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PERIOPERATIVE LOW-DOSE KETAMINE DIMINISHES POST-OPERATIVE CAESAREAN PAIN, NAUSEA & VOMITING AFTER SPINAL ANAESTHESIA

PERİOPERATİF DÜŞÜK-DOZ KETAMİN SPİNAL ANESTEZİ UYGULANAN GEBELERDE POSTOPERATİF SEZERYAN AĞRISINI, BULANTI VE KUSMA SIKLIĞINI AZALTIR MI?

İpek Saadet EDİPOĞLU*, Fatma Sevinç ÇELİK*, Derya Özden OMAYGENÇ,**

ABSTRACT

Objective: Despite various developments in the treatment of post-operative caesarean pain, there are still difficulties in satisfying patients due to individual differences. Ketamine is used as a potent anaesthetic and an effective analgesic since 1960's. The purpose of our study is to observe the effects of low-dose ketamine applied following spinal anaesthesia for postoperative analgesia and nausea & vomiting in pregnant patients.

Materıal and Method: We examined the Visual Analogue Scales values of 120 patients at the 1^{st}, 2^{nd}, 4^{th}, 12^{th}, 24^{th}, and 48^{th} hours and evaluated nausea & vomiting. We also recorded the first additional analgesic demands and ketamine associated adverse events.

Results: We detected significant differences between the visual analogue scale values of ketamine and control group in the 2^{nd}, 4^{th} and 12^{th} hours. Significant differences were also seen in the first analgesic demand periods. We found a significant decrease in nausea and vomiting and insignificant elevation of psychodysleptic findings in ketamine group.

Conclusion: We believe that low-dose ketamine can be effectively used to sustain analgesia in pregnant patients who received spinal anaesthesia. We further believe that the effect of ketamine in decreasing nausea and vomiting, in exchange of low levels of neuropsychiatric symptoms, is a remarkable subject.

Keywords: Ketamine; VAS; analgesia.

ÖZET

Amaç: Postoperatif ağrı sezaryen operasyonlarını takiben karşımıza çıkan en büyük sorunlardan birisi olmaya devam etmektedir. Akut ağrı tedavisindeki gelişmelere rağmen kişisel farklılıklar nedeniyle hastaları yeterince memnun etmek her zaman mümkün olamamaktadır. Ketamin 1960 yıllardan beri güçlü bir anestetik ve etkin bir analjezik olarak kullanılmaktadır. Bu çalışmada amacımız, sezaryen operasyonu için, spinal anestezi yapılmış gebelerde, uygulanan düşük doz ketaminin, postoperatif ağrı, bulantı ve kusma üzerine etkilerini incelemektir.

Gereç ve Yöntem: Çalışmaya, 120 hasta retrospektif olarak dahil edildi. Hastaların ağrı durumlarını değerlendirmek için Vizüel Analog Skala değerlerini 1., 2., 3., 4., 12., 24. ve 48. saatlerde inceledik. Bununla birlikte, postoperatif dönemdeki bulantı & kusma, ilk analjezik talep sürelerini ve ketamine bağlı oluşabilecek yan etkileri de kayıt altına aldık.

Bulgular: Vizüel Analog Skala değerlerinde 2., 4., ve 12. saatlerde ketamin grubunda anlamlı azalmalar olduğunu tespit ettik. Bu anlamlılığın 30. dakikada 1., 24. ve 48. saatlerde olmadığını gözlemledik. Hastaların postoperatif ilk analjezik talep sürelerinde ve bulantı & kusma oranlarında ketamin grubunda kontrol grubuna göre anlamlı azalma olduğunu saptadık. Psikodisleptik bulgularda ise ketamin grubunda anlamlı olmayan bir artış gördük**.**

Sonuç: Bu sonuçlar ışığında, düşük doz ketaminin, sezaryen operasyonlarında, spinal anestezi yapılan gebelerde, mevcut ağrı tedavilerini desteklemek için, etkin bir ilaç olduğunu düşünüyoruz. Aynı zamanda ketaminin postoperatif bulantı ve kusma oranlarında azalma sağlamasının da, önemli bir konu olduğu kanaatindeyiz**.**

Anahtar kelimeler: Ketamin; VAS; analjezi.

