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Intrathecal dexmedetomidine: Useful or not?

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Abstract

Spinal anesthesia is used commonly intra operatively. However, local anesthetics are associated with relatively short duration of action. A number of adjuvants have been used to prolong the postoperative analgesia.

Objectives: To evaluate role of dexmedetomidine added to heavy bupivacaine 0.5% intrathecally for lower abdominal surgeries. Subjects and methods: Sixty two patients were randomly divided into one of two group, Group (D) received 3.5 mL volume of 0.5% hyperbaric bupivacaine and 5 µg dexmedetomidine in 0.5 mL of preservative free normal saline intrathecally. Group (P) received 0.5 ml normal saline added to the same dose of heavy 0.5% bupivacaine and served as placebo.

Results: There was significantly less time needed to reach T8 sensory level, 2-segment regression, and time to reach Bromage 3in group (D) compared to group (P). There was significantly more time needed for first requirement of analgesia in group (D) compared to group (P). There was a significantly less analgesic dose requirement in group (D) compared to group (P).

Conclusion: Receiving Dexmedetomidine at a dose of 5 µg provides earlier sensory and motor blockade, less postoperative analgesic requirements, less shivering among patients of lower abdominal surgery under intrathecal anaesthesia with no sedation effect or neurologic complications.

Keywords: Intrathecal; Dexmedetomidine; Shivering; Spinal anaesthesia; Adjuvantst

Introduction

Spinal anesthesia is the most commonly used technique for lower abdominal and perineal surgeries. However, local anesthetics-when used alone-is associated with relatively short duration of action, thus early analgesic intervention is needed in the postoperative period.

A number of adjuvants have been used to prolong the postoperative analgesia [1,2]. Dexmedetomidine, a new highly selective α2-agonist, is under evaluation as a neuraxial adjuvant. It provides stable hemodynamic condition, good quality of intra-operative analgesia and prolonged post-operative analgesia with minimal side effects [3].

Based on earlier human studies, it is hypothesized that intrathecal Dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects [4,5].

In the current study, the aim is to evaluate the role of Dexmedetomidine when added to heavy Bupivacaine 0.5% intrathecally among patients subjected to lower abdominal surgeries.

Materials and Methods

A double blinded randomized controlled trial was started after the approval of the Ethical Committee of the Medical Research Institute, Alexandria University. Written informed consent was obtained from all study participants. 62 patients presenting to indirect inguinal hernia repair surgery, during the period from 1st of January 2013 till end of March 2013 were included in the study.

Inclusion criteria were patients with American Society of Anesthesiologists (ASA) physical status I or II, of either sex, aged between 18 till 60 years, presenting for lower abdominal surgeries.

Exclusion criteria were patient allergic to any of the drugs used and/or suffering from neurologic diseases, coagulopathy, cardiac diseases, obesity or hypertension.

Patients were randomly divided into one of two groups using sealed envelope technique. The first group (D) received the drug under investigation while the second group (P) received a placebo.

All patients were preloaded with Ringer's solution 15 mL/kg. They were monitored with automated noninvasive blood pressure, pulse oximetry, and electrocardiogram. Patients received no premedication during the 24 hours prior to the study.

Following patient positioning in the sitting position and local skin infiltration using 2 ml of Lidocaine 2%, a 25 G pencil point spinal needles were introduced through L4-L5 interspaces under strict aseptic precautions. Group (D) patients received 3.5 ml volume of 0.5% hyperbaric Bupivacaine and 5 *µg* Dexmedetomidine in 0.5 ml of preservative free normal saline intrathecally. Meanwhile, Group (P) received normal saline added to the heavy Bupivacaine 0.5% which served as placebo. Medications were prepared by a third party (another colleague) so that both patient and investigator were blinded. Intrathecal injection in either group was given over approximately 10 seconds. Immediately after completion of injection, patients were made to lie supine. Oxygen (2 L/min) was applied to each patient via face mask. Patients were monitored intra-operatively for their mean blood pressure and pulse every 5 minutes for the first 30 minutes, then every 10 minutes thereafter till end of surgery.

