Original article

Comparing effect of oxytocin versus oxytocin-propranolol combination on labor progression

Elahe Amiri1, Maryam Yazdani1, Somayyeh Noei Teymoordash1*,
Amir Hossein Salimi Kordasiabi2

1. Obstetrics and Gynecology, Research & Development Center Hospital Sayyed Shirazi, Golestan University of Medical Sciences, Golestan, Iran.
2. Medical Doctor, Research & Development Center Hospital Sayyed Shirazi, Golestan University of Medical Sciences, Golestan, Iran.

*Correspondence: **Somayyeh Noei Teymoordash**, Specialist of Obstetrics and Gynecology, Research & Development Center Hospital Sayyed Shirazi, Golestan University of Medical Sciences, Golestan, Iran. Deniznoei00@gmail.com

Abstract:

Introduction: Elective induction of labor increase the risk of cesarean section rate. pharmacological methods Including prostaglandins and oxytocin that are used. Another thing that may be helpful in the process of induction (propranolol), which is a type 1 and 2 beta-adrenergic receptor blocker. Stimulation of these receptors inhibits uterine contractions. Due to the inconsistent results from different studies as well as the small number of studies in this field, and the importance of the potential side effects of high doses of oxytocin on the health of the mother and fetus, this study aimed to evaluate the use of propranolol plus oxytocin compared with oxy oxytocin alone on the progress of the delivery.

Methods: This study was a controlled double-blind clinical trial, and 50 cases in each group. inclusion and exclusion criteria were considered. In Group oxytocin, oxytocin was started in 2 mIu / ml, and every 15 minutes in the same amount was added to the good contractions (three good contractions in 10 min), respectively, then 8 hours continued. In the propranolol group, before induction, 2 mg propranolol intravenously and slowly at a speed of 1 mg per minute were injected and then with oxytocin induction was established as above. Delivery and patient follow-up data were recorded.

Findings: In our study, the effect of propranolol on labor were investigated, propranolol has been able to reduce the duration of latent phase in the case group than the control group. (P =0.000). The mean duration of the active phase and second stage of labor were studied in two groups was not statistically significant, (P =0.703) for the duration of the active phase and (P =0.509) for the second stage of labor. In our study delivery and the cause of cesarean delivery and Apgar score at 5 minutes' infants were compared. in our study, the cesarean rate in the control group was higher, but the difference was not statistically significant (P =0.106).

Conclusion: In total, according to the studies and research it seems that propranolol can be used to help labor.

Keywords: propranolol, oxytocin, labor

Introduction:

The normal delivery period is different in women, and normal delivery in primigravid women has a slow progression, which is associated with many fetal complications and is one of the important reasons for emergency cesarean delivery. Disturbances in normal delivery, especially in non-advanced societies, are a common problem (1).

Induction of labor is always a concern in the case of an inappropriate cervix (1) and the use of methods to prepare the cervix has always been desirable. Shortening the delivery time to reduce the complications caused by it has always been a concern at the same time, induction of elective childbirth increases the risk of cesarean section by two to three times (2-4).

The cause of 30% of cesarean sections is the failure of the labor process or dystocia (5). One of the major causes of dystocia leading to cesarean section is stopped labor due to decreased activity of the uterus muscles (6-8), which can lead to increased labor time, fetal distress and maternal problems.

Various methods are used to prepare the cervix, including mechanical methods (9) and pharmacological methods.

One of the pharmacological methods is the use of prostaglandins and the use of oxytocin, which alone or in combination with other methods for the preparation of cervix is used. Maternal pain that can be accompanied by anxiety in the mother can lead to increased catecholamines in the blood, which, by stimulating beta-adrenergic receptors in the uterus, can reduce the severity of uterine contraction and imbalance in the labor process.

Another possible contributing factor in the induction of labor is propranolol, a blocker of beta-adrenergic receptors of type 1 and type 2. The stimulation of these receptors inhibits contractions of the uterus. In some studies, propranolol has been shown to cause contractions in the uterus and some other studies have acknowledged that using it can reduce the delivery time without having a harmful effect on the infant.

Propranolol is categorized by the Food and Drug Administration (FDA) as Group C medications during pregnancy, and its administration to stimulate delivery does not affect the overall fetal heart rate and maternal general health. Although some studies have shown that propranolol alone or in combination with oxytocin can be effective in reducing cesarean section, there are other studies that show no such decrease, and only the effect of it is limited to reducing the duration of labor or the amount of oxytocin consumed.

