Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Obstetrics and Gynecology

A Study to Evaluate the Effect of Dexmedetomidine as Intrathecal Adjuvant to Ropivacaine for Hemodynamic Stability and Postoperative Analgesia in Gynecological Surgeries

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Original Research Article

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Article History
Received: 16.05.2018
Accepted: 27.05.2018
Published: 30.05.2018

DOI:
10.36347/sjams.2018.v06i05.076

Abstract: Many adjuvants have been used with local anesthetics in spinal anesthesia but none has been found ideal. We have conducted this prospective randomized double blind study to evaluate the effect of intrathecal dexmedetomidine when added to isobaric ropivacaine in spinal anesthesia. 50 female patients who underwent vaginal hysterectomies under spinal anesthesia were included in this study and were randomly allocated in to two groups. Group C received intrathecal 3 ml of 0.75% isobaric ropivacaine + 0.5 ml normal saline and group D received intrathecal 3 ml of 0.75% isobaric ropivacaine + 5 µg dexmedetomidine in 0.5 ml of normal saline. Following intrathecal administration, onset of sensory and motor blockade, maximum dermatomal level achieved, duration of analgesia, hemodynamic parameters and incidence of side effects were observed. Onset of sensory and motor block was earlier in group D compared to group C which was statistically significant. Block regression was significantly delayed with the addition of intrathecal dexmedetomidine (Group D) as compared to ropivacaine alone (Group C). Both, time to two segment regressions and time to regression to S2 were delayed significantly in group D. The duration of analgesia was also significantly prolonged in group D (348.00±23.02 min) as compared to group C.(207.60±17.23min) There were no significant difference in haemodynamic parameters and incidence of side effects in both the groups. The addition of dexmedetomidine(5 µg) to isobaric ropivacaine in spinal anesthesia produces significantly longer sensory and motor blockade along with prolonged postoperative analgesia, and haemodynamic stability without any significant side effects.

Keywords: Dexmedetomidine, Ropivacaine, Intrathecal, Gynecological

INTRODUCTION

Spinal anaesthesia is a commonly used anaesthesia technique for infraumbilical surgeries as it blunts not only the "stress response" to surgery, but also reduces intraoperative blood loss. Bupivacaine is the most commonly used local anesthetic for spinal anaesthesia; however it has cardio and neuro toxic side effects. An enantiomer-specific amide type local anesthetic, ropivacaine, which has lower potential for cardiac and central nervous systemic toxicity was introduced in 1996.It shows greater differentiation between sensory and motor blockade along with improved hemodynamic stability[1].

But its duration of action is limited. Various adjuvants have been used intrathecally to improve the quality and duration of the spinal anaesthesia along with prolonged postoperative analgesia [2]. The most commonly used agents have been opioids, such as morphine, fentanyl and tramadol. However addition of opioids has been associated with unwanted side effects like respiratory depression, pruritus, and nausea and vomiting. Various other drugs such as clonidine, magnesium sulfate, neostigmine, ketamine and midazolam, have also been used but none has been found ideal. Dexmedetomidine, is a novel and highly selective alpha-2 adrenoceptor agonist, have antinociceptive action for both somatic and visceral pain. Various studies have proved the efficacy and

safety of intrathecal dexmedetomidine in combination with bupivacaine [3]. But very little data is available in literature on usage of dexmedetomidine with ropivacaine in spinal anaesthesia. Therefore we have done this study to evaluate the effect dexmedetomidine as adjuvant to isobaric ropivacaine in spinal anaesthesia in the patients undergoing vaginal hysterectomy.