Patients were assessed for occurrence of shivering, time to reach

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T-8 sensory level (every 2 minutes) using loss of pin prick sensation, and loss of motor functions indicated by time to reach Bromage 3using Modified Bromage Scale.

Modified Bromage Scale is scored 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 able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle [6].

Moreover, assessment was done for 2-segment regression, first time to require analgesia, and total analgesic consumption of intravenous Nalbuphine over 24 hours. Also, patients were assessed intra-operatively for occurrence of shivering, hypotension, bradycardia, nausea, vomiting, prurutis, sedation (using *Ramsay Sedation Scale*), and any other side-effects.

Hypotension was defined as a decrease of mean blood pressure by more than 30% from baseline or a fall of systolic blood pressure below 90 mmHg, and was treated with 8mg IV dose of ephedrine and IV fluid as required. Meanwhile Bradycardia is defined as heart rate <60/min.

Statistical analysis

Analysis of data was conducted using SPSS system files (SPSS package version 18). Descriptive statistics including frequency, distribution, mean, and standard deviation were used to describe different characteristics. Kolmogorov- Smirnov test was used to examine the normality of data distribution. Univariate analyses including: t-test and Mann Whitney test was used to test the significance of results of quantitative variables. Chi-Square test and Fisher's Exact test were used to test the significance of results of qualitative variables. The significance of the results was at the 5% level of significance.

Results

As regards personal characteristics, mean age of group (D patients was 39.7 ± 9.9 years compared to 37.9 ± 8.6 years among group (P) patients. Male patients constituted 58.1% among group (D) and 45.2% among group (P). Moreover, patients of both groups had nearly equal mean weight; 79.4 ± 5.8 kg among group (D) and 76.9 ± 5.5 kg among group (P).

Similarly, mean surgical time were 56.2 ± 6.1 minutes and 59.9 ± 10.4 minutes respectively. No significant differences were observed between both groups regarding any of these variables (Table 1).

Concerning block characteristics, the mean time to reach T8 sensory level and mean time to bromage 3 were significantly shorter among group (D) patients (7.7 ± 1.5, 7.9 ± 1.5 minutes respectively)as compared to group (P), (10.6 ± 2.4, 10.3 ± 1.6 minutes respectively); (P<0.0001).

Meanwhile, the mean 2-segment regression time was significantly longer among group (D) patients (120.3 ± 13.8 minutes) compared to group (P), (92.3 ± 9.9 minutes); P<0.0001 (Table 2).

Analgesia requirements were significantly lowered among group (D) as compared to group (P) where a longer time was recorded to need first analgesia (381.0 ± 16.0 minutes, 259.0 ± 14.1 minutes respectively) and lower total analgesic consumption in 24 hours (8.0 ± 1.5 mg, 15.8 ± 2.2 mg respectively); (P<0.0001) Table 3.

Mean blood pressure assessed intra-operatively showed significantly lower results among group (D) compared to group (P) at all recorded timing except at 30 and 40 minutes intra-operatively (Table 4 and Figure 1).

	Group D (n=31)	Group P (n=31)	Significance
Age(year)			
Min-Max	25-56	22-50	*t*=0.779 P=0.439
Mean ± SD	39.7 ± 9.9	37.9 ± 8.6	
Gender			
Male	18 (58.1%)	14 (45.2%)	X^2=1.03 P=0.309
Female	13 (41.9%)	17 (54.8%)	
Weight (kg)			
Min-Max	68-88	65-85	*t*=1.724 P=0.09
Mean ± SD	79.4 ± 5.8	76.9 ± 5.5	
Surgical time (min)			
Min-Max	47-65	44-75	*t*=1.712 P=0.092
Mean ± SD	56.2 ± 6.1	59.9 ± 10.4	

t: t-test X^2: Chi-Square test

Table 1: Demographic data of studied patients in the studied groups.

	Group D (n=31)	Group P (n=31)	Significance
Time to T8 (min)			
Min-Max	6-10	6-14	Z=4.615 P<0.0001*
Mean ± SD	7.7 ± 1.5	10.6 ± 2.4	
2 segment regression (min)			
Min-Max	90-140	80-110	t=9.208 P<0.0001*
Mean ± SD	120.3 ± 13.8	92.3 ± 9.9	
Time to bromage 3 (min)			
Min-Max	6-10	8-12	Z=4.854 P<0.0001*
Mean ± SD	7.9 ± 1.5	10.3 ± 1.6	

t: t-test Z: Mann Whitney test *Significant at P ≤ 0.05

Table 2: Block characteristics among the studied groups.

