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ORIGINAL ARTICLE

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Intrathecal bupivacaine with clonidine or dexmedetomidine as adjuvant in gynecological surgery: an enigma

Rupesh Choudhary[1], Jyoti Pathania[1], Anoop Sharma[2], Aparna Sharma[1*] and Rahul Sharma[1]

Abstract

Background Addition of adjuvants to routinely used intrathecal drugs is cornerstone in safe and effective prolongation of single shot spinal block for gynecological surgery. In resource deficient countries, where epidural anesthesia is usually not used because of cost factor, adjuvants are routinely used to prolong the effect of regional anesthesia. Alpha 2 agonists are considered best drugs as adjuvants, but there is inconclusive data in literature about the block characteristic, dose at which to be used and side effect after use of these drugs.

Methods Clonidine 30 µgm or dexmedetomidine 5 µgm was used intrathecally as an adjuvant with 15 mg bupivacaine 0.5% in 90 female patients undergoing gynecological surgery in this randomized, prospective, single blind study.

Results The mean time to onset of sensory block a (T6 level) and time to attain maximum sensory height were significantly early in group D over group C (124.44 ± 20.64 s, 175.09 ± 68.01 s, $p < 0.0001$) and (13.53 ± 2.97 min, 18.64 ± 4.82 min, $p < 0.0001$)respectively. Time to two segment sensory regression, total duration of analgesia, duration of motor blockade was (115.24 ± 8.9 min, 370.60 ± 17.98 min, 316.67 ± 21.39 min) in group D and (103.58 ± 11.25 min, 323.91 ± 23 min, 273.51 ± 18.95 min) in group C respectively ($p < 0.001$). The post-operative visual analogue scale score (VAS) was more in group C at 240 min onwards ($p \leq 0.01$). Analgesic use and intraoperative complications were similar in both the groups. ($p > 0.05$).

Conclusions We recommend clonidine 30 µg over dexmedetomidine 5 µg as an adjuvant to intrathecal bupivacaine, to effectively and safely prolong the effect of single shot spinal anesthesia.

Keywords Clonidine, Dexmedetomidine, Hysterectomy, Bupivacaine, Analgesia, Anesthesia

Key message

Clonidine is more cost-effective adjuvant over dexmedetomidine in single shot spinal anesthesia.

Background

Among various type of regional anesthesia techniques, single shot spinal anesthesia is still the first choice for lower abdominal/lower limb surgery because of its rapid onset, superior blockade, lower risk of infections, lesser failure rate, and cost effectiveness (Chestnut et al. 2014). It blunts the stress response to surgery and decreases the incidence of postoperative thromboembolic events, time

*Correspondence:
Aparna Sharma
aparnasharmaraina@gmail.com
[1] Department of Anaesthesia, IGMC, Shimla, Himachal Pradesh 171001, India
[2] Gynecology and Obstetrics, IGMC, Shimla, Himachal Pradesh 171001, India

to ambulation, voiding, and complete resolution of block after surgery enabling early discharge (Frey et al. 1998). Major drawback of single shot spinal anesthesia is its short duration of block and lack of postoperative analgesia so intrathecal adjuvants have gained popularity which aim at prolonging duration of block (Kaur 2010). Opioid adjuvants cause pruritus, nausea, vomiting, delayed respiratory depression prompting further research towards α2-adrenergic agonists including dexmedetomidine and clonidine. There is still ambiguity in literature about the dose and the drug to be preferred for such lower abdominal surgery (Gupta et al. 2011).

Methods

This prospective randomized single blind study was conducted from October 2020 to September 2021 after taking clearance from research ethics committee of the institute and was registered with CTRI no /2020/10/028408. ASA I and ASA II female patients aged between 35 and 60 years undergoing hysterectomy were included in this study.