In a study by Margani et al. In 2016 in Kurdistan, Iran, the effect of oxytocin alone on oxytocin plus oral and intravenous propranolol in the development of delivery was studied. The duration of the first stage of labor in the oxytocin alone group was 197.25 ± 66.9 min, more than oral oxytocin with oral propranolol (128.25 ± 35.29) min and oxytocin with intravenous propranolol (122 ± 23) min. This difference was significant between the three groups.

Also In the study of Kashanian et al. In Tehran, Iran University of Medical

Sciences, the effects of oxytocin alone and administration of oxytocin and propranolol on labor were studied. The mean interval between initiation of induction and dilatation of 3-4 hours in the propranolol group on the first day was significantly lower than that of oxytocin group (11).

Considering the discrepancy between the results of various studies as well as the few studies done in this field, the importance of the potential side effects of high dose oxytocin on maternal and fetal health, this study was conducted to evaluate the use of propranolol plus oxytocin compared to oxytocin alone on the progression of labor.

Methods:

This study was a double-blind clinical trial in Sayyad Shirazi Hospital in Gorgan, Iran. The number of subjects was determined based on the formula for determining the number of samples, in each group, 50 were determined.

The conditions for entry into the study and exclusion criteria were considered. All patients agreed to participate in the study. Also, arrest labor cases were excluded for reasons such as inadequate uterine contraction, pelvic misalignment, inappropriate presentation, macrosomal embryos, or anatomical abnormalities of the mother. Patients were randomly assigned to one of two groups.

All initial examinations were done by the researcher and then the induction was initiated by the researcher and continued and control until delivery by other colleagues (obstetric and obstetrical assistants, medical students or midwives), who had no information about the injection of propranolol and also the patient had no information about the induction (double-blind).

In the oxytocin group, oxytocin was started at 2 mIU / ml and increased every 15 minutes to achieve the desired contractions (3 good contractions in 10 minutes) or up to a maximum of 30 mIU / ml and then at this rate, it lasted for a maximum of 8 hours.

In the case of entering the active phase, the induction continued until delivery, and if the active phase did not start (dilatation 3-4 cm) after 8 hours, the inoculation was discontinued and the patient was transferred to the department and the next day the induction was performed as The above.

In the absence of response to induction at the end of the second day, a cesarean section was performed. In the propranolol group, 2 mg of propranolol was given intravenously and slowly at a rate of 1 mg/min before induction, and then induction with oxytocin was performed as above.

On the second day, 2 mg intravenous propranolol was injected and the entire induction procedure was continued according to the oxytocin group. Blood pressure of patients every one hour and heart rate of the fetus was monitored every 15 minutes. Patients' status was followed up and the information was recorded.

Statistical Analyses:

The collected data were analyzed by SPSS software version 18. The mean and frequency and percentage are used to describe the data. Chi-square test (2 χ) was

used to compare the groups. Also, for quantitative data, independent t-test and Mann-Whitney test were used.

Findings:

According to the implementation method, as previously explained, the necessary interventions were performed in each group. The mean age of the patients was (23.79±4.2) years, the maximum age was 35 and the minimum age was 16 years.

The mean age was in the control group 24.44 ± 4.30 years and this was 23.31 ± 3.60 years for the case group. This difference in age was not significant in the two groups (P=0.105). The mean gestational age in control group and in case group was 38.34 ± 0.96 and 38.36±1.12 weeks, respectively. The difference between the mean gestational age in the two groups was not significant. (P=0.704).

In both groups, the duration of the latent phase, the active phase and the duration of the second stage of labor, from the time of fullness of the patient to the delivery, were examined and recorded. Initially, the duration of the latent phase was evaluated in the case group, with an average of 6.14 ± 4.81 hours. In the control group, the mean time was 7.41 ± 6.7 hours.

On the other hand, according to the Mann-Whitney test, the difference between the two groups was statistically significant. (P=0.0001). On the other hand, the average active phase and second stage of labor were examined in two groups and also compared with Mann-Whitney test, which was not statistically significant, (P =0.703) For the duration of the active phase and (P = 0.509) for the second stage. As is evident from these results, the use of intravenous propranolol in mothers has reduced the delivery time of the latent phase.