Analgesia needs	Group D (n=31)	Group P (n=31)	Significance
First time to require analgesic (min)			
Min-Max	360-400	240-280	Z=6.81 P<0.0001*
Mean ± SD	381.0 ± 16.0	259.0 ± 14.1	
Total analgesic consumption (mg)			
Min-Max	6-10	10-18	Z=6.818 P<0.0001*
Mean ± SD	8.0 ± 1.5	15.8 ± 2.2	

Z: Mann Whitney test *Significant at P ≤ 0.05

Table 3: First time to require analgesic and total analgesic consumption.

Intra-operative time (minutes)	Mean blood pressure		t-test (P)
	Group D (n=31)	Group P (n=31)	
Baseline	96.7 ± 1.5	95.8 ± 2.1	0.057
5	84.9 ± 2.5	89.0 ± 3.2	<0.0001*
10	85.2 ± 3.4	89.3 ± 3.9	<0.0001*
15	75.4 ± 2.8	78.3 ± 2.3	<0.0001*
20	70.7 ± 4.8	78.5 ± 2.8	<0.0001*
25	66.7 ± 8.5	73.3 ± 2.5	<0.0001*
30	71.6 ± 4.9	71.7 ± 6.0	0.927
40	72.8 ± 4.8	72.7 ± 3.9	0.908
50	73.8 ± 2.5	75.5 ± 2.1	0.008*
60	73.7 ± 3.9	75.7 ± 2.5	0.018*
70	73.6 ± 3.3	75.3 ± 2.3	0.023*
80	73.1 ± 3.2	75.5 ± 2.4	0.001*

*Significant at P ≤ 0.05

Table 4: Intra-operative assessment of mean blood pressure among the studied groups.

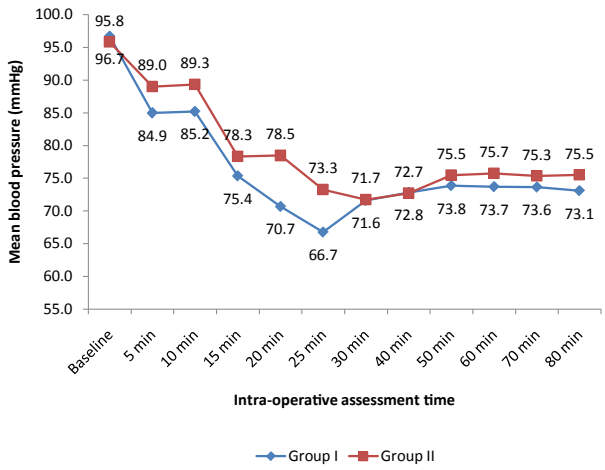

Figure 1: Mean blood pressure assessed intra-operatively among the studied groups.

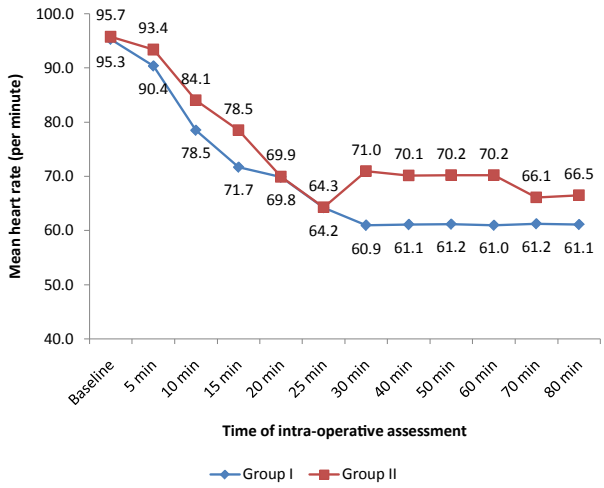

Figure 2: Mean heart rate assessed intra-operatively among the studied groups.

