Ketamine for labor[2].

There was a significant difference between the two groups in terms of mean VAS of the patients so that the mean VAS of the patients was significantly lower than the intravenous group from 10 minutes after the intervention until the end of labor in the spinal group (P = 0.02, P = 0.01). In a study conducted by Khoshraftar *et al.*, the

results showed that spinal cord ketamine alone could cause pain during labor, which is similar to our study, and in 2009, in a study entitled "The effect of ketamine for relieving labor pain" by Joselyn *et al*., 30 samples at Whittington Hospital in London were evaluated. As a result of this study, low-dose ketamine injections were found to relieve acceptable labor pain in the mothers and with good results in the infant. However, more studies are needed to evaluate the effectiveness and side effects of ketamine-related pain relief[24], and in 2014 a study entitled "Study of the Effect of Oral Ketamine to Reduce Pain During Natural Labor in Nigerian Patients" by Okorie et al., was stated that the use of low doses of Ketamine to reduce side effects should be further investigated[25]. The results were consistent with our study. In India (2013), a study entitled "Study of the effect of low-dose ketamine for pain relief - a preliminary study of 100 patients" by Jagatia *et al*., a low dose of Ketamine was used, and no side effects have been reported in both mother and infant. It also did not affect the timing of the labor process. Because receiving Ketamine reduces maternal pain and reduces maternal fatigue, and patients receiving Ketamine are very cooperative during labor, thus facilitating the labor process and medical care[2]. Comparison of the mean score of the satisfaction of the patients being candidates for painless labor in the two infusion groups of Ketamine with a low dose and fentanyl was examined in terms of minutes, and a significant difference was observed between the two groups and the mean satisfaction score in the fentanyl group 2.4 ± 0.89 was significantly higher than in the ketamine group 0.91 ± 0.68 (P = 0.01).

The infant's Apgar values were not significantly different in the first and fifth minutes (P = 0.4). However, it shows a lack of any neonatal side effects in both groups, similar to the previous articles in which the use of Ketamine did not affect the infant's Apgar in the first and fifth minutes. Taken being ineffective on Apgar, each method is considered a safe method for infants[5].

Conclusion

In general, considering the results obtained in this study, it is considered that this method is more effective due to its better anti-pain effect and fewer maternal and neonatal side in the case of knowledgeably accepting spinal injection by the pregnant woman effects. However, the intravenous method can also be used as an easy, reliable, effective, and pain-relieving method at a moderate level and without neonatal side effects. Therefore, it is recommended that low-dose spinal be used for women to reduce pain.

Acknowledgments

The authors would like to thank the Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, Arak, Iran, for the significant supports.

References

1. Minville V, Fourcade O, Girolami JP, Tack I. Opioid induced hyperalgesia in mice model of orthopedic pain: preventive effect of Ketamine. Br J Anesth 2010; 104(2):231-8

2. Krishna Jagatia JM, Neha Patel. LOW-DOSE KETAMINE FOR PAINLESS LABOUR: A COMPARATIVE STUDY OF 100 PATIENTS. International Journal of Medical Science and Public Health. 2013; 2(3):707-11.

3. Cunningham F.H, Leveno KJ, Bloom SL, Spong CY, D asheJ S, Hoffman BL, et al. Obesterical Analgesia And Anesthesia.In:Williams Obestetrics.24 ed.McGraw Hill Education;2014.p.20-504.

4. Pamela F, Mark DR. Anesthesia for Obstetrics In: Miller RD, editor. Miller›s Anesthesia.8 ed. Philadelphia: Churchill Livingstone, Elsevier; 2015. p. 56-2327.

5. Ahmed EH, Hiam A, Magdi A, Fikria S, Mahmoud E, karim HI. Intravenous infusion of paracetamol versus intravenous pethidine as an intrapartum analgesic in the first phase of Labor.10-118:7; 2012.

6. Sadia A, Muhammad W, Attiya A, Nargis D, Sajjad A. Effect of epidural analgesia on labor and its outcomes. Jayub med coll Abbottabad.50_146 :) 1(27; 2015.

7. Keshin HL, Keshin EA, Tabuk M, Caglar GS. Pethidine versus tramadol for pain relief during labor. Int J Gynaecol obstet.6-82:11;2003.

8. Pandya ST. Labouranalgesia: recentadvances. Indian J Anesth.8-54:400; 2010.

9. Minty RG, Ien K, Alana M. Single-dose intrathecal analgesia to control labourpain.Canadian Family Physician.575 -53:437 ;2007.

10. Jaap V, Elske S, Marije R. Intravenous Anesthetics In: Miller RD, editor. Miller›s Anesthesia. 8 ed. Philadelphia: Churchill Livingstone, Elsevier; 2015. p. 49_845.

11. Kim RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. J Pain Palliat Care Pharmacother. 2002;16(3):27-35.

12. Madineh H REM, Ghaherei H, Akhlaghi M, Gangi F. The effect of intravenous low dose ketamine on postoperative pain. Shahrekord University of medical sciences journal. 2005; 7(2):29-34.

13. Schmid R SA, Katz J. Use and efficacy of low-dose Ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82(2):111-25.

14. Kwok RF LJ, Chan MT, Gin T, Chiu WK. Preoperative Ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg. 2004;98(4):1044-9.

15. Ivani G VC, Tonetti F. Ketamine: a new look to an old drug. Minerva Anestesiol. 2003;69(5):468-71.

16. Argiriadou H HS, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M, et al. Improvement of pain treatment after major abdominal surgery by intravenous S+-ketamine. Anesth Analg. 2004;98(5):1413-8.

17. McGlone RG HM, Joshi M. The Lancaster experience of 2.0 to 2.5 mg/kg intramuscular ketamine for paediatric sedation: 501 cases and analysis. Emerg Med J. 2004;21(3):290-5.

18. Vadivelu N, Mitra S, Narayan D.Recent advances in postoperative pain management. Yale J Biol Med 2010;83(1):11-25. 2.

19. Arroyo-Novoa CM, Figueroa-Ramos MI, Miaskowski C, Padilla G, Paul SM, Rodríguez-Ortiz P,et al. Efficacy of small doses of Ketamine with morphine to decrease procedural pain respondes during open wound care. Clin J Pain 2011;27(7):561-6.

20. Honarmand A, Safavi M, Karaky H. Preincisional administration of intravenous or subcutaneons infiltration of low dose ketamine suppresses post operative pain after appendectomy. J Poul Res 2012;5(1):1-6.

21. Benítez-Rosario MA, Salinas-Martín A, GonzálezGuillermo T, Feria M. A strategy for conversion from subcutaneous to oral ketamine in cancer pain patients: effect of a 1:1 ratio. J Pain Symptom Manage 2011;41(6):1098-105.

22. Maroof M, Hakim, Seema, Khan RM, Ahmed SM. Low Dose Ketamine Infusion Is Effective In Relieving Labor Pain. Anesthesia & Analgesia.9-86:380; 1998.

23. Khoshraftar A, Moazami F, Ashrafi B. Evaluation of the effect of single dose sputum inside the spinal cord on the duration of labor and analgesia of pregnant women in the first abdomen. Scientific Journal of Hamadan University of Medical Sciences and Health Services. 2008; 1(47): 6-22.

24. Joselyn AS. Joel S. Ketamine for labour analgesia. Correspondence. 2009:122-23.

25. Okorie O EH, Iroezindu MO, Obuna JA, Okike CO. Evaluation of Oral Ketamine for Pain Relief during Normal Labour in Nigerian Parturients. JMSCR. 2014;2(5):904-25.