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Spinal Bupivacaine-Dexmedetomidine versus Bupivacaine-Fentanyl for lower Limb Amputation Surgery. Effects on Early Stump and Phantom Pain

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Background: In neuroaxial anesthesia, there was many adjuvants used with the purpose of increasing anesthesia duration and reduction of postoperative analgesia.

Objective: comparison between dexmedetomidine and fentanyl when added to 0.5% hyperbaric bupivacaine, for lower limb amputation on early stump and phantom pain after spinal anesthesia.

Patients and Methods: Ninety patient arranged for lower limb amputation surgery were randomly allocated into three groups (each 30 patients). Each patient received 2 ml of hyperbaric bupivacaine (0.5%) plus 0.5 ml normal saline in control group (Group B) or 5μ dexmedetomidine diluted in 0.5 ml normal saline in BD group or 25 μ fentanyl diluted in 0.5 ml normal saline in BF group. Anesthesia, analgesia, sedation, hemodynamic changes, adverse effects and post-operative pain up to one month were recorded.

Results: The studied groups showed no significant differences regarding demographic characteristics and hemodynamic (heart rate and mean arterial pressure). Patients in group BD had significant increase of sensory and motor block time compared to BF B groups. Post-operatively, there was a significant decrease of pain in BD group in the first 24 hours when compared to control or BF group. The postoperative mean total consumption of analgesics during the first day was significantly decreased in BD when compared to BF and control groups.

Conclusions: dexmedetomidine (5μg) represents a good alternative to fentanyl (25μg) as a spinal adjuvant to bupivacaine in surgery for the lower limb.

Keywords: Dexmedetomidine; Hyperbaric bupivacaine; Fentanyl; Phantom . pain; Stump pain.

Introduction

Multiple pathologic processes developed after lower limb amputation surgery such as pain of phantom limb and stump. The incidence of developing phantom pain and stump pain varying from 49% to 83% in various trials[1]. Phantom pain is a neuropathic pain, tingling or sharp throbbing, arising from a part of the body which is no longer there. On the other side, stump pain, is a nociceptive pain arising from the stump and usually resolves after a few weeks as the wound heals [2].

Management of postoperative pain is a challenge issue facing anesthesiologists in daily practice, irrespective of marked advances in pharmacotherapy of PO pain[3] .

Searching literature, authors could identify trials, which studied different aesthetic maneuvers and adjuvant drugs on the incidence of postoperative phantom pain and sensation. However, the ideal safe and effective adjuvant is not exist yet.

Aim of the work: to investigate the effect of adding dexmedetomedine (5μg) or fentanyl (25μg) to hyperbaric bupivacaine (0.5%) in spinal anesthesia for lower limb amputation surgery on early stump and phantom limb pain.

Patients and Methods:

A prospective, controlled, randomized double-blind study was carried out from April 2016 to November 2018 at Al-Azhar University Hospital (New Damietta). Patients age 20 years or more, of ASA class I to III, who had no previous amputation and who had were psychologically normal were included in the study. Ninety patients fulfilling the inclusion criteria and who were planned for lower limb amputations constitute the study participants. On the other side, patients who refused to participate, those who had contraindication to regional anesthesia (e.g. bleeding diathesis, or local infection), those with significant coexisting diseases (e.g. kidney, heart, liver), those with known allergy to any of allocated drugs, patients with chronic pain or neuropathy, or those with long-term opioid use were excluded from the study.

The study protocol was approved by the Research/Ethics Committee, Faculty of Medicine, Al-Azhar University, and an informed written consent was signed by each patient.

Patients were classified randomly into three equal groups. The randomization was done after generating randomization list by a personal computer and each number was preserved in a sealed envelope, which opened by a nurse (not participating in the study) just before anesthesia.

Syringes containing the study drugs were prepared by an anesthetist who carried no role in the study, and handed to the anesthesiologist doing the procedure who was unaware of the drugs. Each Syringe was filled with 2.5 ml of drugs.

Bupivacaine group (Group B). Patients was receive intrathecal hyperbaric bupivacaine (0.5%) (sunnypi-vacaine) 10 mg plus 0.5 ml of normal saline.

Bupivacaine-dexmedetomidine group (Group BD). Patients was received intrathecal hyperbaric bupivacaine (0.5%) 10 mg plus 5μg dexmedetomidine (Precedex, Hospira Inc., USA) in 0.5 ml of normal saline (prepared by diluted 1 ml of dexmedetomidine in 10 ml normal saline).