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* Süleymaniye Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Anesteziyoloji Bölümü,
** Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Anesteziyoloji Bölümü, İstanbul, Türkiye
(Corresponding author/İletişim kurulacak yazar: dripeks@yahoo.com)

INTRODUCTION

The treatment of acute pain in pregnant patients is of significant importance in the modern medical practice. Furthermore, individuals may have differences in post-op pain due to various factors such as age, genetics, physiologic factors and pain sensitivity (1-3). Despite various developments in the treatment of post-caesarean section pain, there are still difficulties in satisfying patients and relieving pain due to individual differences (1,4). A survey of 2014 reports that 86% of patients had post-operative pain and 75% of patients had medium/severe pain in the early post-op period (5). Also, nausea and vomiting may limit effective post-op pain management for all patients (6). For this purpose, studies on the control of post-operative acute pain continue to provide a solution with different analgesic drugs with fewer side effects (7-9).

Ketamine is one of the important drugs that are effectively used in multimodal analgesia during caesarean section operations and that is subject of the studies (7,10,11). Ketamine usually shows its pharmacologic effects via NMDA (N-Methyl-D-Aspartate) antagonism (12,13). It is also effective via mechanisms other than glutamate. Ketamine is used as an effective anaesthetic drug with potent efficacy since its first discovery in 1960's (12). Opioid-sparing effects of ketamine may be useful for achieving better analgesia with less PONV (6).

The purpose of our study is to retrospectively study the effects of low-dose ketamine applied after the baby is removed on post-op analgesia in pregnant patients following spinal anaesthesia. Our secondary aim is to evaluate ketamine's effects on postoperative nausea and vomiting.

MATERIAL AND METHOD

We studied retrospectively the files of pregnant patients that received spinal anaesthesia in our hospital in the last six months. We gathered data by examining all the patients' files and post-spinal follow-up forms between January-2015 and July-2015 (ethics committee approval: 2015-128, date: 25/06/2015). Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's committee.

We included the patients of ages between 18-40 who preferred spinal anaesthesia and whose files and post-op forms are filled in full and complete manner. The patients who have BMI>40, history of migraine, chronic pain, psychiatric disturbance or who suffered from neurologic disorder were excluded from our study. We accepted the files of patients whose spinal anaesthesia were performed in single entry.

We applied routine spinal anaesthesia between L3-L4 with 26 G spinal needle in our hospital. All patients received hyperbaric bupivacaine 0.5% (12 mg) intrathecal together with 20 µg fentanyl. In case of hypotension, ephedrine and 500 ml crystalloid were applied..

The patients were divided into two groups from their files (ketamine group and control group). The first group consisted of patients that received 0.15 mg/kg intravenous ketamine infusion within 10 minutes after the baby is removed. The second group consisted of patients who did not receive ketamine. We administered 0.03 mg/kg of midazolam and 50 µg fentanyl for control group. It is our routine sedation for caesarean section operation after the baby is removed. Operation time and period between the time of spinal and skin incision were taken from patient files. In the postoperative period, all patients received intramuscular diclofenac and intravenous tramadol for postoperative analgesia in our hospital. Any additional analgesic demands for 'breakthrough pain' was treated with supplementary tramadol doses for both groups. Also, patients who had PONV were treated with ondansetron. During the postoperative visits patients were asked if they had headache or symptoms like diplopia and/or hallucination.

We reviewed the VAS (Visual Analogue Scales) values of the patients on these forms at the 30^{th} minute, 1^{st}, 2^{nd}, 4^{th}, 12^{th}, 24^{th}, and 48^{th} hour. We recorded VAS values, first analgesic demands and postoperative complications of the patients. VAS is a scale for patients to describe the level of their pain. The values vary between 0-10. 0 represents no pain and 10 represents the most severe pain. PONV was described as sustained nausea with requirement of antiemetic and/or vomiting.