Patients with hypersensitivity to the study drugs or on beta blockers, having any bleeding disorders or with decreased platelet counts $\leq$ 50,000/µl, patients having spinal column deformities or those undergone any spine surgery, with difficult access to spinal, or those having infection at the local site were excluded from the study. All eligible willing participants were taken and assigned to group C or D according to random allocation software [Randomizer, Package in R]. Preoperative assessment was done for each patient and written informed consent was taken. VAS score was explained to the patient preoperatively. Initially 100 patients were assessed for eligibility but there was failure of block in 6 patients and 4 patients refused to cooperate during assessments perioperatively hence total of 10 patients were excluded and final analysis was done on 90 patients.

Patients were premedicated with tablet Alprazolam 0.5 mg one night before and at 6AM on the day of surgery.Patients were cannulated with 18 G cannula and ringer lactate solution was started. Baseline electrocardiogram (ECG), noninvasive blood pressure (NIBP), heart rate (HR), and oxygen saturation (SPO2), respiratory rate (RR) was recorded. Single shot spinal anesthesia was given in L3-L4 interspace with 26 G spinal needle via median/para median approach. Intrathecally, 3 ml (15 mg) of bupivacaine heavy with 0.2 ml (5 mcg) dexmedetomidine in group D and 3 ml (15 mg) of bupivacaine heavy with 0.2 ml (30 mcg) clonidine in group C was given. Dexmedetomidine 1 ml (50 µg) was diluted to 2 ml by using1 ml of normal saline, out of which 0.2 ml (5 µg) of dexmedetomidine was used. Injection clonidine 1 ml (150 µg) was taken and 0.2 ml (30 µg) out of this 1 ml was taken in group C. Injection clonidine (cloneon) and injection dexmedetomidine (dexmed) of Neon Laboratories, India was used in the study.

Onset of sensory block was checked bilaterally, every 15 s by pin prick method with 23 gauge hypodermic blunt needle at midclavicular line, from the time of injecting drug into subarachnoid space till complete analgesia at the level of T-6 was achieved and the surgery was started. Maximum level achieved was the highest level seen in four consecutive tests. Two segment regression was taken as the time taken for two segment regressions from the highest level of sensory block achieved every 15 min perioperatively. The total duration of analgesia (TDOA) was calculated from the onset of sensory block to the time VAS score $\geq$ 4 was achieved.

Onset of motor block was assessed every 15 s by asking the patient to move their legs till complete motor block was achieved as per modified Bromage scale $\leq$ 2. Duration of motor block was taken as the time from complete motor block (modified bromage $\leq$ 2) to full recovery, that is the time when lower limb could be moved freely (modified Bromage 6) done every 30 min, postoperatively. Modified Bromage scale was recorded as score 1 = Complete block (unable to move feet to knee, score 2 = almost complete block (able to move feet only, score 3 = partial block (just able to move knees), score 4 = detectable weakness of hip flexion while supine (full flexion of knees, score 5 = no detectable weakness of hip flexion while supine, score 6 = able to perform partial knee bend.

Hemodynamic parameters like heart rate (HR), mean arterial blood pressure (MAP), respiratory parameters like respiratory rate (RR) and SPO2, were recorded every 5 min initially till 15 min, followed by every 10 min till the end of surgery. Any reduction of MAP more than 30% below baseline or MAP $\leq$ 65 was considered as hypotension and was treated with the help of intravenous fluid bolus and incremental doses of vasopressor agent mephenteramine 6 mg intravenously. Bradycardia < 50 per minute was treated with injection atropine 0.6 mg. Subjects were monitored for occurrence of adverse events like nausea, vomiting, desaturation, hypotension, bradycardia (requiring atropine), excessive sedation, and shivering. Postoperative pain was assessed using visual analogue scale (0–10), every 1 h till VAS $\geq$ 4 was recorded and type of rescue analgesic used was allowed as per the institutional protocol and its 24-h analgesic dose requirement was noted.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results on continuous measurements were presented on Mean ± SD (min–max) and categorical as frequency (percentage). Normality of the data was assessed using Shapiro–Wilk test. Inferential statistics like

chi-square test/Fisher's exact test. Independent *t* test was applied to check difference between the groups. The significance of level adopted was 5%.