The birth weight of newborns was compared between the two groups, which in the case group was 2961.66±186.16 grams and 3036.6±329.9 in the control group, and this was not statistically significant. (P=0.322)

The two groups were compared in terms of the type of delivery, the reason of Caesarean section and Apgar score of 5 minutes. The results of this study showed that in the control group, 16 cases (32%) had cesarean delivery and in case of group 9 cases (18%) had cesarean delivery, although the delivery rate of cesarean was higher in the control group, but this difference was not statistically significant based on the Chi-squared test. (P=0.106)

Among the cases of cesarean section in the case group, there were 3 cases of arrest of dilatation, 4 cases did not respond to induction and 1 case of fetal distress. In the control group, 7 cases of cesarean section were discontinued, and 9 cases did not respond to induction.

According to the 5 minute Apgar score, the two groups were compared, in the case group 8.66 ± 0.71 and in the control group was 8.64 ± 0.52, which was not statistically significant. (P=0.874).

Discussion:

Several studies have been conducted on new methods for preventing cesarean delivery, due to decreased contractions of the uterus and due to increased complications of

cesarean delivery. In Nuli-par women, active labor management has reduced the duration of labor, but there is not enough evidence for a decrease in cesarean section (25-28).

This study was a double-blind clinical trial in Sayyad Shirazi Hospital in Gorgan. The number of subjects in each group was 50. According to the criteria for entry and exit, patients were randomly assigned to one of the groups in one of two groups. The mean age of the control group was (24.44 ± 4.30) years and this was 23.31 ± 3.60 years for the case group.

In our study, the effect of propranolol on the duration of delivery was studied. In this study, propranolol has been able to short the latent phase in the case group compared to the control group. (P = 0.0001). On the other hand, the mean active phase and the second stage of labor were examined in two groups, which was not statistically significant (P = 0.703) for the duration of the active phase and (P =0.509) for the second stage.

According to the results of our study in the study of Ziolkowski et al. (14) in Poland in 1994 (sample size 60) and Palomaki et al (15) in Finland in 2006 with a sample size of 107 such as our study, the duration of the latent phase of labor in The propranolol group was significantly less than the control group .in Kashanian et al. (10) in Iran in 2009 with a sample size of 150 pregnant women, The mean response time for induction to delivery and duration of labor in propranolol group was lower than the control group and In another study by Mitrani (16), the administration of propranolol in a labor-induced disorder accelerated the labor process, which is consistent with our findings. It seems that accelerating the labor process is due to the presence of beta-adrenergic receptors on myometers and their containment, which can increase uterine contractions (17, 10).

Propranolol, in the in-vitro environment, looses the smooth muscle of the uterus of the non-pregnant rat and contributes to the contraction of the smooth muscle of the pregnant rat, and in another study (18), propranolol has been opposed to the inhibitory effects of the contraction of rhythoderin. It seems that the level of beta 2 adrenergic receptor decreases in the duration of the labor relative to the non-pregnant uterus (19), and this may reflect the down-regulation of these receptors during labor and as a result of the onset of uterine contractions At this time (20, 21)

Propranolol, a beta-1 and beta-2 adrenoreceptor blocker, apparently does not appear to affect beta-3 clay found in myometer. And administration of propranolol in maternal horses has been significantly reduced at the time of exiting embryo membranes (22).

Based on the above studies, propranolol seems to be used to improve the course of labor. In a study (15) on 107 women who were arrested in the first stage of labor due to inadequate uterine contractions, propranolol was injected intravenously into one or two doses of 2 mg, followed by oxytocin, and in the other group, only oxytocin was given.

In this study, the prevalence of cesarean in propranolol group was not changed, but the duration of labor in this group was shorter, and on the other hand, it was not problematic for newborns. Therefore, the

researchers suggested that propranolol can be effective in stopping the course of labor as help. These results are consistent with the results of our study.