Statistical Analysis

We used the SPSS.20 (SPSS Version 20.0, SPSS Inc., Chicago, IL. USA) programme for statistical analysis. In addition to using descriptive statistics methods (average, standard deviation, median, frequency) for examining the study data, we also used student-t test in comparing the parameters showing normal distribution for the comparison of quantitative data. Mann Whitney-U test is used in comparing the parameters not showing normal distribution in the two groups. Significance is valued at $p<0.05$.

RESULTS

120 patients were included in the study. After applying the shortfall and exclusion criteria on files, we studied the remaining patient files, 60 of which constituted the 'ketamine group' and 60 constituted the 'control group'. We did not detect any differences in the demographic data of the two groups including age, BMI, gestation period, the period between the time of spinal anaesthesia and skin incision, and the duration of operation. There was no statistically significant difference in the demographic data of the two groups ($p<0.05$) (Table 1).

Table 2 shows the analgesic data of the patients. Accordingly, we determined significant differences between the ketamine group and the control group in the first analgesic demand period ($p=0.003$). We further determined statistically significant differences between the two groups based on their post-operative VAS values at the 2^{nd}, 4^{th} and 12^{th} hours ($p<0.0001$). There was no significant difference between the ketamine

group and the control group at the 30th minute, 1st, 24th, and 48th hour (p>0.05).

We observed as post-op complications, nausea and vomiting (PONV) in 2 patients in the ketamine group (3.3%) and 11 patients in the control group (18.3%). Nausea and vomiting were of statistically significant importance between the two groups (p=0.015). We further realized psychodysleptic findings due to the use of ketamine in 5 patients in the ketamine group (p=0.023) (Table 3). Among these findings, 3 patients were diagnosed with hallucination and 2 patients were diagnosed with diplopia. 1 patient had headaches in the control group. We did not observe any other major complications.

Table 1: Demographic Data

	Group 1 Ketamine (n: 60) (mean ± SD)	Group 2 Control (n: 60) (mean ± SD)	p-value
Age	28.68±5.82	28.43±4.82	0.935
BMI	33.54±4.61	33.85±4.94	0.843
Gestation (weeks)	38.40±1.29	38.02±1.67	0.163
Operation period (minutes)	27.30±7.36	27.93±5.34	0.118
Period between the time of spinal and skin incision (seconds)	30.17±12.17	30.48±9.47	0.329

p<0.05 values were considered significant. BMI: body mass index. n: number of patients. SD: standard deviation*

Table 2: First analgesic demand period and VAS values

	Group 1 Ketamine (n : 60) (mean ± SD)	Group 2 Control (n: 60) (mean ± SD)	p-value
30th minute	0.2±0.57	0.05±0.22	0.105
1st hour	2.62±1.39	2.88±1.27	0.242
2nd hour	4.92±1.82	6.32±2.20	0.0001*
4th hour	4.17±2.22	6.88 ±1.94	0.0001*
12th hour	3.07±1.70	4.93±1.96	0.0001*
24th hour	2.20±1.28	2.45±1.24	0.131
48th hour	1.33±1.10	1.15±1.24	0.214
First analgesic demand (minutes)	181.00±80.03	140.06±62.16	0.003*

p<0.05 values were considered significant. VAS: Visual Analogue Scales. n: number of patients. SD: standard deviation*

Table 3: Complications

	Group 1 Ketamine (n: 60) (mean ± SD)	Group 2 Control (n: 60) (mean ± SD)	p-value
Nausea and Vomiting	2 (3.3%)	11 (18.33%)	0.015*
Psycodisleptic side effects (Diplopia + Hallucination)	5 (8.3%)	0	0.023*
Headache	0	2 (3.33%)	0.156

p<0.05 values were considered significant. n: number of patients. SD: standard deviation*

DISCUSSION

As a result of our study, we found that the use of low-dose ketamine at the 2nd, 4th, and 12th hours after the baby is removed significantly decreases the VAS values of the patients that received spinal anaesthesia. We also noted that such use of ketamine significantly prolongs the period of first analgesic demand. Concerning complications, we noted that postoperative nausea and vomiting (PONV) are significantly low in the ketamine group. On the other hand, the findings of diplopia and hallucination experienced in the ketamine group did not appear in the control group at all.