Results

The mean age of the patients, in group C and group D was 47.11 ± 7.92 and 48.20 ± 6.70 years respectively ($p = 0.484$). Mean weight (kg) in group C and group D was 57.22 ± 3.75 and 59.48 ± 4.88 respectively ($p = 0.061$). Thirty-three patients in group C and group D were of ASA-1 grade while 12 patients were of ASA-11 grade in both the groups ($p = 1$) (Table 1).

The mean onset time of sensory block at T6 level was 175.09 ± 68.01 s in group C and 124.44 ± 20.64 s in group D. The mean time to reach the maximum sensory height was 13.53 ± 2.97 min in Group D and was 18.64 ± 4.82 min in group C. Mean time to two segment regression of the block was 103.58 ± 11.25 min in group C and 115.24 ± 8.91 min in group D respectively. Mean time to onset of motor block in seconds (modified Bromage scale ≤ 2) for group C and group D was115 ± 8.11 and 74.6 ± 14.19 respectively. Mean duration of motor blockade in minutes (modified bromage scale = 6) for group C and group D was 273.51 ± 18.95 and 316.67 ± 21.39 respectively Mean TDOA time in minutes for group C and group D was 323.91 ± 23.0 and 370.60 ± 17.98 respectively ($p \leq 0.001$) (Table 1).

The maximum height reached was T4 in all the patients of group C. Four patients achieved T2 level, 1 had T3 level, 39 had T4 level and one had T6 level in group D ($p = 0.026$) (Fig. 1).

Table 1 Demographic profile and characteristics of block

	Group C Mean ± SD ($n = 45$)	Group D Mean ± SD ($n = 45$)	*P* value
Age (years)	47.11 ± 7.92	48.20 ± 6.70	0.484
Weight (kg)	57.22 ± 3.75	59.48 ± 4.88	0.061
ASA1 status	33(73.3%)	33(73.3%)	1.00
ASA11 status	12(26.7%)	12(26.7%)	
Onset sensory (s)	175.09 ± 68.01	124.44 ± 20.64	0.001*
Max sensory time (min)	18.64 ± 4.82	13.53 ± 2.97	0.001*
Two segment regression (min)	103.58 ± 11.25	115.24 ± 8.91	0.001*
Onset motor (s)	115 ± 8.11	74.6 ± 14.19	0.001*
Duration motor (min)	273.51 ± 18.95	316.67 ± 21.39	0.001*
Total duration of analgesia (min)	323.91 ± 23.0	370.60 ± 17.98	0.001*

* Statistically significant ($p < 0.05$)

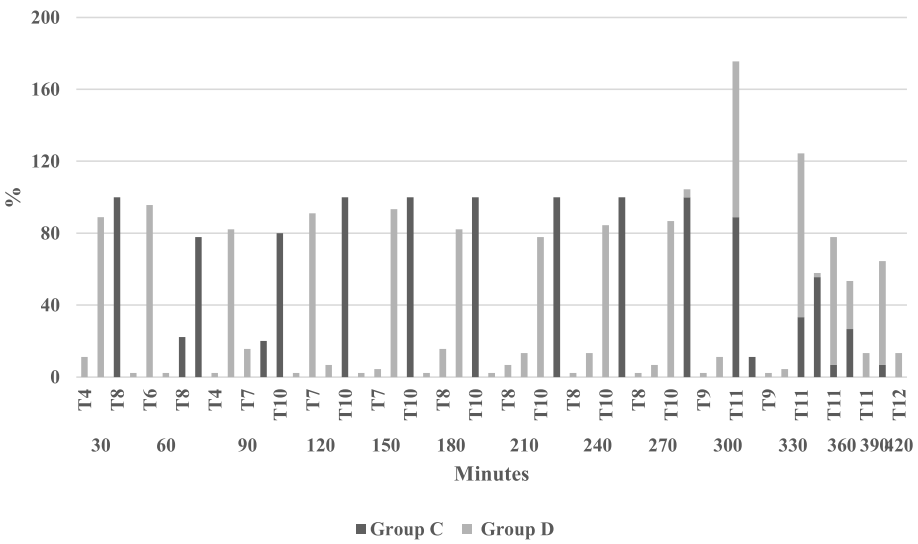

Fig. 1 Sensory level achieved in both the groups during peri- and postoperative period

No statistically significant difference was observed between the groups for heart rate, Spo2, and the percentage fall in mean arterial pressure from the baseline ($p > 0.05$). There was a similar fall in blood pressure in both the groups when compared to the baseline MAP ($p \leq 0.05$) (Table 2).

