Comparison of the Post-Caesarean Analgesic Effect of Adding Dexmedetomidine to Paracetamol and Ketorolac: A Randomized Clinical Trial

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Abstract

Background: Paracetamol and non-steroidal anti-inflammatory drugs (e.g. ketorolac) can be considered for mild to moderate post-caesarean pain. As a selective α-2 agonist adrenergic receptor, dexmedetomidine has analgesic and sedative effects without causing respiratory depression.

Objectives: This study aimed to evaluate the effects of adding dexmedetomidine to paracetamol or ketorolac on post-caesarean pain and the associated complications thereof.

Methods: Sixty pregnant women, who were candidates for caesarean section with spinal anesthesia, were randomly assigned to either of two groups of 30 patients. For post-operative pain management, an intravenous patient-controlled analgesia (PCA) device was used for 24 hours. Dexmedetomidine (3 µg kg⁻¹) was added to paracetamol (35 mg kg⁻¹) in the group DP and to ketorolac (1 mg kg⁻¹) in the group DK. Visual analog scale (VAS), Ramsay sedation scale, hemodynamic changes, rescue analgesic (meperidine) consumption, patient satisfaction, and possible complications were recorded at 6, 12, and 24, hours after surgery, and compared afterward.

Results: The pain score was significantly lower in the DK group than in the DP group (P < 0.05). The hemodynamics and sedation scale were similar in both groups. The total meperidine consumption was higher in the DP group, but it was not significantly different. Maternal satisfaction was greater in the DK group (P < 0.05). Concerning complications, the two groups did not show statistically significant differences (P = 0.4).

Conclusions: The addition of dexmedetomidine to ketorolac, compared with its addition to paracetamol, causes further reduction in the post-operative pain score and provides more satisfaction.

Keywords: Analgesia, Caesarean Section, Dexmedetomidine, Ketorolac, Paracetamol

1. Background

Post-operative pain management is of prime importance and can be performed through various methods (1). A wide range of medications including opioids, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentin, pregabalin, tramadol, ketamine, and so forth, have been used alone or in combination to achieve this purpose (2-4). Beside systemic drugs, other anesthesia techniques including neuraxial techniques, transverse abdominis plane (TAP) block, wound injection, and intraperitoneal instillation have already been used for pain management after obstetric and gynecologic surgery (5-9). Paracetamol has limited effects to preclude and control post-caesarean pain (10). Ketorolac has been used to control post-operative pain, and its pharmacokinetics were reported safe for caesarean section (11, 12). Compared to opioids, non-narcotic analgesics such as paracetamol and ketorolac have less respiratory and awareness complications for newborn infants, but higher amounts of them are needed to produce adequate analgesia, if administered alone, which can cause adverse effects in the newborn. However, the use of multi-modal analgesia not only does give rise to sufficient pain relief after caesarean section, but also decreases the amount of the analgesic drug doses.
required for postoperative pain relief and their side effects (13). Dexmedetomidine is a selective central α2-adrenergic receptor agonist that has analgesic, sedative, and anxiolytic properties, and does not cause respiratory depression (14).

2. Objectives

This study aimed to evaluate the impact of adding dexmedetomidine to paracetamol and ketorolac in the i.v. PCA device on post-caesarean pain.

3. Methods

After receiving the institutional Ethics Committee’s approval (Ref: IR.IUMS.REC.1395.27278) and obtaining informed written consent, 60 parturient patients candidates for undergoing caesarean section in a university hospital were assigned in a randomized double-blind clinical trial. The sample size was estimated by:

\[
 n = \left( \frac{Z_{1-\frac{d}{2}} + Z_{1-\beta}}{\sigma_1^2 + \sigma_2^2} \right)^2 (\mu_1 - \mu_2)^2 
\]

\( (d = \mu_1 - \mu_2 = 1.2), P = 90, \alpha = 0.05 \)

Parturients undergoing elective caesarean delivery under spinal anesthesia were recruited between January and June 2016 by double-blinded block randomization.