MATERIALS AND METHODS

After institutional ethics committee approval this prospective randomised double blind study was conducted on 50 patients. All patients were aged between 18-65 years with ASA grade I or II, posted for vaginal hysterectomy under spinal anesthesia. This study was conducted in a tertiary care hospital in Odisha from Sept 2015 to Oct 2017**.**Patients who refused for spinal anesthesia, patients with known history of head injury, psychiatric diseases, patients with known history of allergy to any test drugs and patients suffering from major hepatic, renal or cardiovascular dysfunction, were excluded from the study. Thorough pre- anesthetic evaluation was done and consent was taken and was explained regarding the anesthesia protocol. In operating room they were preloaded with 15 ml/kg of lactated Ringer's solution after putting iv cannula. Noninvasive blood pressure (NIBP), pulse oximeter, electrocardiogram (ECG) were attached to all patients and baseline heart rate,blood pressure and SpO2 were recorded. Lumber puncture was performed in L_3-L_4 or L_4-L_5 intervertebral space in sitting position through midline approach using 25G Quincke's needle.

Patients were randomized on the basis of sealed envelope technique to receive one of the following study drugs.

Group C: 3 ml volume of 0.75% isobaric ropivacaine (22.5 mg) and 0.5 ml of normal saline.

Group D: 3 ml volume of 0.75% isobaric ropivacaine (22.5 mg) with 5µg dexmedetomidine in 0.5 ml of normal saline.

Study drug was prepared by an anesthesiologist blinded to the study protocol. The anesthesiologist performing the block was blinded to the study drug. The drug was injected intrathecally over 10 to 15 seconds. Immediately after intrathecal injection, patients were then made supine position. The level of sensory block was checked by loss of pinprick sensation by 23 G hypodermic needle and dermatomal levels were tested at every 2 minutes until the highest level of block was achieved. Testing was then conducted every 10 minutes until the time of two segment regression of block and recovery to S_2 dermatome.

Motor block was evaluated using the modified Bromage Scale [4] as follows –

Bromage 0 - The patient is able to move the hip, knee and ankle.

Bromage 1- The patient is unable to move the hip, but is able to move the knee and ankle.

Bromage 2-The patient is unable to move the hip, and knee, but is able to move the ankle.

Bromage 3- The patient is unable to move the hip, knee, and ankle.

Haemodynamic parameters like HR, SBP, DBP and MAP were recorded every 3 minutes after administration of spinal anesthesia for first 15 minutes and subsequently every 5 minutes thereafter. Hypotension was defined as BP below 90 mm Hg or fall more than 20% of base line and was treated with iv fluids and vasopressor (ephedrine 5mg). Any fall in heart rate less than 60 beats was treated with injection atropine 0.6 mg. Highest dermatome level of sensory blockade, the time to reach this level from the time of spinal injection, and time to S_2 sensory regression were recorded. After commencement of surgery, patient's sedation level was evaluated by Modified Ramsay Sedation Score [5].

The incidence of adverse effects such as nausea, vomiting, shivering, itching, pruritus, respiratory depression, sedation and hypotension were recorded. Postoperatively, pain scores were recorded by using Visual Analogue pain scale (VAS). (0= no pain, 10= the most severe pain), initially every 1 hour for 2 hours, every 2 hours for next 8 hours and then after every 4 hours till 24 hours. Injection Paracetamol 1gm IV was given as rescue analgesia when VAS≥4[6].

Power analysis suggested that a sample size of 23 patients per group was required to achieve a power of 80% and a level significance of 0.05 to be able to detect a difference in the mean duration of analgesia by 60 min between the groups. Interpretation of the data was carried out and analyzed using statistical package for social sciences (SPSS version 19, IBM Corp, NY, USA). Data was represented as mean ± standard deviation for continuous data and frequency (percentage) or median (range) for nonparametric (categorical) data. The two groups were compared using analysis of variance. The proportion of adverse effects was compared using Chi-square test. $P < 0.05$ was considered statistically significant. $P < 0.001$ was considered highly statistically significant.

RESULTS

50 patients were included in the study. The groups were comparable with respect to demographic characteristics (Table 1).