When compared between the groups, mean VAS score was significantly more in group C from 240 min onwards in postoperative period ($p \leq 0.021$) (Fig. 2). The return of motor power was earlier in group C as compared to Group D from 90 min onwards in postoperative period ($p \leq 0.041$) (Table 3).

Injection paracetamol [PCM] 1 gm was used as rescue analgesic if VAS ≥ 4 was achieved in any patient. In group C, 10 patients received PCM as compared to 8 patients in group D. One patient in each group received 1 dose, 5 in group C and 2 in group D received 2 doses and 4 in group C and 5 in group D received 3 doses of PCM in 24 h postoperative period ($p = 0.693$). Hypotension was seen in 5 patients of group C and 4 patients of group D. Three patients in both the groups required 2

Table 2 Mean arterial pressure recorded perioperatively in both the groups

Time	Group C Mean ± SD	*P* value With respect to baseline	Group D Mean ± SD	*P* value With respect to baseline	*P* value (group C Vs group D)
PO	77.96 ± 5.51	–	78.22 ± 5.86	–	0.825
5 min	70.62 ± 7.67	0.031*	72.53 ± 6.33	0.004*	0.201
10 min	69.91 ± 7.72	0.001*	70.13 ± 7.06	0.001*	0.887
15 min	73.53 ± 9.6	0.001*	73.49 ± 9.02	0.001*	0.982
20 min	72.51 ± 9.26	0.001*	72.8 ± 9.2	0.001*	0.882
30 min	75.11 ± 7.6	0.001*	74.47 ± 7.3	0.001*	0.683
40 min	75.76 ± 6.18	0.001*	75.87 ± 6.17	0.001*	0.932
50 min	76.11 ± 5.29	0.006*	75.51 ± 5.47	0.091	0.598
60 min	76 ± 5.02	0.011*	75.38 ± 4.51	0.002*	0.538
70 min	76.53 ± 3.53	0.001*	76.56 ± 3.94	0.003*	0.978
80 min	75.82 ± 3.9	0.020*	76.11 ± 4.28	0.002*	0.739
90 min	75.78 ± 5.93	0.001*	76.22 ± 6.04	0.006*	0.726
100 min	74.31 ± 5.19	0.001*	74.69 ± 5.47	0.001*	0.738
110 min	77.27 ± 4.63	0.001*	77.73 ± 4.65	0.001*	0.635
120 min	75.78 ± 5.41	0.005*	75.69 ± 5.43	0.004*	0.938

* Statistically significant ($p < 0.05$)