Bupivacaine-fentanyl group (Group BF). Patient was received intrathecal hyperbaric bupivacaine (0.5%) 10 mg combined with fentanyl (fentanyl citrate, Hospira Inc., USA) 25μg in 0.5 ml of normal saline (prepared by diluting 2 ml of fentanyl in 4 ml normal saline).

Pre-anesthetic assessment was done prior to the surgery. Assessment was done regarding history and complete general and systemic examination. Routine laboratory studies include CBC, liver function, renal function, random blood sugar, and coagulation profiles were taken and ECG was done. After confirmation of fasting hours, patient was brought to operating theatre. Preoperative check list included anesthesia equipments (machine, systems for oxygen delivery, airways, crash cart and all equipments for resuscitation) and all were kept ready. The patient was monitored regarding HR, electro-cardiography, SpO_2, blood pressure and RR. Readings were recorded and kept at the baseline data. Intravenous access achieved by insertion of 18G cannula, preloaded by 10 ml/kg of Ringer's lactate before spinal anesthesia. Subarachnoid block was done under complete aseptic technique and the drug administration carried out at L3–4 or L4-5 intervertebral spaces using 25-gauge spinal needle, while the patient was in the sitting position. The aesthetics were injected at a rate of 2 ml/sec, and all patients converted to the supine position.

The primary outcome was to assess the time of the first occurrence of stump or phantom limb pain in the first postoperative month.

Mean numeric rating scale (NRS) values for the severity of pain during the postoperative period and every week after surgery was recorded for one month. Patients were instructed to record the number of days in each week with pain symptoms during the month after surgery and any analgesic

medications were recorded, and the effect of pain on daily life or sleep at night was documented.

Postoperative stump or phantom limb pain were managed by tricyclic antidepressant (Amitriptyline; starting at 10 mg or 25 mg every night for elderly and younger patients respectively, with a maximum dose of 125 mg/day). Alternatively, anticonvulsant (Gabapentin; starting at 300 mg PO per day to maximum of 900-1200 mg/day). Patients who were not responding to a single drug, combination of tricyclic antidepressant and anticonvulsant were used.

Secondary outcomes included sensory testing (pinprick test) and dermatomal levels were tested every 2 min until the highest level had reached. When T6 sensory blockade level achieved, surgery was allowed. Assessment of sensory level was done every 10 min until the point of two segment regression of the block was reached. Further assessment was done at 20-min intervals until the recovery of S1 dermatome. Motor block was tested by modified "Bromage scale" [4]

Oxygen (10 L/min) was administered via a face mask and hemodynamic variables i.e. heart rate (HR), Mean arterial pressure (MAP) and (SpO_2) were noted by an anesthetist blinded to the patient group 5 min before performed spinal anesthesia and every 5 minutes for 30 minutes after intrathecal injection then every 10 minutes till the termination of surgery. If Mean arterial pressure (MAP) decreased by 20% below the baseline or SBP measured < 90 mmHg or dropped by more than 30% from baseline, hypotension was confirmed and treated by incremental IV doses of ephedrine 5mg and IV fluid as required. Also, if HR became < 50 beats/min, 0.5 mg of atropine sulphate was injected intravenously. These parameters were recorded every 10 min in the post-anesthesia care unit (PACU) for one hour then at 4-hour intervals postoperatively in the ward for 24 hours.

Side effects (e.g. sedation, dizziness, pruritus, respiratory depression, hemodynamic instability or postoperative nausea and vomiting) were documented. In addition, time for postoperative analgesia defined as the interval between intrathecal injection and the first requirement for analgesic supplement.

Sedation was assessed intraoperatively every 15 min after drug injection and up to 100 min postoperatively by using Ramsay sedation score [4].

Patients was educated preoperatively to use the Numerical rating scale (NRS)[5] for pain assessment. Postoperative pain score was assessed at 4 hours interval for 24 hours using the NRS. For PO pain, paracetamol 1 g was given IV every 8 hours and if pain persists, pethidine 25 mg IV was administered.

Statistical Analysis: Statistical analysis: mean and standard deviation were calculated for numerical data, while frequencies and percentages were calculated for categorical variables. Groups were compared by one way analysis of variance and chi square tests. A p value < 0.05 was set as the level of significance.