Table-1: Patient's characteristics

Variables	Group C	Group D	P value
Age (yrs.)	37.77±12.38	40.76±10.35	0.3547
Sex(M/F)	19/6	17/8	0.7528
Height(cm)	164.16±13.32	159±11.4	0.12
Weight(kg)	59.92±5.41	61.52±6.33	0.3360
ASA Physical status(I/II)	15/10	14/11	0.7528

Table-2: Comparison of block characteristics

Block characteristics	Group-C	Group-D	P-value
Onset of sensory block in mins	3.96±1.2	2.98±1.3	<0.001
Onset of motor block in mins	5.2±0.8	4.3±1.2	<0.001
Height of block	T5	T6	>0.001
Time to maximum cephalad spread in mins	12.20±0.829	11.01±0.6	>0.001
Time for two segment regression in mins	96.81±12.35	122.52±5.32	<0.001
Time for regression to S2 in mins	186.00±18.87	330.60±22.56	<0.001
Total duration of analgesia in mins	207.60±17.23	348.00±23.02	<0.001

The results regarding the characteristics of sensory as well as motor block are summarized in (Table2).Onset of sensory and motor block was earlier in group D compared to group C which was statistically significant. There was no statistical difference in height of block achieved and time to achieve highest level of block. Block regression was significantly delayed with the addition of intrathecal dexmedetomidine (Group D) as compared to ropivacaine alone (Group C). Both, time to two segment regressions and time to S2 regression were delayed significantly in group D. The duration of analgesia was also significantly prolonged with the addition of dexmedetomidine(348.00±23.02 min) as compared to ropivacaine alone.(207.60±17.23min) There were no serious adverse effects in the any patients. Only 1 patient in group C and 2 patients in group D had hypotension which required treatment with a single dose of 6mg ephedrine. There was no significant difference in side effects in both groups.

Table-3: Comparison of adverse effects

Side Effects	Group C	Group D	P value
Shivering	5	3	>0.001
Hypotension	1	2	>0.001
Nausea	2	2	>0.001
Vomitting	0	0	>0.001
Bradycardia	1	2	>0.001
Neurological Sequel	0	0	>0.001

DISCUSSION

In this study we have tried to evaluate the efficacy and safety of intrathecal dexmedetomidine in combination with ropivacaine. α_2 adrenoceptor agonist like clonidine has been extensively used in anaesthetic practice for their sympatholytic, sedative, analgesic, and anaesthetic-sparing effects[7]. Ropivacaine is a newer amide local anesthetic, which is less toxic to the central nervous system and cardiovascular system and shows rapid recovery of motor function [8]. Hyperbaric ropivacaine produces more predictable and reliable sensory and motor block, with faster onset than a plain solution. Since commercial preparations of hyperbaric ropivacaine are not yet available, adjuvants to isobaric solution are being investigated to prolong the duration of action of plain ropivacaine. Addition of fentanyl,clonidine and dexmedetomidine have been studied to prolong the effect on sensory and motor block duration of bupivacaine [9,10]. In this study we have tried to evaluate the efficacy and hemodynamic stability of intrathecal dexmedetomidine in combination with isobaric ropivacaine. Dexmedetomidine is a highly selective α_2 agonist with a 10 times greater $\alpha 2/\alpha 1$ selectivity than clonidine α_1 receptors [11]. Dexmedetomidine has most commonly used as an adjuvant to local anaesthetic agents in regional blocks including in neuraxial blocks. Al-Ghanem *et al. [12]* and Al-Mustafa *et al. [23]* in their studies found that the effect of dexmedetomidine is dose dependent and that the onset of sensory blockade was more rapid and duration is prolonged with the use of dexmedetomidine which was similar to