Similarly, the assessed heart rate intra-operatively showed significantly slower mean among group (D) compared to group (P) at all recorded timingexceptat20 and 25 minutes intra-operatively (Table 5 and Figure 2).

Occurrence of complications was significantly less encountered among group (D) patients (32.3%) I relation to group (P) patients (58.1%), P=0.041. The most frequent complications observed among group (D) were bradycardia (25.8%) and hypotension (25.8%). Meanwhile, the most frequent complications noticed among group (P) were vomiting (41.9%) and hypotension (19.4%).No significant differences were observed between both groups regarding any of the encountered complications except for shivering which was significantly more frequent among group (P) and bradycardia which was observed only among group (P). However sedation was absent in both studied groups (Table 6).

Discussion

Local anesthetics are commonly used for intrathecal anesthesia, but the major problem is the relatively short duration of action, thus early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as clonidine and midazolam, and others have been studied to prolong the effect of spinal anesthesia [1,2].

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α2-adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing and results in symoathlytic effect, causing hypotension, bradycardia, sedation, and analgesia [7].

Dexmedetomidine have been used in animal studies intrathecally with no adverse neurotoxicity or neurologic deficits [8,9]. Kanazi et al. used a small intrathecal dose of dexmedetomidine (3 μg), in combination with bupivacaine on humans for spinal anesthesia. Results showed a shorter onset of motor block and a prolongation in the duration of motor and sensory block with hemodynamic stability and lack of sedation [10].

Administration of an α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation [11]. At spinal cord level, activation of both α2-C and α2-ARs, in the neurons of superficial dorsal horn especially lamina II, directly reduces pain transmission, by suppressing the release of pro-nociceptive transmitter, substance P and glutamate from primary

Intra-operative time (minutes)	Mean blood pressure		t-test (P)
	Group D (n=31)	Group P (n=31)	
Baseline	95.3 ± 3.1	95.7 ± 2.2	0.537
5	90.4 ± 2.6	93.4 ± 2.6	<0.0001*
10	78.5 ± 3.1	84.1 ± 2.5	<0.0001*
15	71.7 ± 2.9	78.5 ± 3.1	<0.0001*
20	69.8 ± 2.4	69.9 ± 3.5	0.933
25	64.2 ± 3.1	64.3 ± 3.3	0.968
30	60.9 ± 2.1	71.0 ± 2.5	<0.0001*
40	61.1 ± 2.6	70.1 ± 2.0	<0.0001*
50	61.2 ± 2.2	70.2 ± 2.2	<0.0001*
60	61.0 ± 2.4	70.2 ± 2.3	<0.0001*
70	61.2 ± 2.3	66.1 ± 1.9	<0.0001*
80	61.1 ± 2.2	66.5 ± 2.8	<0.0001*

[P]: P value for Mann Whitney test P: P value for t-test *significant at P ≤ 0.05

Table 5: Intra-operative assessment of mean heart rate among the studied groups.

Complications	Group D (n=31)		Group P (n=31)		Significance
	No.	%	No.	%	
Absent	21	67.7	13	41.9	X^2=4.17 P=0.041*
Present	10	32.3	18	58.1	
#Type of complications					
Nausea	2	6.5	3	9.7	FE_P=0.631
Vomiting	0	0.0	2	6.5	FE_P=0.167
Shivering	2	6.5	12	41.9	X^2=8.96 P=0.003*
Bradycardia	8	25.8	0	0.0	FE_P=0.043*
Hypotension	8	25.8	6	19.4	X^2=0.09 P=0.766

X^2: Chi-Square test FEP: Fisher's Exact test *Significant at P ≤ 0.05
#Categories are not mutually exclusively
Test of significance is conducted between complication and those who are free of complications

Table 6: Intra-operative complications observed among the studied groups.

afferent terminals, and by hyperpolarizing spinal interneurons via G-protein-mediated activation of potassium channels [12,13].

In our study, we aimed to evaluate the role of dexmedetomidine added to heavy bupivacaine 0.5% intrathecally for lower abdominal surgeries.