Results

A total of 90 patients were included and classified into three equal groups (B[control], bupivacaine-fentanyl [BF] and bupivacaine-dexmedetomedine [BD]). No significant difference between groups was found regarding patient's age, gender, weight or and height. In addition, baseline, intraoperative and postoperative HR values did not differ significantly among studied groups. Bradycardia was observed more in BD than BF and B groups, but the difference was insignificant.

Baseline, intra- and post-operative values of MAP were statistically non-significant between studied groups. Hypotension recorded more in BD than BF and B groups, but this was statistically insignificant, and the total amount of ephedrine requirements was not statistically different between groups.

The sensory was presented in table (1) and there was no significant difference between BD, BF and B groups in the highest level of block reached. Block regression was significantly slower in BD when compared to BF or B groups. Also, time of two segment and S1 regression were significantly longer in BD group. The time to reach Bromage 3 was statistically insignificant among studied groups. However, the regression to Bromage 0 was significantly slower in BD group and finally, the time to ask analgesic was significantly longer in BD when compared to BF or B groups.

Nausea and/or vomiting reported in four patients in BD and three patients in BF group compared to two patients in control group, all there was no significant difference between groups. Similarly, there was insignificant difference between groups as regard to sedation score.

Post-operative NRS showed a significant decrease in BD group in the first 24 hours, when compared to B or BF groups (Table 2). The postoperative mean total consumption of analgesia was significantly decreased in BD group compared to B or BF groups (table 3).

There were no significant difference between the studied groups in the incidence or severity of the phantom pain in the first month post-operative (table 4). The phantom pain affect the ability of sleep of the patients, connection to community and their daily activities to the same degree in the three studied groups in the first postoperative month with no significant difference.

Table (1): Characteristics of spinal block in the studied groups

	Group B(n=30)	Group BF(n=30)	Group BD(n=30)	F	P
Time to reach T 10 (min)	5.07±.0.28	5.04±.0.30	4.92±0.23	2.667	0.075
Time to reach peak sensory block (min)	10.03±0.53	10.15±0.46	10.04±0.38	0.613	0.54
Time to reach complete motor block (Bromage 3) (min)	9.29±0.42	9.02±0.35	9.15±0.51	2.908	0.06
Time to sensory regression to S1 segment (min)	142.86±7.69	188.13±7.51	291.53±11.62	2083.532	0.000*
Time to motor block regression (Bromage 0) (min)	115.97±6.82	153.03±6.90	244.33±12.50	1567.237	0.000*

Table (2): NRS and Post-operative analgesic requirement in the first 24 hours among studied groups

	Group B (n=30)		Group BF (n=30)		Group BD(n=30)		F	P value
	Mean	SD	Mean	SD	Mean	SD		
NRS Preoperative	5.13	1.074	4.93	1.172	4.97	1.129	0.27	**0.763**
NRS 1-hr postop.	1.07	0.785	1.00	0.743	0.63	0.490	3.48	0.035*
NRS 4-hr postop.	4.07	1.081	3.43	0.935	2.03	1.189	28.19	0.000*
NRS 8-hr postop.	4.83	0.913	4.33	0.994	4.17	0.791	4.42	0.013*
NRS 12-hr postop	4.53	1.042	5.10	0.960	4.23	0.858	6.35	0.00٣*
NRS 16-hr postop	4.13	1.332	4.37	0.999	3.63	0.928	3.47	0.035*
NRS 20-hr postop	3.87	1.167	3.80	1.064	3.20	0.961	3.55	0.03٣*
NRS 24-hr postop	3.13	1.008	3.07	0.868	2.53	0.681	4.35	0.01٦*

Table (3): paracetamol and pethidine dosage among the three studied groups. Data are presented as mean and Stander deviation

	Group B (n=30)		Group BF(n=30)		Group BD(n=30)		F	P Value
	Mean	SD	Mean	SD	Mean	SD		
Paracetamol (g)	3.63	0.669	3.60	0.814	3.10	0.759	4.767	0.011*
Pethidine(mg)	26.67	26.207	22.50	20.075	11.67	17.036	3.910	0.024*

Table (4): NRS value and the incidence of phantom pain in the first month postoperatively among the three studied groups

	Group B (n=30)		Group BF (n=30)		Group BD (n=30)		F	P
	Median	SD	median	SD	median	SD		
1st week	4(0-4)	0.774	5(0-5)	0.964	4(0-4)	0.913	0.395	0.675
2nd week	4(3-7)	1.137	4(2-6)	0.960	4(3-7)	1.022	2.835	0.064
3th week	4(2-7)	1.241	4(3-7)	1.694	3(3-6)	1.098	0.873	0.421
4th week	4(0-6)	1.306	4(2-6)	1.269	4(2-6)	1.143	0.779	0.462
Phantom pain	16 (53.3%)		17 (56.7%)		15 (50%)		0.26#	0.87

