ORIGINAL ARTICLE

A comparative study of ketorolac vs dexmedetomidine to attenuate tourniquet induced cardiovascular response in lower limb surgery

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ABSTRACT

Background & Aims: This prospective, randomized, double-blind study was undertaken to compare the effect of ketorolac or dexmedetomidine to attenuate tourniquet induced rise in blood pressure and heart rate in lower limb orthopedic surgery under general anesthesia.

Methodology: One hundred, American Society of Anesthesiologist class I and II patients for elective lower limb surgery under general anesthesia were enrolled, to receive either 30 mg ketorolac (Group KL) or 0.5 μg/kg dexmedetomidine (Group DX) intravenously before inflation of tourniquet. Systolic blood pressure, diastolic blood pressure and heart rate were recorded before induction of anesthesia and at 0, 15, 30, 45, 60, 75 min after tourniquet inflation, just before tourniquet deflation and at 15 min after tourniquet deflation. Incidence of tourniquet induced hypertension, postoperative analgesic requirements, patient satisfactory score and any side effects were also recorded.

Results: Systolic blood pressure, diastolic blood pressure and heart rate significantly increased at 45, 60, 75 min after tourniquet inflation and just before tourniquet deflation in ketorolac group as compared to dexmedetomidine group ($P < 0.05$). Incidence of tourniquet induced hypertension was more with ketorolac than with dexmedetomidine ($P=0.01$). The total diclofenac consumption during first 24 hrs of postoperative period was significantly less with ketorolac compared to dexmedetomidine ($P=0.001$).

Conclusion: Dexmedetomidine is more effective in attenuating tourniquet induced cardiovascular responses when compared to ketorolac.

Key words: Ketorolac; Dexmedetomidine; Hemodynamics; Postoperative analgesia

Citation: Kaur S, Sunita. A comparative study of ketorolac vs dexmedetomidine to attenuate tourniquet induced cardiovascular response in lower limb surgery. Anaesth Pain & Intensive Care 2016;20(4):404-410

Received: 13 Sep 2016; **Reviewed:** 16, 20 Sep 2016**; Corrected:** 22 Sep 2016**; Accepted:** 2 Oct 2016

INTRODUCTION

Pneumatic tourniquet was introduced by Harvey Cushing in 1904.[1] Its use has now become essential in orthopedic surgery to provide bloodless surgical field. Modern pneumatic tourniquets are designed to minimize the incidence of complication; still pain and hypertension, observed 30-60 minutes after inflation of the tourniquet are very common.[2]

A rise in systolic or diastolic arterial pressure of more than 30% in patients with a tourniquet inflated for more than 30 min has been termed as tourniquet induced hypertension.[3] Tourniquet induced hypertension occurs more during lower limb surgeries and under general anesthesia. It could be serious in patients with cardiovascular diseases, glaucoma and neurological diseases.

It has been suggested that tourniquet induced hypertension and tachycardia represents activation

of the sympathetic nervous system in response to the development of tourniquet pain.[4] Various drugs like ketamine,[5] remifentanil,[6] dextromethorphan[7] and clonidine[8] have been used intravenously to attenuate tourniquet induced hypertension. The search for the ideal agent continues and led us to try these two drugs, ketorolac and dexmedetomidine.

Ketorolac tromethamine is a NSAID with a potent analgesic efficacy. Many studies suggest the role of ketorolac in reducing tourniquet pain when used intravenously.[9,10] Dexmedetomidine, a highly selective $\alpha_2$adrenoreceptor agonist, has been the focus of interest for their potent sympatholytic, analgesic and hemodynamic stabilizing properties with lack of respiratory depression effect.[11]

Till date no studies have compared dexmedetomidine with ketorolac, for their effect on attenuating tourniquet induced hypertension and postoperative analgesia. Our primary aim was to test the hypothesis that intravenous ketorolac when given before inflation of tourniquet, decrease the tourniquet induced cardiovascular responses and postoperative analgesic requirement and to compare it with dexmedetomidine in patients undergoing lower limb surgery under general anesthesia. Patient satisfaction score and side effects if any were studied as secondary objectives.

METHODOLOGY

After obtaining the permission of appropriate authority of the institute and written informed consent from patients, hundred patients scheduled for elective lower limb surgery at our University Hospital were enrolled in the study. The study was designed as a prospective, randomized and double-blinded, study.

Patients of either gender, aged between 25 and 55, ASA physical status -I or II, scheduled for elective lower limb orthopedic surgery with use of pneumatic tourniquet under general anesthesia were included in the study. Obese patients (BMI > 30 kg/m^2), those having an allergy to study drugs, patients with poorly controlled hypertension, on chronic analgesic medication, opioids or substance abuse, polytrauma and crush injuries, peripheral vascular disease and deep vein thrombosis, history of sickle cell disease or trait, significant cardiovascular, respiratory, renal, hepatic dysfunction, neurological or psychiatric disease or on concurrent medication were excluded. Patient or surgeon refusal also resulted in exclusion from the study.