When the VAS values are reviewed, Menikiti et al. had conclusions similar to our findings in their randomized controlled study on 60 patients (11). In their study, the decrease in the VAS values statistically starts from the first hour. On the other hand, we did not detect in our study, statistically significant changes at the 30th minute and 1st hour during which spinal anaesthesia sustained its effect. Although the control group had higher VAS values in the 1st hour, it did not reach significance level and we think that the spinal anaesthesia that continued to be effective in some patients caused this result. Similarly, in both studies, the VAS values at the 2nd hour were noted to be significant (11). Furthermore, similar to our findings, Sen et al. found in their study, including 90 pregnant patients, that compares 0.15 mg/kg intravenous ketamine, with intrathecal fentanyl, and the control group, that the first analgesic demand period is shorter and post-op pain scores are lower for ketamine group (10). The literature indicates studies of obstetric surgery that supports the use of ketamine (14,15). Han et al. (14) applying 0.5 mg /kg dose of ketamine reported a significant decrease in the 2nd hour and Behaveen (15) applying 0.5 mg/kg subcutaneous dose before and after the operation caused significant decrease in the VAS values in the 2nd, 4th, 6th and 12th hours.

On the contrary, there are also reports against the effectiveness of ketamine. Bilgen et al. in their studies involving 140 pregnant patients who received general anaesthesia and 0.25 mg/kg, 0.5 mg/kg and 1 mg/kg iv. doses of ketamine concluded that the morphine consumption is not significantly affected (7). However, we believe, the outcomes of the two studies are different as different anaesthesia techniques were used in the two studies. Dahl et al. failed to prove opioid sparing effect of single dose of 0.4 mg/kg ketamine in their study concerning the patients of abdominal hysterectomy (16). Bauchat et al., too, failed to prove the effects of intravenous use of 10 mg. ketamine post-delivery during the post-op period (17). There are further other studies that fail to prove the analgesic effects of ketamine in gynaecologic operations (18,19).

Heesen et al. reported in their meta-analysis involving 953 pregnant patients that received general anaesthesia and spinal anaesthesia that ketamine administration improves post-op analgesia (20). They also observed that it prolongs the period of the first analgesic demand and decreases pain in the second hour (20). These results are in accordance with our findings. However, in addition to these findings, we also detected very significant decrease in the pain scores at the 4th and 12th hours. As it is known, ketamine oxidases via microsomal enzyme system (N-demetilation) and it metabolizes into 80% of nor-ketamine. 5% of ketamine also reduces to of hydroxy-ketamine and there are three other metabolites of less importance. Nor-ketamine is another active metabolite that hydroxylases into 6-hydroxy nor-ketamine (21). Nor-ketamine is an analgesic molecule that is as effective as 20-30% of ketamine (22). Although its pharmacokinetics is not well-known, the analysis of plasma concentration subsequent to the application of single shot ketamine shows a slow pace of elimination. Nor-ketamine continues to exist longer than 5 hours after the application (12,22). This fact may explain the continued significantly low scores of pains at the 4th and 12th hours in our study.

Ketamine affects nervous system and creates local anaesthetic effects. The primary mechanism of its analgesic and anaesthetic effects on the central nervous system and spinal cord receptors resembles NMDA receptor antagonism (23). We believe that ketamine takes an effective role in analgesia by this way. In our opinion, ketamine will have an important place in multimodal analgesia to be applied post-caesarean.