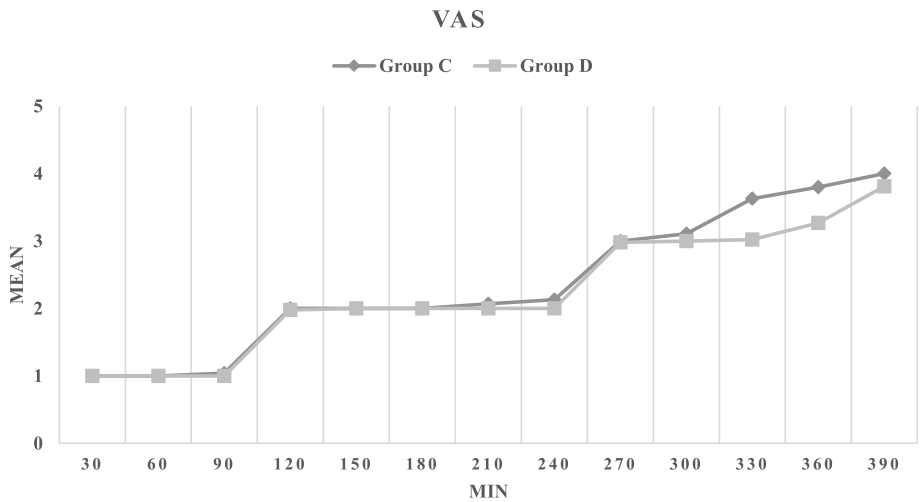

Fig. 2 Visual analogue scale (VAS score) recorded at various time interval in the two groups

Table 3 Motor grade recorded in both the groups perioperative and postoperative period

Motor grade	Group C Mean ± SD	Group D Mean ± SD	*P* value
30 min	1 ± 0	1 ± 0	–
60 min	1.07 ± 0.25	1 ± 0	0.080
90 min	1.31 ± 0.59	1 ± 0	0.001*
120 min	2.11 ± 0.32	2 ± 0	0.021*
150 min	2.20 ± 0.5	2 ± 0	0.009*
180 min	3.09 ± 0.29	3 ± 0	0.041*
210 min	3.16 ± 0.42	3 ± 0	0.016*
240 min	4.11 ± 0.32	4.07 ± 0.33	0.517
270 min	5.47 ± 0.5	4.91 ± 0.29	0.001*
300 min	5.71 ± 0.46	5.27 ± 0.45	0.001*
330 min	6 ± 0	5.66 ± 0.48	0.070

* Statistically significant ($p < 0.05$)

Table 4 Side effects and use of rescue analgesia in the study groups

Variable		Group C *N* (%)	Group D *N* (%)	*P* value
Inj PCM	0	35(77.8)	37(82.2)	0.693
	1GM	1(2.2)	1(2.2)	
	2 GM	5(11.1)	2(4.4)	
	3 GM	4(8.9)	5(11.1)	
Vasopressor	0	40(88.9)	41(91.1)	0.839
	12 MG	03(6.7)	03(6.7)	
	6 MG	02(4.4)	01(2.2)	
Side effects	Bradycardia	05(11.1)	01(2.2)	0.657
	Nausea, Vomiting	03(6.7)	01(2.2)	
	Shivering	03(6.7)	0	
Attempt	01	45(100)	45(100)	–

Statistically in significant ($p > 0.05$)

doses of inj mephenteramine and 2 patients in group C and 1 in group D required single dose of vasopressor (inj mephentermine) ($p = 0.839$). Five patients had bradycardia, 03 patients complained of nausea, and 03 patients had shivering in group C. While bradycardia was seen in 01 patient, nausea in 01 patient and vomiting in 01 patient of group D ($p = 0.657$) (Table 4).

Discussion

Spinal anesthesia using hyperbaric bupivacaine 0.5% is the most commonly used neuraxial anesthetic technique for total abdomen hysterectomy, as it is cheap, easy to perform and provides simple, effective analgesia of short duration in patients. It is often associated with inadequate analgesia, visceral pain, nausea, and vomiting leading to patient discomfort. Opioids based adjuvants mildly prolong the duration of analgesia but are associated with side effects of pruritus, nausea vomiting and delayed respiratory depression. Clonidine when used intrathecally as an adjuvant in (15–150 mcg/kg) dose is associated with bradycardia, hypotension and sedation (Elia et al. 2008). Dexmedetomidine, although is a highly specific and selective alpha 2 adrenoceptor agonist with α2:α1 binding selectivity ratio of 1620:1, as compared to 220:1 for clonidine, should decrease the unwanted side effects of α1 receptors but the ambiguity about the exact dose at which it should be used persists (Kanazi et al. 2006).