Randomization to one of the two equally distributed groups was done by computer-generated random numbers and allocation to each group was done from opaque sealed envelopes. The study drugs either ketorolac 30 mg or dexmedetomidine 0.5 μg/kg as per the sealed envelope instruction, was loaded into a 20 ml syringe and normal saline was added to achieve a volume of 20 ml by an independent anesthesiologist blinded to the study and the syringe was labeled as 'study drug'.

The patients were divided randomly into two groups of 50 patients each.

Group KL: The patients received ketorolac 30 mg intravenously over 10 minutes, prior to inflation of tourniquet.

Group DX: The patients received dexmedetomidine 0.5 μg/kg intravenously over 10 min, prior to inflation of tourniquet.

All the patients in both the groups received oral lorazepam 2 mg orally at night of the operation. Demographic data were recorded. On arrival at the operating-theatre, routine monitoring like electrocardiogram, pulse oximetry, noninvasive blood pressure, capnography and bispectral index (BIS) were established. The BIS electrodes were placed on the forehead and on the lateral angle of orbit and connected to BIS monitoring system. The IV access was secured with 18 G cannula on the dorsum of the hand.

All the patients were premedicated with glycopyrrolate 0.2 mg 30 minutes before induction. After proper pre-oxygenation for 3minutes, general anesthesia was induced with intravenous propofol (2 mg/kg) and fentanyl (2 μg/kg). Intubation of trachea was facilitated by suxamethonium 1 mg/kg.

Anesthesia was maintained with 50% nitrous oxide, 50% oxygen and isoflurane 1%. Muscle relaxation was maintained with i.v. vecuronium bromide 0.08 mg/kg followed by additional

top-up doses of 0.02 mg/kg, using a nerve stimulator to maintain muscle relaxation at <2 twitches (using a train-of-four sequence) of adductor pollicis muscle measured every 15 min. Bispectral index was used to monitor the level of anesthesia and BIS maintained between 40 and 60 with adjustment of isoflurane concentration. The lungs were mechanically ventilated to maintain end tidal CO_2 between 35 to 45 mmHg.

The pneumatic tourniquet, over cotton layer was applied on the thigh of the operated side after exsanguinations of the limb by crepe bandage. The tourniquet was inflated to a pressure 100 mmHg

above patient's baseline systolic blood pressure (SBP).

Additional dose of fentanyl 50-100 μg was administered for intraoperative analgesia. If SBP rose to 200 mmHg or higher, such patients would be excluded from the study. All patients received fluid in the form of Ringer lactate as per standardized calculation.

After surgery, the tourniquet was deflated and the patients were extubated after reversal of neuromuscular blockade with intravenous 0.05 mg/kg neostigmine and 0.01 mg/kg glycopyrrolate, and the patients were shifted to post anesthesia care unit (PACU).

In PACU, Pain score were noted by using the verbal rating scale of 0-10, 0 being no pain, 1-3 mild, 4-6 moderate, and 7 or more as severe pain.[12] Patients with VRS score of 5or more received infusion of injection diclofenac 1 mg/kg as rescue analgesic.

The following observations were recorded by the attending anesthesiologist unaware of study medication;

1. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and bispectral index (BIS) were recorded, just before induction of anesthesia (baseline), 0 min (just before tourniquet inflation), 15, 30, 45, 60, 75 min after tourniquet inflation, just before tourniquet deflation, and 15 min after tourniquet deflation.
2. Incidence of tourniquet-induced hypertension (defined as an increase of systolic or diastolic blood pressure >30% from baseline).
3. Time to first postoperative analgesic requirement and postoperative total dose of diclofenac required, during the first 24 h after surgery.
4. Postoperative side effects such as sedation graded on five point scale[13] (1. Fully awake and oriented, 2. Drowsy, 3. Eyes closed, arousable to command, 4. Eyes closed, arousable to physical stimulation and 5. Eyes closed, unarousable to physical stimulation), nausea and vomiting, hypotension, bradycardia, shivering, respiratory depression.
5. Patient satisfaction was assessed at the end of procedure using the 7 point Likert-like verbal rating scale[14] with questions like 'where will you put your experience on this scale?'

Statistical analysis: Repeated measure ANOVA was used to compare the hemodynamic parameters and bispectral index at different time interval group. The patient characteristics (nonparametric data) was analyzed using the "Chi-square tests" and the inter group comparison of the parametric data was done using the Student's *t*-test.

RESULTS

There were no statistical differences in patient's demographic data, baseline vital data, tourniquet time and duration of surgery (Table 1).