When we analysed postoperative complications, we determined that the use of ketamine significantly reduces PONV. Yet, we also observed increased psycodisleptic symptoms such as diplopia and hallucination in the ketamine group. Our findings are in line with Laskowski's findings in his recent compilation of post-op analgesic studies (24). They also mentioned that ketamine reduces the use of opioid and decreases PONV and reported increased levels of neuropsychiatric findings. Since we routinely inform our patients before applying ketamine about its potential side effects in our hospital, the patients usually tolerate psychodisleptic symptoms well, such as diplopia and hallucination. Kose et al. observed, although in insignificant levels, increased neuropsychiatric findings and less PONV after spinal anaesthesia (25). A study also indicates that, although insignificant, less number of nausea incidents occur in patients who receive ketamine (26). Furthermore, in that study, both groups suffered from the undesired effects of morphine and irritating physiologic events in similar levels (27). A Cochrane database review evaluating the postop analgesic effectiveness of ketamine, reported that perioperative ketamine reduces postop opioid requirements and reduces PONV (6). There are also studies that do not report significant differences in the ketamine and the control groups in terms of side-effects (10,15,27).

Shabana et al. explained their diminished incidence of PONV in their study with reduced incidence of hypotensive episodes that ketamine provides by its sympathomimetic and vagolytic effects (28). Candrakartan suggested that the reason that ketamine decreases PONV incidence can be its opioid sparing effect in his recent review for multimodal therapies for PONV (29). We think that both mechanisms played a role for our patients. The limitation of our study is that it is a retrospective study. It may have a bias due to the

nature of its methodology and it relies on the trustworthiness of the data collectors.

CONCLUSION

In conclusion, based on the data obtained in our study, we believe that low-dose ketamine can be effectively used to sustain analgesia in pregnant patients that received spinal anaesthesia. We further believe that the effect of ketamine in decreasing nausea and vomiting, in exchange of low levels of neuropsychiatric symptoms, is a remarkable subject.

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Author Contributions:

Study concept and design: Edipoglu and Celik. Analysis and interpretation of data: Edipoglu, Celik and Omaygenc. Drafting of the manuscript: Edipoglu. Critical revision of the manuscript for important intellectual content: Edipoglu, Celik and Omaygenc. Statistical analysis: Omaygenc.