The two groups were compared in terms of the type of delivery, the reason of Caesarean section and Apgar score of 5 minutes. The results of this study showed that in the control group, 16 cases (32%) had cesarean delivery and in case of group 9 cases (18%) had cesarean delivery, although the delivery rate of cesarean was higher in the control group, but this difference was not statistically significant based on the Chi-squared test. (P = 0.106). In a randomized trial similar to the present study, in 1997 in Florida, with a sample size of 430 cases, it was found to be 50% lower in cesarean rate (29), but we failed to confirm this finding, and in the study Direkvand Moghadam et al. (12) In Iran in 2009 with a sample size of 146 pregnant women, the prevalence of cesarean section in the placebo group was higher than the propranolol group, which is not consistent with the results of our study.

One of the reasons is that the rate of baseline cesarean in hospitals varies in two studies; on the other hand, Palomaki et al. (15) in Finland in 2006 showed a significant difference in the type of delivery in women under study. Did not give The reason for this is the lack of clarity in the timing of the second dose of propranolol and the consideration of the parity of the patients studied, which certainly affects. However, all pregnant women we studied were Nulliparous, but the results were consistent with the other studies. Since propranolol has a half-life of 2-3 hours, it effects in 1 hour after injection (30). In studies that saw a decrease in cesarean rate in the case group, the frequency of injections of propranolol was more than once, and it seems that Repeated injection of propranolol may have a better effect on reducing cesarean section.

According to the 5 minute Apgar score, the two groups were compared, in the case group 8.66 ± 0.71 and in the control group was 8.64 ± 0.52, which was not statistically significant. (P =0.874).

In a study by Direkvand Moghadam et al. (12), the results of the study indicate that in the two groups, Apgar in the first and fifth minutes of the infant, are similar. In a study on 107 women who had an arrest of labor due to inadequate uterine contractions, propranolol was injected intravenously in one or two doses and then oxytocin was injected, and in the other group, only oxytocin was given. In this study, the neonates of the two experimental and control groups were similar in terms of the first and fifth minutes of the Apgar score and were not statistically significant, which is consistent with our study.

Sanchez et al. (23) In 1997, in Florida, in a study of women with insufficient contractions of the uterus in the first stage of labor, in the test group, with oxytocin infusion, 2mg propranolol was injected intravenously, and in the group Oxytocin with placebo, only oxytocin infused and They concluded that the neonates of the two groups were in the same condition in Apgar scores. There was no significant difference between the two groups in terms of Apgar scores and PH of the umbilical artery.

Conclusions:

In general, according to the studies and the present study, it seems that propranolol can

be used to help the course of labor. If labor is shortened based on indications in labor, our results indicate that propranolol is an appropriate drug for shortening labor time. It is suggested that a study with a higher sample size be considered. It is also suggested that possible complications in the case and control group should be considered, and a study should be designed to evaluate the effects of multiple doses of propranolol.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

References:

1- Cunningham FG. Leveno KJ. Bloom SL. Hauth JC. Gilstrap III. et al. Williams Obstetrics. 22 ed. MC Graw- Hill: New York: 2005. p. 536-537.

2- Mobasheri E, Jafarpour H, Rezaei A, Piraste Far Z, Bakhshi T. The Role Of Antibiotics Therapy On Maternal Complication In Women With Premature Rupture Of Membranes. 2017; 6(2): 53-58

3- Maslow AS. Sweeny AL. Elective induction of labor as a risk factor for cesarean delivery among low-risk women at term. Obstet Gyneocol 2000; 95: 917-922.

4- Smith KM. Hoffman MK. Sciscione A. Elective induction of labor in nulliparous women increases the risk of cesarean delivery. Obstet Gynecol 2003; 101: 455.

5- Hinshaw K, Simpson S, Cummings S, Hildreth A, Thornton J. A Andomized Controlled Trial Of Early Versus Delayed Oxytocin Augmentation To Treat Primary Dysfunctional Labour In Nulliparous Women. BJOG 2008; 115(10):1289-95.

6- American College of Obstetrics, Gynecology Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin Number 49, December 2003; Dystocia and Augmentation of Labor. Obstet Gynecol 2003; 102:1445- 54.

7- O'Driscoll K, Foley M, Macdonald D. Active Management of Labor as an Alternative to Cesarean Section for Dystocia. Obstet Gynecol 1984; 63:485-90.

8- Schuitemaker N, Van Roosmalen J, Dekker G, Van Dongen P, Van Geijn H, Gravenhorst JB. Maternal Mortality after Cesarean Section in the Netherlands. Acta Obstet Gynecol Scand 1997; 76:332 4.