Chi square test

Discussion

Different adjuvants added to regional anesthetics aiming to increase the action duration and diminish the required dose with significant reduction of post-operative pain. Adjuvant such as opioids in small dose offered good analgesia as its systemic use with reduction of systemic hazardous effects. Small dose of fentanyl added to spinal anesthesia could lead to rapid onset of action and better surgical block with rapid motor function recovery which permits for earlier disposition [5]. Dexmedetomidine is the drug which has higher affinity to α2 adrenoreceptors (10 times more than clonidine) [6] which causes it to be a more effective sedative and analgesic agent than clonidine without cardiovascular side effects from α1 receptor activation[7]. The intrathecal dexmedetomidine prolongs the sensory block when combined with spinal bupivacaine and produces its analgesic effect by inhibiting the release of transmitters of C fibers and by hyperpolarization of postsynaptic dorsal horn neurons [8,9].

Prolongation of motor block by α2 adrenoreceptor agonists might be due to impairment of excitatory amino acids release from spinal interneuron [10]. Administration of intrathecal α2-receptor agonists had antinociceptive effects for both somatic and visceral pain [1].

This study has shown that, adding 5μg dexmedetomidine to hyperbaric bupivacaine prolongs significantly sensory and motor blockade. In addition, it provided good quality of intraoperative analgesia and hemodynamic stability. Previously, in clinical study, intrathecal dexmedetomidine (3μg) added to bupivacaine significantly reduce the onset of motor block and increase sensory and motor block duration with hemodynamic stability and absence of sedation [11].

Al-Ghanem et al.[12] evaluated the effect of 5μg dexmedetomidine versus 25μg fentanyl intrathecal addition to 10mg isobaric bupivacaine in vaginal hysterectomy and showed that, dexmedetomidine significantly prolongs motor and sensory block when compared with fentanyl.

The mean time taken for onset of Bromage 3 was insignificant among studied groups and these results are comparable to Gupta et al[13]. However, the mean time taken for regression to Bromage 0 was significantly longer in dexmedetomedine group. Comparable results were reported by Al-Ghanem et al.[12]. In addition, Al Mustafa et al. [14] used different doses of dexmedetomidine (5 μg and 10μg) and reported that, dexmedetomedine prolongs spinal anesthesia duration in a dose-dependent manner.

In the present study, the duration of analgesia is prolonged in BD group and the mean time for rescue analgesia was significantly longer. A wide variation was reported regarding the time for first rescue analgesia in previous studies. For example, Gupta et al.[13], Eid et al.[15] reported dose-dependent prolongation effect on motor and sensory block with reduction of analgesic needs as intrathecal dose of dexmedetomedine increased (5, 10, and 15μg).

The action of fentanyl was explained by its combination to opiate receptors in the brain and spinal cord, as it constrains the nociceptive transmitter substance P release [16]. The local anesthetics and fentanyl combination expands the quality and increase the regional anesthesia duration[14]. In addition, Jain et al. [17] stated that fentanyl has high lipid solubility that enables rapid penetration of neural tissue with subsequent rapid onset of action. Siddik-Sayyid et al. [18] showed that the duration of spinal analgesia was significantly prolonged by the addition of fentanyl, and there was a dose-dependent effect of fentanyl on the duration of analgesia. Cowan et al. [19] found that consumption of postoperative analgesics was significantly reduced in intrathecal fentanyl group when compared with bupivacaine control group.

Present study demonstrated that hemodynamic changes (hypotension & bradycardia) did not show differ significantly between groups. Philipp et al.[20] showed that there are inhibition of sympathetic activity by activation of Postsynaptic α2-adrenoceptors in the central nervous system and thus can reduce heart rate and blood pressure but the hemodynamic stability in current work may be attributed to small dose of dexmedetomidine or the low sensory block level at T10 (which needed to be achieved in lower limb amputation surgery) [21]. Comparable to the results of the present study, Shukla et al.[22] demonstrated that the intrathecal addition of dexmedetomidine (5μg) to bupivacaine is associated with hemodynamic stability in lower limb surgery and the sensory level was Tl0. On the other hand, Al Ghanem et al.[12] reported a decrease of heart rate and blood pressure with intrathecal dexmedetomidine (5μg) in genealogical procedures. It may be attributed to high level required in this procedures (T4).