our study. In a study conducted by Kanazi *et al. [13]* they observed that 3 µg dexmedetomidine or 30 µg clonidine added to spinal bupivacaine prolonged the duration of sensory and motor block to same extent with minimal side-effects in urologic surgical patients. Similar findings were observed in our study where we observed that there was a significant prolongation in duration of both sensory as well motor blockades in the group receiving intrathecal dexmedetomidine along with ropivacaine. Similar block characteristics were found by Gupta *et al*. [14] and Gupta *et al*. [22] the mechanism of action by which spinal alfa-2 adrenoceptor agonist prolongs the motor and sensory block is not well known [15]. The local anaesthetics act by blocking sodium channels, whereas the alfa-2 adrenoceptor agonist acts by binding to pre-synaptic C-fibres and post-synaptic dorsal horn neurons. The analgesic action of intrathecal alfa-2 adrenoceptor agonist is by depressing the release of C-fibre transmitters and by hyperpolarisation of post-synaptic dorsal horn neurons [16] There may be synergistic effect of action of the local anaesthetic and the alfa-2 adrenoceptor agonist as studied by Salgado *et al*.[17] which explain the prolongation of sensory block when added to spinal local anaesthetics. Khaw *et al*. [18], in their study evaluated different doses (10, 15, 20 and 25 mg) of ropivacaine in cesarean section. The effective dose (ED50 and ED95) for spinal ropivacaine was calculated to be 16.7 mg (ED50) and 26.8 mg (ED95). Kessler *et al*.[19], in their study concluded that isobaric ropivacaine (22.5 mg) was suitable for spinal anesthesia for lower abdominal gynaecological surgery. Various other studies have reported that 5 µg intrathecal dexmedetomidine is safe and devoid of any neurotoxic side effect [20], hence, we used 5 µg dexmedetomidine along with 22.5mg isobaric ropivacaine (0.75%). In our study there was a significant delay in the time to fist rescue analgesia in group receiving intrathecal dexmedetomidine and there was a significant reduction in the analgesic consumption in the first 24 hours. Similar findings are observed by Mahendru *et al.* [21]**,** Gupta *et al*. [22] and Al-Mustafa *et al*.[23] Talke *et al*. [24], concluded that α-2 adrenergic agents also have anti-shivering property. In our study shivering was noted in 5 patients in Group C and in 3 patients in Group D which may be due to dexmedetomidine. They also found that the combination of ropivacaine and dexmedetomidine provided excellent hemodynamic stability which was similar to our study. Qi X *et al*. [25] conducted a randomized controlled study in patients undergoing operative hysteroscopic procedure under spinal anaesthesia. They concluded that intrathecal dexmedetomidine produced prolonged motor & sensory blockade and less pruritus compared with fentanyl in hysteroscopic surgery which was similar to our study.

Kelkar *et al*. [26] compared the efficacy and safety of 20 mg and 15 mg isobaric Ropivacaine for C-section. They concluded that a total of 20 mg isobaric ropivacaine had good efficacy and safety profile in C-section. 15 mg isobaric ropivacaine proved to be inadequate as it failed in 40% of cases. In a study conducted by Parmar *et al*. [27] by using 22.5mg isobaric ropivacaine (3ml of 0.75% intrathecally) and 5µg of dexmedetomidine + ropivacaine 22.5mg, dexemeditomidine significantly prolongs the sensory and motor blockade.

Shah a *et al*. [28] conducted the study on heamodynamic effect of intrathecal dexmeditomidine added to ropivacaine intraoperatively and for post op analgesia. They found that, onset of sensory block was earlier and duration of analgesia was prolonged in dexmedetomidine group which was similar to our study. So dexmedetomidine can be effectively and safely used as an intrathecal adjunct to ropivacaine. Our study was limited by its small sample size so large randomized controlled studies are to be done to firmly establish the efficacy and safety of intrathecal dexmedetomidine.

CONCLUSION

Our study reveals that dexmedetomidine when added to isobaric ropivacaine intrathecally for gynecological surgery, provides prolonged sensory and motor blockade, better postoperative analgesia, reduced requirement of rescue analgesic in first 24 hour and excellent haemodynamic stability with minimal side effects

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