Researchers have used dexmedetomidine in 2, 3, 5, 10, 15, and 20 μgm concentrations with varying results. Higher concentrations than 5 μgm use is associated with higher incidence of hypotension and bradycardia, although the duration of analgesia is substantially prolonged. Hence, we used dexmedetomidine in 5 μgm dose and compared it with 30 μgm clonidine used intrathecally in the patients (Naaz et al. 2016). Our results on block characteristics, of the drugs used were similar to those seen by Mallika Ganesh et al. (2018), Rahul Ranjan et al. (2018), Naaz S (2016), Sarma J et al. (2015), and Elshalakany et al. (2017), albeit different dose of adjuvant used and different endpoints taken for initiating surgery. In our study, onset of sensory block was in 124.44 ± 20.64 s in group D over 175.09 ± 68.01 s in group C.

Mallika Ganesh et al. (2018) and Rahul Ranjan et al. (2018) reported early onset of analgesia than seen in our study. It was 1.4 ± 0.5 min with clonidine and 1.2 ± 0.4 min with dexmedetomidine in the study by Mallika Ganesh et al. and was 1.02 ± 0.15 min, 1.62 ± 0.49 min with dexmedetomidine and clonidine respectively in the study by Ranjan et al. The early onset of analgesia could be as they had taken time to reach sensory block to T10 level and we had taken onset at T6 level which is at higher dermatome. Sarma J et al. (2015) and Naaz Shagufta (2016) reported late onset of sensory block than seen in our study which could be as they had assessed the onset of block every 1 min whereas in our study we recorded it every 15 s. They reported mean onset time (min) of 6.320 ± 1.168 and 2.15 ± 0.74 in their respective studies in the group where 5 μgm dexmedetomidine was used as an adjuvant.

We observed 13.53 ± 2.97 min, mean time to reach maximum sensory block in dexmedetomidine group over 18.64 ± 4.82 min seen in clonidine group and it was comparable to that seen in the study by Naaz Shagufta et al. (2016) as they too observed maximum sensory block in 14.43 ± 3.11 min in their dexmedetomidine group. Our results were not in accordance with the results seen by Om Suthar et al. (2015) as they

observed faster time to reach the maximum height with clonidine over dexmedetomidine and it was 14 ± 4.11 in clonidine group and 17 ± 4.51 in dexmedetomidine group which could be as they had used lower dose of 3 μg dexmedetomidine in their study.

Researchers who used more concentration of clonidine (50 μgm) or dexmedetomidine 10 μgm reported prolonged time to two segment regressions than seen in our study. Thus, our study was not in accordance to the study done by Sarma J et al. (2015) as they observed more time to two segment regression that is 120 min as compared to 103.58 min seen in our study, which could be because they had taken higher dose of clonidine (50 μg) as compared to 30 μg clonidine used in our study. Our results for two segment regressions of 115.24 ± 8.9 min in dexmedetomidine group were similar to those of Eid HA et al. (Eid et al. 2011) and Elshalakany et al. (Elshalakany et al. 2017) as they too observed similar time of two segment regression, as it was 121.3 ± 10.2 min and 128.7 ± 11.4 min.

Mallika Ganesh et al. (2018) observed faster onset of motor blockade in both the groups as it was 1.1 ± 0.04 min (66 ± 2.4 s) in dexmedetomidine group and 1.6 ± 0.05 min (96 ± 3 s) in clonidine group, than 74.6 ± 14.19 s (group D) and 115 ± 8.11 s (group C) seen in our study. They could have reported early onset of block in both the groups due to more volume of bupivacaine used (3.5 ml) in their study as compared to 3 ml used in our study.

Sarma J et al. (2015) and Naaz S et al. (2016) assessed onset of motor blockade every 1 min hence could have reported higher onset time of 9.520 min for clonidine group and 10.760 min for dexmedetomidine group as compared to our study.

Total duration of motor blockade in our study was 316.67 ± 21.39 min in group D and 273.51 ± 18.95 min in group C ($p < 0.001$). Sarma J et al. and Naaz S et al. (2016) reported lower total duration of motor blockade of 253.20 ± 38.04 min and 251.4 ± 46.5 min respectively in the group,where they used 5 μg dexmedetomidine.Mallika Ganesh et al. (Ganesh and Krishnamurthy 2018) reported total duration of 302.6 ± 36.6 min (group D) which is comparable to that seen in our study.