9- Hemlin J. Moller B. Extraamniotic saline infusion is promising in preparing the cervix for induction of labor. Acta Obstet Gynecol Scand 1998; 77: 45-9.

10- Kashanian M, Zarin Z . Comparison of the effect of oxytocin alone and the administration of oxytocin-propranolol on the onset of labor - A randomized, double-blind study. Feyz Scientific-Research Quarterly. 10 (2): 7-11

11- Sharami S. H, et al. Effect of Oxytocin Plus Propranolol on The Success of Labor Augmentation. Journal of Guilan University of Medical Sciences, No: 82, Pages: 57-64

12- Ashraf Direkvand Moghadam et al., Comparison Effect of Oral Propranolol and Oxytocin Versus Oxytocin only on Induction of Labor, Journal of Clinical and Diagnostic Research. 2013 Nov, Vol-7(11): 2567-2569

13- Direkvand-Moghadam A, Jaafarpour M, Khani A, Taheri S, Delpisheh A. The

effect of oral propranolol plus oxytocin versus oxytocin only on the process and outcome of labor: A double-blind randomized trial. Iran J Nurs Midwifery Res. 2014 Sep;19(5):491-5.

14- Ziółkowski K. Induction of Labor in Prolonged Pregnancy with Propranolol as a Personal Evaluation. Pol Tyg Lek 1994; 49(8-9):184-5.

15- Palomäki O, Uotila J, Tammela O, Kaila T, Lavapuro M, Huhtala H, Tuimala R. A Double Blind, Randomized Trial on Augmentation of Labour with A Combination of Intravenous Propranolol and Oxytocin Versus Oxytocin Only. Eur J Obstet Gynecol Reprod Biol 2006; 125(1):44-9.

16- Mitrani A, Oettinger M, Abinader EG, Sharf M, Klein A. Use of Propranolol in Dysfunctional Labour. Br J Obstet Gynaecol 1975; 82(8):651-5.

17- Flier JS. Underhill LH. Adrenergic Receptors- Evolving Concepts and Clinical Implications. N Engl J Med 1996; 334: 580.

18- Dennedy MC. Houlihan DD. Mc Millan H. Morrison JJ. Beta 2-and beta3-adrenoreceptor agonists: human Myometrial selectivity and effects on umbilical artery tone. Am J Obstet Gynecol 2002; 187: 641-647.

19- Chanrachakul B. Matharoo-Ball B. Turner A. Robinson G. Broughton-Pipkin F. Arulkumaran S. et al. Reduced expression of immunoreactive beta2-adrenergic receptor protein in human myometrium with labor. J Clin Endocrinol Metab 2003; 88: 4997-5001.

20- Bardou M. Loustalot C. Cortijo J. Simon B. Naline E. Dumas M. Et al. Functional, biochemical and molecular biological evidence for a possible beta (3)-adrenoceptor in human near-term myometrium. Br J Pharmacol 2000; 130: 1960-1966.

21- Rouget C. Bardou M. Breuiller-Fouche M. Loustalot C. Qi H. Naline E. Et al. Beta 3-adrenoceptor is the predominant beta-adrenoceptor subtype in human myometrium and its expression is up-regulated in pregnancy. J Clin Endocrinol Metab 2005; 90: 1644-1650.

22- Ingarden J. Dubiel A. Rauluszkiewicz S. The effect of administration of a beta blocker in periparturient mares. Equine Vet J Suppl 1998; 27: 19-20.

23- Pergialiotis V, Frountzas M, Prodromidou A, Prapa S, Perrea DN, Vlachos GD. Propranolol and oxytocin versus oxytocin alone for induction and augmentation of labor: a meta-analysis of randomized trials. Arch Gynecol Obstet. 2016 Apr;293(4):721-9.

24- Outi Paloma¨ki , Jukka Uotila , Outi Tammela , Timo Kaila, Merja Lavapuro , Heini Huhtala , Risto Tuimala. A double blind, randomized trial on augmentation of labour with a combination of intravenous propranolol and oxytocin versus oxytocin only. European Journal of Obstetrics & Gynecology and Reproductive Biology 125 (2006) 44–49.

25- American College of Obstetrics, Gynecology Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin number 49, December 2003: dystocia and augmentation of labor. Obstet Gynecol 2003;102:1445–54.