In our study, the onset of the sensory block was earlier in group I (dexmedetomidine group), compared to group II. It ranged 7.7 ± 1.5, and was significantly earlier than group II (control group). Similar to our results, Ogan et al. showed an earlier significant peak sensory block in the dexmedetomidine group compared to the other groups [14]. Shukla et al. also showed that the onset time to reach peak sensory level was shorter in dexmedetomidine group as compared with the control group [13]. In our study, time to Bromage 3 was 7.9 ± 1.5 minutes, which was significantly less than in the control group. Shukla et al. showed that there was significant difference with the time to Bromage 3 [15]. Ogan SF et al. also showed significant reduction in the time to reach Bromage 1, compared to control group [14]. As regards the 2-segment regression, it ranged from 90-140 minutes in group I with a mean of 120.3 ± 13.8 minutes. Gupta et al. showed a mean of 125.6 ± 16.5 minutes by adding 5 μg dexmedetomidine intrathecally to ropivacaine [16]. Eid et al. showed a prolongation of 2-segment regression time in her study after adding 10 μg dexmedetomidine to bupivacaine [17]. Moreover, her study showed a dose dependent increase of 2 segment regression time by increasing the dose from 10 μg to 15 μg of intrathecal dexmedetomidine (103 ± 28.7 minutes, 200.6 ± 30.9 minutes respectively).

As regards the first time to require analgesia, and total analgesic consumption of nalbuphine in 24 hours, group I showed a significant increase in time to first analgesic dose (381.0 ± 16.0, versus 259.0 ± 14.1 in the control group), and significant decrease in the total analgesic consumption. In agreement with our results, Eid and colleagues, showed a significantly longer time to first analgesic request compared to control group [17]. Ashraf and colleagues also showed a significant longer time to first analgesic request (3.30 ± 0.87 hours,) compared to control group (0.23 ± 0.11 hours) [7].

As regards the intraoperative side effects, shivering occurred in 2 patients in the group I, and in 12 patients in group II. An explanation of the decreased incidence of shivering in the dexmedetomidine group, is the decrease shivering threshold by 2 degrees [18]. In agreement with our results, Usta et al. stated in their study that intravenously administered dexmedetomidine infusion inhibited shivering under spinal anaesthesia [19]. Karaman and colleagues showed that intravenous loading dose followed by infusion of dexmedetomidine decreased incidence of shivering compared to placebo. Moreover, the intensity of shivering in the 3 observed cases was lower in the dexmedetomidine group than in the placebo group (P>0.05) [20].

Bradycardia occurred in 8 cases compared to none of the study patients in the control group. Bradycardia in the dexmedetomidine group is believed to be due to postsynaptic activation of central alpha 2 adrenoceptors (α2-ARs) results in sympatholytic effect, leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery [21].

Dexmedetomidine evokes a biphasic blood pressure response: A short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different α2-AR subtypes: the α-2B AR is responsible for the initial hypertensive phase, whereas hypotension is mediated by the α2A-AR. The initial response lasts for 5 to 10 minutes and is followed by a decrease in blood pressure of approximately 10% to 20% below baseline and a stabilization of the heart rate, also below baseline values; both of these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulating effects [22].

In our study, 8 (25.8%) patients developed hypotension starting from 20 minutes following the spinal injection in group I, versus 6 (19.4%) in group II with insignificant differences between the two groups. However, it responded well to intravenous ephedrine and fluid. In agreement with our results, Kanazi et al. showed insignificant effect of dexmedetomidine on mean blood pressure when added to intrathecal bupivacaine [5]. Al-Mustafa and colleagues, using 5 *μg,* and 10 *μg* dexmedetomidine, found a dose dependent, but still insignificant, decrease on the mean blood pressure when compared to the bupivacaine (control) group [4].

Nausea with or without vomiting was associated with the hypotensive episodes. This may be explained by the fact that increased vagal activity after sympathetic block causes increased peristalsis of the gastrointestinal tract, which leads to nausea [23]. In agreement with our results, kang et al. showed that incidence of intraoperative nausea during spinal anaesthesia for ceasarean section correlated well with hypotension [24].

Dexmedetomidine at a dose of 5 *μg* provided earlier sensory and motor blockade, less postoperative analgesic requirements, less shivering for patients under intrathecal anaesthesia for lower abdominal surgery with no sedation.

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