In our study, the time to two segment regression, total duration of analgesia, and total duration of motor blockade was 36.6 min, 46.7 min, and 43 min early in clonidine group over dexmedetomidine group. Our results were similar to those seen by Zang et al. (2016) who did a meta-analysis of 7 studies with 354 subjects and performed quantitative analysis of onset, duration of analgesia and time to first analgesic required and found it to be 10.8 min, 22.3 min, and 38.6 min early in clonidine group. They did not observe any difference in motor blockade duration between the two groups.

In our study, bradycardia was observed in 5 patients of group C as compared to 1 patient of group D. Both the groups were having almost similar episodes of hypotension and vasopressor use perioperatively. Although more episodes of nausea, vomiting, and shivering were observed in clonidine group as compared to dexmedetomidine, but statistical significance could not be achieved ($p > 0.05$). Our results for adverse effect associated with these drugs were similar to that seen by Jiang J et al. (2021) who did a meta-analysis of 14 studies having Jadad score ≥ 4 where these drugs were used intravenously and intrathecally with local anesthetics. They deduced that incidence of bradycardia, hypotension, dizziness, headache was 9–11% more and shivering and nausea vomiting was 9%less in clonidine group. They observed similar incidence of dry mouth in both the groups and all these side effects were statistically insignificant ($p > 0.05$).

Thus, the total duration of the block prolongation of 36–40 min by dexmedetomidine which is up to eight time costly than clonidine is debatable in resource limited countries like ours. Even the postoperative analgesic requirements and reported side effects are similar with the use of these two drugs in many studies done worldwide[14].

Limitations

The major limitation of our study was inclusion of only female patients undergoing gynaecological surgery. Invasive blood pressure monitoring was not done perioperatively. Single dose of these adjuvants (5 μgm for dexmedetomidine and 30 μgm for clonidine) was used in the study. Thus, more multicentric studies on this subject are advocated at varying concentration of adjuvants to frame a definitive rule about their efficacy for safe anesthesia practice.

Conclusions

We recommend clonidine 30 μg over dexmedetomidine 5 μg as an adjuvant to intrathecal bupivacaine, to effectively and safely prolong the effect of single shot spinal anesthesia.

Abbreviations

ASAL	American Society of Anesthesiologist physical status
VAS	Visual analogue scale score
PCM	Injection paracetamol
TDOA	Total duration of analgesia
Spo2	Saturation of peripheral oxygen
μgm	Microgram

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Nil

Authors' contributions
RC: concept, design, acquisition, analysis or interpretation of data, drafting the work and revising it for intellectual content, final approval of the version. JP: concept, design, acquisition, analysis or interpretation of data, drafting the work and revising it for intellectual content, final approval of the version. APS: concept, design, acquisition, analysis or interpretation, final approval of the version. AS: drafting the work and revising it for intellectual content, concept, design, acquisition, analysis or interpretation of data, final approval of the version, agreement to be accountable for all aspects of the work of all authors. RS: concept, design, acquisition, analysis or interpretation of data, drafting the work and revising it for intellectual content, final approval of the version. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available [due to COVID pandemic, the uploading site of Indian council of medical research site which gives the CTRI no. was not working at optimal conditions. Hence, the data could not be uploaded but is available in excel sheet master chart. This was attached with the thesis submission also and can be provided if desired] but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval taken and research registered in CTRI India. Ethical no.: HFW(MC-11) B (12)ETHICS/2020/13925/dated 31 August 2020 Shimla. Name of the committee: Institutional ethics committee IGMC, Shimla, Himachal Pradesh, India 171001. Institution name: Indra Gandhi Medical College, Shimla (a government run institution). CTRI No.: 2020/10/028408.

Consent for publication
All authors and participants consent for publication. (In the informed consent proforma to be signed by the participants, consent of publication was included at serial nos. 6 and 9. The form can be uploaded if desired.)

Competing interests
The authors declare that they have no competing interests.

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