REFERENCES

1. Pan PH. Post cesarean delivery pain management: multimodal approach. Editorial. Int J Obstet Anesth 2006; 15:185–8.
2. Turk D C, Okifuji A. Assessment of patients' reporting of pain: An integrated perspective. Lancet 1999; 352:1784–8.
3. Pan PH, Coghill R, Houle TT, Seid MH, Lindel WM, Parker RL, Washburn SA, Harris L, Eisenach JC. Multifactorial preoperative predictors for post caesarean section pain and analgesic requirement. Anesthesiology 2006; 104: 417–25.
4. Dolin S T, Cashman J N, Bland J M. Effectiveness of acute postoperative pain management: I. Evidence from published data. Br J Anaesth 2002; 89: 409–23.
5. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014; 30:149-160.
6. Bell RF, Dahl JB, Moore RA, Kalso EA. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;1:CD004603. doi: 10.1002/14651858.
7. Bilgen S, Köner O, Türe M. Effect of three different doses of ketamine prior to general anaesthesia on postoperative pain following caesarean delivery: a prospective randomized study. Minerva Anestesiol 2012; 78:442-9.
8. Lavand'homme P. Chronic pain after vaginal and caesarean delivery: a reality questioning our daily practice of obstetric anaesthesia. Int J Obstet Anesth 2010; 19:1-2.
9. Minoshima R, Kosugi S, Nishimura D, Ihara N, Seki H, Yamada T, Watanabe K, et all. Intra- and postoperative low-dose ketamine for adolescent idiopathic scoliosis surgery: A randomized controlled trial. Acta Anaesthesiol Scand. 2015; 59(10):1260-8. doi: 10.1111/aas.12571.
10. Sen S, Ozmert G, Aydin ON, Baran N, Caliskan E. The persisting analgesic effect of low-dose intravenous ketamine after spinal anaesthesia for caesarean section. Eur J Anaesthesiol. 2005; 22:518–23.
11. Menkiti ID, Desalu I, Kushimo OT. Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients. Int J Obstet Anesth 2012; 21:217–21.
12. Mion G, Villevieille T. Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). CNS Neurosci Ther 2013; 19:370–80.
13. Kohrs R, Durieux ME. Ketamine: Teaching an old drug new tricks. Anesth Analg 1998; 87:1186–93.
14. Han SY, Jin HC, Yang WD, Lee JH, Cho SH, Chae WS, Lee JS, Kim YI. The effect of low-dose ketamine on post-caesarean delivery analgesia after spinal anesthesia. Korean J Pain. 2013; 26: 270–6.
15. Behaeen K, Soltanzadeh M, Nesioonpour S, Ebadi A, Olapour A, Aslani SMM. Analgesic effect of low dose subcutaneous ketamine administration before and after cesarean section. Iran Red Crescent Med J. 2014; 16(3):15506. doi: 10.5812/ircmj.15506.
16. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. Does ketamine have preemptive effects in women undergoing abdominal hyster-ectomy procedures? Anesth Analg. 2000; 90: 1419–22.
17. Bauchat JR, Higgins N, Wojciechowski KG, McCarthy RJ, Toledo P, Wong CA. Low-dose ketamine with multimodal postcesarean delivery analgesia: A randomized controlled trial. Int J Obstet Anesth.2011; 20: 3–9.
18. Aubrun F, Gaillat C, Rosenthal D, Dupuis M, Mottet P, Marchetti F, Coriat P, Riou B. Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. Eur J Anaesthesiol. 2008; 25: 97–105.
19. Karaman S, Kocabaş S, Zincircioğlu C, Firat V. Has ketamine preemptive analgesic effect in patients undergoing abdominal hysterectomy? Agri. 2006 Jul; 18: 36-44.
20. Heesen M, Böhmer J, Brinck EC, Kontinen VK, Klöhr S, Rossaint R, Straube S. Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. Acta Anaesthesiol Scand 2015; 59: 414–26.
21. Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A, Kharasch E, Sarton E. Effect of Rifampicin on S-ketamine and S-norketamine Plasma Concentrations in Healthy Volunteers after Intravenous S-ketamine Administration. Anesthesiology 2011; 114: 1435-45.
22. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after IV, nasal and rectal administration in children. Br J Anaesth 1996;77: 203–7.
23. Pai A, Heining M. Ketamine. Contin Educ Anaesthesia, Crit Care Pain. 2007; 7: 59–63.

24. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anesth. 2011; 58: 911–23.
25. Kose EA, Honca M, Dal D, Akinci SB, Aypar U. Prophylactic ketamine to prevent shivering in parturients undergoing Cesarean delivery during spinal anesthesia. J Clin Anesth 2013; 25:275–80.
26. Remérand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, Laffon M, Fusciardi J. The early and delayed analgesic effects of ketamine after total hip arthroplasty: A prospective, randomized, controlled, double-blind study. Anesth Analg. 2009; 109: 1963–71.
27. Kwok RFK, Lim J, Chan MT V, Gin T, Chiu WKY. Preoperative ketamine improves postoperative analgesia after gynaecologic laparoscopic surgery. Anesth Analg. 2004; 98: 1044–49.
28. Shabana AM, Nasr ES, Moawad HE. Effect of ketamine on intraoperative nausea and vomiting during elective caesarean section under spinal anaesthesia: A placebo-controlled prospective randomized double blinded study. Egypt J Anaesth 2012;28:169–74.
29. Chandrakantan A, Glass PSA. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth 2011;107(1): 27–40.