The side effects (e.g. nausea and/or vomiting, hypotension, bradycardia, decreased oxygen saturation, pruritis and shivering during intra- and post-operative period) revealed non-significant difference between studied groups. Similar observations were reported by Sunil et al.[23], Gupta et al.[13], and El-lakany[24].

In the present work, minimal sedation was recorded and there was no significant difference between groups, as reported by Mahendru et al. [25] and this could be attributed to the small dose used in this study. On the other hand, the higher dose (15μg) of dexmedetomidine used intrathecally by Eid et al. [15] showed significantly higher sedation scores which can be beneficial for patients undergoing lengthy complex surgeries.

Current work reported that the mean total consumption of analgesia in first postoperative day was significantly lower in dexmedetomedine group. Mahendru et al. [25] found that intrathecal addition of dexmedetomedine (5μg) as adjuvant to hyperbaric bupivacaine prolong postoperative analgesic duration and associated with low analgesic consumption.

In the present study, there were no significant changes in the incidence of phantom pain after surgery within first 4week between the three groups. Jensen et al. [26] show comparable results and documented that phantom pain developed in 72% of adult patients after amputation within 8 days. Other study showed that phantom pain occurs immediately after amputation and may last for long time [27].

Current study founded that the addition of dexmedetomidine (5μg) to intrathecal bupivacaine affect the early post-operative pain by its nociceptive action but did not affect the incidence or severity of phantom pain and sensation in one-month post-operative. The difference in the efficacy of dexmedetomidine on the early post-operative pain and late phantom pain may be due to presence of different multifactorial interactions affecting the CNS, peripheral nerves, sympathetic system, genetic predisposition and psychological factors which included in the existence of phantom pain and sensations [28]. Katz and Melzack[29] reported that pre-emptive analgesia especially peripheral one may prevent the onset of long-lasting pain by early intervention before the occurrence of acute pain. The peripheral anesthesia prevents the peripheral nociceptive input from reaching higher centers and spinal cord, however the pre-emptive analgesia does not affect onset of phantom pain or phantom sensation after amputation.

Previous study demonstrated that the regional anesthesia may reduce the acute and chronic pain incidence by preventing the establishment of central sensitization. So, the postoperative local anesthetic infusion may prevent the occurrence of central sensitization due to the effect of neurogenic inflammatory response of the surgery may be a source of noxious inputs to the CNS for a long time[30].

Gehling et al. showed that the use of epidural block preoperatively might be effective prophylaxis for phantom pain but it did not prevent completely the phantom pain it only increases the patients number who recall less pain postoperatively [31].

Another study founded that the patients with epidural anesthesia or peripheral nerve block within the first week recalled less pain in comparison with patients who had spinal anesthesia. Although the epidural block reduce pain intensities of the phantom pain after amputation during first postoperative week, this advantage disappear at 14 to 17 weeks after amputation [1].

Ong et al. [32] evaluate the efficacy of spinal anesthesia on the post-operative phantom pain and show that patients with spinal and epidural anesthesia had milder form of pain comparative to general anesthesia in the first week.

In conclusion, dexmedetomidine (5μg) appear to be a good alternative to 25μg fentanyl as an adjuvant to spinal bupivacaine in lower limb surgery. It offers intraoperative hemodynamic stability, good intra- and post-operative analgesia, and minimal side effect with reduction of post-operative analgesic requirements. It also prolongs the duration of sensory and motor block. However, it had not any effect on the incidence of phantom limb pain.

References

1. **Sahin SH, Colak A, Arar C, Tutunculer E, Sut N, Yilmaz B, et al.** A retrospective trial comparing the effects of different anesthetic techniques on phantom pain after lower limb amputation. Curr Ther Res Clin Exp. **2011**; 72(3):127-37.

2. **Subedi B and Grossberg GT.** Phantom limb pain: mechanisms and treatment approaches. Pain Res Treat. **2011**; 2011:864605.

3. **Desmond DM, Maclachlan M.** Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. Int J Rehabil Res. **2010**; 33(3):279-82.

4. **Elshalakany N, El-Shaer A, Rabie A, Moharram A, Elsofy A.** Dexmedetomidine as adjuvant to hyperbaric bupivacaine in spinal anesthesia for inguinoscrotal surgery. Ain-Shams J Anaesthesiol. **2017**;10(1):264-71

5. **Weeks SR, Anderson-Barnes V, Tsao JW.** Phantom limb pain: theories and therapies. Neurologist. **2010**; 16(5):277–286.