The study was registered in an international database (Ref: IRCT201601147984N24). The inclusion criteria comprised full-term pregnancy, the age of 18 - 38 years, ASA physical status I - II, elective caesarean delivery, primary or repeat caesarean section, Pfannenstiel incision, and being under spinal anesthesia. The exclusion criteria consisted of drug abuse, bleeding disorders, severe mental disorders, history of allergy to study drugs, gastrointestinal disease, obesity (BMI above 35), conversion to another method of anesthesia, pre-eclampsia and complications during the surgery.

Spinal anesthesia was established using hyperbaric bupivacaine (2.5 mL bupivacaine 0.5%, AstraZeneca, France). On arrival to the recovery room, parturients were randomly allocated to one of the two groups using a random number table. Participants and anesthesiologist performing pain assessments were blinded to group allocation. For post-operative pain management, an i.v. patient-controlled analgesia (PCA) device (Autofuser, ACE Medical Co., South Korea) was used for all patients in both groups. In the DP group, 3 μg kg\(^{-1}\) of dexmedetomidine (Precedex, Hospira Inc., USA) was added to 35 mg kg\(^{-1}\) of paracetamol (Apetel, Cobel Darou, Iran) up to 2 g, and in the DK group the same dose of dexmedetomidine was added to 1 mg kg\(^{-1}\) of ketorolac (Ketorolac, Exir, Iran). The PCA device was set to deliver a continuous infusion rate of 4 mL hr\(^{-1}\).

Patient assessment was done by a physician not aware of the PCA drugs at rest, 6th, 12th, and 24th hour after surgery. Pain score was obtained using a visual analog scale (VAS), (0 = no pain and 100 = worst pain imaginable). Ramsay sedation score (0 - restless, 1 - tranquil, 2 - sleepy, 3 - confused but responsive to verbal commands, 4 - unresponsive to verbal commands, and 5 - no response to painful stimuli), hemodynamic changes (blood pressure and heart rate), complications, patient’s characteristics, and satisfaction rate (exceeded expectation, matched expectation, and less expectation) were recorded.

When the pain score was greater than 30, meperidine (25 mg) was i.v. administered. Complications such as blood pressure and heart rate changes, nausea, vomiting, respiratory depression, bleeding, and dizziness were evaluated and treated, if identified.

The data collected were analyzed using the SPSS version 18 software. Employing the Kolmogorov-Smirnov test, the data were evaluated for normal distribution and accordingly, the Wilcoxon test was used for non-normal distribution data, t-test for normal distribution data, and the Fisher’s Exact test for variables with absolute values like the presence of special symptoms. Differences between the two groups were analyzed applying the Mann-Whitney test; the Wilcoxon test was used for intra-group analysis statistical comparisons with a Bonferroni correction. The Friedman test was employed to analyze the differences between pain assessment hours in the two groups. The qualitative data analysis was performed using the Chi-Square test and P values of < 0.05 were considered significant.

4. Results

Patient characteristic data, pain score, and analgesic consumption are given in Table 1. Pain scores at various times were meaningfully lower in the DK group than in the DP group. Although in the DP group, the rescue meperidine administration dose was higher during the first 24 hours, it did not lead to a significant difference between the two groups.

The Ramsay sedation score was 1 in both groups at 6, 12, and 24 hours during the post-operative period, with no difference between the two groups. The satisfaction rate was higher in the DK group than that in the DP group, which showed a statistically significant difference (Table 2).

With regard to complications, one from each group had dizziness and one patient in the DP group suffered nausea. Complications like vomiting, pruritus, sedation,
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Prostaglandins in the central nervous system (17). It may be risky for both mother and newborn (21). In our study, the addition of dexmedetomidine to lower doses of paracetamol (2 g) not only did cause analgesia, but also reduced the incidence of complications.