26- Ha¨ger RM, Daltveit AK, Hofoss D, Nilsen ST, Kolaas T, Oian P, et al.

Complications of Cesarean deliveries: rates and risk factors. Am J Obstet Gynecol 2004;190:428–34.
27- Jackson N, Paterson-Brown S. Physical sequelae of caesarean section. Best Pract Res Clin Obstet Gynaecol 2001;15:49–61.
28- Schuitemaker N, van Roosmalen J, Dekker G, van Dongen P, van Geijn H, Gravenhorst JB. Maternal mortality after Cesarean section in the Netherlands. Acta Obstet Gynecol Scand 1997;76:332–4.
29- Sanchez-Ramos L, Quillen MJ, Kaunitz AM. Randomized trial of oxytocin alone and with propranolol in the management of dysfunctional labor. Obstet Gynecol 1996;88:517–20.
30- Katzung BG. Clinical Pharmacology. Philadelphia; Appletone, 1998.

Tables and Charts:

Figure.1: Comparison of latent phase duration in case and control groups

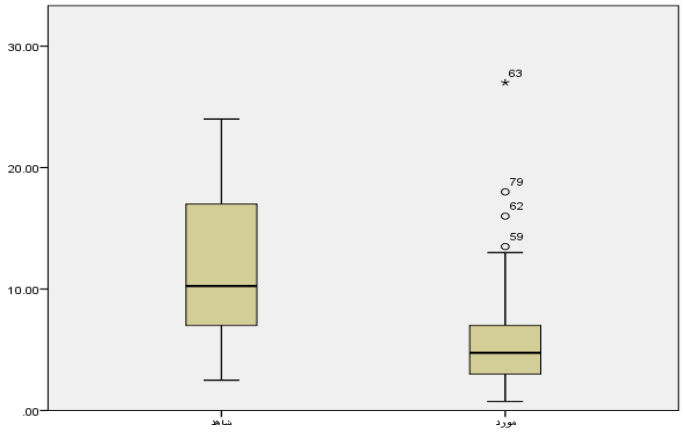

Figure.2: Comparison of active phase duration in case and control groups

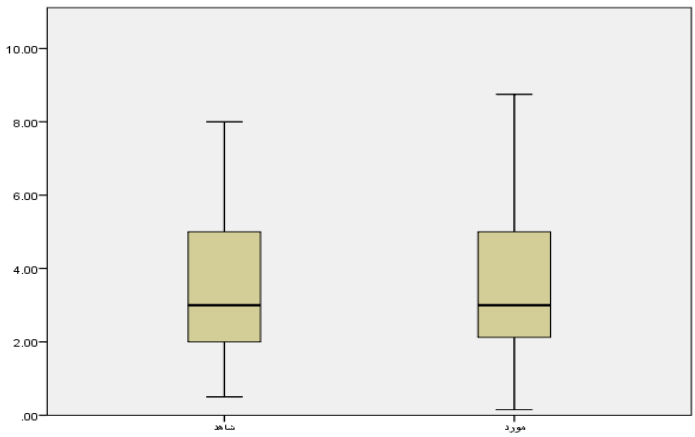

Figure.3: Second stage of labor in case and control group

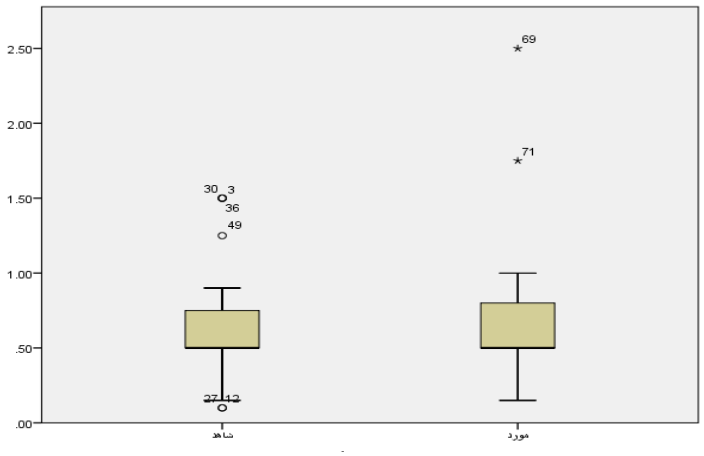

Figure.4: Type of delivery in case and control group.