6. **Nikolajsen L, Ilkjaer S, Christensen JH.** Randomized trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet **1997**; 350:1353-1357.

7. **Ong BY, Arneja A, Ong EW.** Effects of anaesthesia on pain after lower-limb amputation. J Clin Anesth. **2006**; 18(8):600-4.

8. **Schley MT, Wilms P, Toepfner S.** Painful and non-painful phantom and stump sensations in acute traumatic amputees. J Trauma. **2008**; 65:858-64.

9. **McQuay HJ and Moore RA.** eds. Epidemiology of chronic pain. Seattle: IASP Press; **2008**.

10. **Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R**. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. J Anaesthesiol Clin Pharmacol. **2013**; 29 (4): 496-502.

11. **Al-Mahrezi A.** Towards Effective Pain Management: Breaking the Barriers. Oman Med J. **2017**;32(5):357-8.

12. **Al-Ghanem SM, Massad IM, Al Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, et al.** Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. Am J Appl Sci. **2009**; 6: 882–7.

13. **Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK.** A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. J Anaesthesiol Clin Pharmacol. **2011**; 27(3):339-43.

14. **Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, et al.** Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi Med J. **2009**;30(3):365-70.

15. **Eid HE, Shafie MA, Youssef H.** Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine. Ain Shams J Anesthesiol. **2011**; 4:83–95.

16. **Kanjhan R**. Opioids and pain. Clin Exp Pharmacol Physiol. **1995**; 22:397–403.

17. **Jain K, Grover VK, Mahajan R, Batra YK.** Effect of varying doses of fentanyl with low dose spinal bupivacaine for caesarean delivery in patients with pregnancy-induced hypertension. Int J Obstet Anesth. **2004**; 13:215–20.

18. **Siddik-Sayyid SM, Aouad MT, Jalbout MI, Zalaket MI, Berzina CE, Baraka AS**. Intrathecal versus intravenous fentanyl for supplementation of subarachnoid block during caesarean delivery. Anesth Analg. **2002**; 95:209–13.

19. **Cowan CM, Kendall JB, Barclay PM, Wilkes RG.** Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. Br J Anaesth.**2002**; 89:452–8.

20. **Philipp M and Hein L.** Adrenergic receptor knockout mice: distinct functions of 9 receptor subtypes. Pharmacol Ther **2004**; 101: 65-74.

21. **Blake DW.** Dexmedetomidine and hemo-dynamic responses to simulated hemorrhage in heart failure. Anesth Analg **2000**; 91: 1112-1117.

22. **Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C.** Comparative study of intrathecal dexmedeto-midine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. J Anaesthesiol Clin Pharmacol **2011**; 27(4):495-9.

23. **Sunil BV, Sahana KS and Jajee PR.** Comparison of dexmedetomidine, fentanyl and magnesium sulfate as adjuvants with hyperbaric bupivacaine for spinal anaesthesia: a double blind controlled study. Int J Recent Trends Sci Tech **2013**; 9:14–19.

24. **Abdelhamid SA and El-Lakany MH.** Intrathecal dexmedetomidine: Useful or not? J Anesth Clin Res. **2013**; 4:351.

25. **Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R.** A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. J Anaesthesiol Clin Pharmacol. **2013**; 29 (4): 496-502.

26. **Jensen TS, Krebs B, Nielsen J, Rasmussen P.** Phantom limb, phantom pain and stump pain in amputees during the first six months following amputation. Pain. **1983**; 17: 243-256.

27. **Melzack R.** Phantom limb pain: implications for treatment of pathologic pain. Anesthesiol. **1971**; 35: 409-419.

28. **Postone N.** Phantom limb pain A review. Int J Psychiatry Med. **1987**; 17: 57-70.

29. **Katz J and Melzack R.** Pain 'memories' in phantom limbs: review and clinical observations. Pain **1990**; 43: 319-36.

30. **Cousins M J, Power I and Smith G.** Labat lecture: pain—a persistent problem. Reg Anesth Pain Med.**2000**; 25:6–21.

31. **Gehling M, Tryba M**. Prophylaxis of phantom pain: is regional analgesia ineffective? Schmerz. **2003**; 17:11-19.

32. **Ong BY, Arneja A, Ong EW**. Effects of anesthesia on pain after lower-limb amputation. J Clin Anesth. **2006**; 18(8):600-4.