Studies have demonstrated that the analgesic effect caused by ketorolac is similar to that of opioids, but it has fewer side effects and has also a ceiling analgesic effect, and often does not provide adequate analgesia when administered alone. In previous studies, by adding vitamin B complex, the effective dose of ketorolac was reduced by half to lower the chance of side effects (22). Gastrointestinal bleeding and acute renal failure are of the most prominent side effects of ketorolac. In the present study, adding dexmedetomidine to ketorolac not only reduced the dose of ketorolac and the associated complications, but also provided effective analgesia for pain management after caesarean section.

Ready and colleagues demonstrated that postoperative continuous infusion of ketorolac, compared to intermittent administration, decreases morphine consumption (23). Various studies indicate that the administration of ketorolac during lactation, compared to opioid, brings about no recognized side effect on the newborn owing to its inconsiderable amount of secretion in breast milk. High-dose administration of paracetamol can be risky for both mother and newborn (21). In our study, the addition of dexmedetomidine to lower doses of paracetamol (2 g) not only did cause analgesia, but also reduced the incidence of complications.

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In another study conducted by Liew and colleagues, following the single administration of the highest dose of paracetamol (4 g) to manage post-caesarean pain, approximately 5% of the medication was secreted into the breast milk. High-dose administration of paracetamol can be risky for both mother and newborn (21). In our study, the addition of dexmedetomidine to lower doses of paracetamol (2 g) not only did cause analgesia, but also reduced the incidence of complications.

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reducing central sympathetic tone.

In some studies, adding dexmedetomidine as an adjuvant to opioids or local anesthetics led to prolonged intraoperative analgesia, more postoperative pain relief, less nausea and vomiting, and fewer hemodynamic changes (26-28). In a study of pain management after caesarean section, adding dexmedetomidine to sufentanil decreased opioid consumption and increased patient satisfaction (29). In the present study, dexmedetomidine was added to non-opioid analgesics (paracetamol and ketorolac) to avoid opioid infusion and the side effects thereof on both mother and newborn. In patients who are resistant to the effects of opioids, the addition of dexmedetomidine can be useful in controlling the pain (30). Bradycardia and hypotension may occur with dexmedetomidine, thus much care should be taken in setting its infusion dose rate to prevent cardiovascular complications. Sedative and analgesic effects of dexmedetomidine are due to the stimulation of α2-adrenergic receptors in the core part of the locus coeruleus (31). In this study, no cardiovascular complication requiring treatment was observed with the administered dose of dexmedetomidine.

To recapitulate, the results of this study indicate that for post-caesarean pain management, adding dexmedetomidine to lower than usual doses of non-opioid analgesics (paracetamol and ketorolac) can cause appropriate analgesia without producing any considerable complications. In addition, although there was no significant difference, meperidine consumption was slightly higher in the paracetamol group, and in contrast, the satisfaction rate was significantly higher in the ketorolac group than in the paracetamol group. Therefore, it is recommended to undertake further studies with other dosages of these analgesics to achieve more effective drug combinations.

References

1. Imani F. Postoperative pain management. Anesth Pain Med. 2010;1(1):6-7. doi: 10.5812/kowsar.22287523.1860. [PubMed: 25729647]. [PubMed Central: PMC435751].
2. Imani F, Faiz HR, Sedaghat M, Hajjashrafi M. Effects of adding ketamine to fentanyl plus acetaminophen on postoperative pain by patient controlled analgesia in abdominal surgery. Anesth Pain Med. 2014;4(1). doi: 10.5812/aapm.12662. [PubMed: 24660145]. [PubMed Central: PMC496015].
3. Imani F, Rahimzadeh P, Gabapentinoids: Gabapentin and pregabalin for postoperative pain management. Anesth Pain Med. 2012;2(2):52-3. doi: 10.5812/aapm.7743. [PubMed: 24223357]. [PubMed Central: PMC3828164].
4. Imani F, Entezary SR, Alebouyeh MR, Parhizgar S. The maternal and neonatal effects of adding tramadol to 2% lidocaine in epidural anesthesia for cesarean section. Anesth Pain Med. 2011;1(1):25-9. doi: 10.5812/kowsar.22287523.1279. [PubMed: 25729652]. [PubMed Central: PMC3435751].
5. Suppa E, Valente A, Catarci S, Zanfini BA, Draischi G. A study of low-dose S-ketamine infusion as 'preventive' pain treatment for cesarean section. Minerva Anestesiol. 2012;78(7):774-81. [PubMed: 22374377].
6. Faiz SH, Rahimzadeh P, Imani F, Bakhvatiar A. Intrathecal injection of magnesium sulfate: Shivering prevention during cesarean section: a randomized, double-blinded, controlled study. Korean J Anesthesiol. 2013;65(4):293-8. doi: 10.4097/kjae.2013.65.4.293. [PubMed: 24228404]. [PubMed Central: PMC3822016].
7. Wolfson A, Lee AJ, Wong RP, Arheart KL, Penning DH. Bilateral multi-injection iliohypogastric-ilioinguinal nerve block in conjunction with neuraxial morphine is superior to neuraxial morphine alone for postcesarean analgesia. J Clin Anesth. 2012;24(2):298-303. doi: 10.1016/j.jcana.2011.09.007. [PubMed: 22608584].
8. Gharaei H, Imani F, Almasi F, Solimani M. The effect of ultrasound-guided TAPB on pain management after total abdominal hysterectomy. Korean J Pain. 2013;26(4):374-8. doi: 10.3344/kjp.2013.26.4.374. [PubMed: 24156044]. [PubMed Central: PMC3800700].
9. Imani F, Rahimzadeh P, Faiz HR, Abdollahzadeh-Baghaei A. An evaluation of the adding magnesium sulfate to ropivacaine on ultrasound-guided transverse abdominis plane block after abdominal hysterectomy. Anesth Pain Med. 2018;8(4). e71424. doi: 10.5812/aapm.74124. [PubMed: 30250819]. [PubMed Central: PMC5619531].
10. Hassan HI. Perioperative analgesic effects of intravenous paracetamol: Preemptive versus preventive analgesia in elective cesarean section. Anesth Essays Res. 2014;8(3):339-44. doi: 10.4031/ijoa.2015.6.2.14335. [PubMed: 25885321]. [PubMed Central: PMC4259876].
11. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O. Comparison of morphine, ketorolac, and their combination for postoperative pain: Results from a large, randomized, double-blind trial. Anesthesiology. 2005;103(6):1225-32. doi: 10.1095/00045391-200506000-00008. [PubMed: 16306736].
12. Kulo A, van de Velde M, van Calsteren K, Smits A, de Hoon J, Verd土壤seel R, et al. Pharmacokinetics of intravenous ketorolac following caesarean delivery. Int J Obstet Anesth. 2012;21(4):334-8. doi: 10.1016/j.ijoa.2012.06.001. [PubMed: 22907755].
13. Lavioie A, Toledo P. Multimodal postcesarean delivery analgesia. Clin Perinatol. 2013;40(1):443-55. doi: 10.1016/j.clp.2013.05.008. [PubMed: 23972750].
14. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colin MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93(3):382-94. doi: 10.1097/00000542-200009000-00006. [PubMed: 10901487].
15. Parker RK, Holtmann R, White PF. Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? JAMA. 1991;266(4):1994-52. doi: 10.1001/jama.1991.03470140059024. [PubMed: 1895471].
16. Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillon G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. Eur J Cardiothorac Surg. 2007;32(3):527-31. doi: 10.1016/j.ejcts.2007.05.007. [PubMed: 17649995].
17. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elston TS, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. Proc Natl Acad Sci U S A. 2002;99(21):13926-31. doi: 10.1073/pnas.162468099. [PubMed: 12423259]. [PubMed Central: PMC129799].
18. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12(2):146-55. doi: 10.1097/00045391-200505000-00008. [PubMed: 16622982].
19. Hylestved K, Jones M, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. Br J Anaesth. 2002;88(2):199-214. doi: 10.1093/bja/88.2.199. [PubMed: 11878654].
20. Swialk S, Parta N, Chattopadhyay S, Bisui B, Banarjee SS, Chattjee S. A comparative study of the efficacy of intravenous Paracetamol and Dexmedetomidine on peri-operative hemodynamics.
and post-operative analgesia for patients undergoing laparoscopic cholecystectomy. *Anesth Essays Res.* 2013;7(3):331-5. doi: 10.4103/0259-1162.123225. [PubMed: 25885978]. [PubMed Central: PMC473546].

21. Liew Z, Ritz B, Olsen J. Characteristics of acetaminophen users compared with nonusers during pregnancy, behavioral problems, and hyperkinetic disorders—reply. *JAMA Pediatr.* 2014;168(9):965-6. doi: 10.1001/jamapediatrics.2014.983. [PubMed: 25179025].

22. Mibielli MA, Geller M, Cohen JC, Goldberg SG, Cohen MT, Nunes CP, et al. Diclofenac plus B vitamins versus diclofenac monotherapy in lumbar: The DOLOR study. *Curr Med Res Opin.* 2009;25(11):2589-99. doi: 10.3111/13696990903246911. [PubMed: 19731994].

23. Ready LB, Brown CR, Stahlgren LH, Egan KJ, Ross B, Wild L, et al. Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain. A double-blind, placebo-controlled, multicenter study. *Anesthesiology.* 1994;80(6):1277-86. doi: 10.1097/00000542-199406000-00015. [PubMed: 8010474].

24. Pavy TJ, Paech MJ, Evans SF. The effect of intravenous ketorolac on opioid requirement and pain after cesarean delivery. *Anesth Analg.* 2001;92(4):1010-4. doi: 10.1097/00000539-200010000-00038. [PubMed: 11273941].

25. Lowder JL, Shackelford DP, Holbert D, Beste TM. A randomized, controlled trial to compare ketorolac tromethamine versus placebo after cesarean section to reduce pain and narcotic usage. *Am J Obstet Gynecol.* 2003;189(6):559-62. discussion 1562. doi: 10.1016/S0002-9378(03)00068-1. [PubMed: 14700983].

26. Peng K, Liu HY, Wu SR, Cheng H, Ji FH. Effects of combining dexmedetomidine and opioids for postoperative intravenous patient-controlled analgesia: A systematic review and meta-analysis. *Clin J Pain.* 2015;31(12):1097-104. doi: 10.1097/AJP.0000000000000219. [PubMed: 25654534].

27. Rahimzadeh P, Faiz SHR, Imani F, Derakhshian P, Amini A. Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. *BMC Anesthesiol.* 2018;18(1):62. doi: 10.1186/s12871-018-0531-7. [PubMed: 29875020]. [PubMed Central: PMC5999430].

28. Akhondzadeh R, Rashidi M, Gousheh M, Oalpour A, Baniahmad A. The effect of adding dexmedetomidine as an adjuvant to lidocaine in forearm fracture surgeries by supraclavicular block procedure under ultrasound-guided. *Anesth Pain Med.* 2018;8(4). e74355. doi: 10.5812/aapm.74355. [PubMed: 30250821]. [PubMed Central: PMC6139532].

29. Nie Y, Liu Y, Luo Q, Huang S. Effect of dexmedetomidine combined with sufentanil for post-caesarean section intravenous analgesia: A randomised, placebo-controlled study. *Eur J Anaesthesiol.* 2014;31(4):197-203. doi: 10.1097/EJA.0000000000000011. [PubMed: 24445347].

30. Wasiluk IM, Castillo D, Panni JK, Stewart S, Panni MK. Post-partum analgesia with dexmedetomidine in opioid tolerance during pregnancy. *J Clin Anesth.* 2012;23(7):593-4. doi: 10.1016/j.jclinane.2010.09.013. [PubMed: 22050812].

31. Jung HS, Joo JD, Jeon YS, Lee JA, Kim DW, In JH, et al. Comparison of an intraoperative infusion of dexmedetomidine or remifentanil on perioperative haemodynamics, hypnosis and sedation, and postoperative pain control. *J Int Med Res.* 2011;39(5):1890-9. doi: 10.1177/0300060511413900533. [PubMed: 2217991].