The two groups were comparable with respect to their baseline SBP, DBP and HR. After tourniquet inflation a significant rise in SBP and DBP was seen in both the study groups at 45, 60, 75 min after tourniquet inflation and just before tourniquet deflation ($p < 0.05$). A significant rise compared to baseline was also seen in HR in both the study groups at 45, 60, 75 min after tourniquet inflation and just before tourniquet deflation ($p < 0.05$). However, no statistically significant difference in BIS values was found among the study groups (Table 2).

Table 1: Demography and preoperative vitals (mean±SD and number)

Variables	Group KL	Group DX	p value
Age (years)	39.04±13.03	40.88±12.47	0.623
Sex of patients (male: female)	40:60	34:66	-
Weight (kg)	61.42±12.33	63.83±11.01	0.611
Body mass index (Kg/m^2)	22.16 ±12.37	21.23 ±10.41	0.467
Baseline HR(beats/min)	82.63±22.21	78.56 ±14.34	0.487
Baseline SBP(mmHg)	119.24 ±6.1	122.44±4.1	0.543
Baseline DBP(mm Hg)	72.46 ±3.7	75.35±2.3	0.531
Baseline Bispectral index (BIS)	91.22±3.6	93.71±4.3	0.633
Tourniquet time(min)	83.60±15.42	85.54±11.41	0.362
Duration of surgery(min)	110.11±11.31	112.21±17.24	0.645

Table 2: Haemodynamic variables and BIS value (mean±SD)

Timing	Group	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	BIS value
Just BTI (0 min)	KL	120.21±1.2	74.12±2.8	74.52±3.2	58.12±2.2
	DX	121.52±1.7	72.34±3.0	73.21±1.3	59.09±1.7
15 min ATI	KL	126.17±1.4	75.24±4.2	76.63±3.3	54.10±5.2
	DX	122.23±1.6	74.93±2.5	72.32±1.2	53.51±7.0
30 min ATI	KL	127.23±2.1	77.12±2.7	79.52±2.7	49.53±4.1
	DX	124.30±1.9	76.36±3.3	77.15±4.1	48.13±3.2
45 min ATI	KL	134.17±7.8*#	84.92±7.9*#	87.91±5.0*#	51.34±4.5
	DX	126.23±3.9*	80.58±3.2*	84.66±1.1*	53.60±5.3
60 min ATI	KL	138.28±8.3*#	87.74±9.5*#	91.83±2.6*#	46.81±5.5
	DX	130.35±6.6*	83.69±4.3*	88.31±5.1*	49.73±6.2
75 min ATI	KL	140.41±9.1*#	90.68±1.9*#	94.57±2.3*#	51.55±3.9
	DX	132.25±4.2*	85.45±2.2*	90.42±4.1*	54.11±5.3
Just BTD	KL	143.30±9.5*#	86.83±2.6*#	89.51±3.8*#	53.25±2.3
	DX	134.42±3.1*	84.64±1.7*	87.33±1.9*	55.22±1.9
15 min ATD	KL	124.31±4.1	75.46±4.3	77.46±1.4	50.71±5.1
	DX	120.58±2.8	73.11±1.8	72.28±2.6	51.33±4.2

BTI=Before tourniquet inflation, ATI=After tourniquet inflation, BTD=Before tourniquet deflation, ATD=After tourniquet deflation
*Significant difference (P<0.05) compared to baseline
#Significant difference (P<0.05) compared to Group DX

Table 3: Tourniquet induced hypertension expressed in n (%)

Timing	Group KL	Group DX	p value
15 min	0	0	NA
30 min	1(2)	0	0.68
45 min	12(24)	2(4)	0.001
60 min	17(34)	4(8)	0.01
75 min	21(42)	3(6)	0.001
Just before tourniquet deflation	11(22)	3(6)	0.003
Overall	37(74)	9(18)	0.01

Table 4: Postoperative analgesics (mean±SD)

Variables	Group KL	Group DX	p value
Time to first postoperative analgesic requirement (min)	298±83	220±77	0.001
Diclofenac consumption during the first 24hrs after surgery (mg)	34±2.7	55±6.1	0.001

Table 5: Adverse events represented by n (%)

Variables	Group KL	Group DX
Bradycardia	1(2)	6(12)
Hypotension	1(2)	5(10)
Nausea & vomiting	2(4)	3(6)
Sedation score (>3)	1(2)	18(36)
Respiratory depression	0	0

The numbers of patients who showed tourniquet induced hypertension were more in ketorolac group 37/50 (74%) than in dexmedetomidine group 9/50 (18%). (p = 0.01) (Table 3).

Time to first postoperative analgesic request was significantly longer in ketorolac group as compared to demedetomidine group. (p = 0.001) Total postoperative analgesic requirements during first 24hrs were also less in ketorolac group compared to dexmedetomidine group. (p = 0.001) (Table 4).

The adverse effects were noted during intraoperative and postoperative period. Sedation scores were significantly higher in the dexmedetomidine group (p = 0.01). Bradycardia, hypotension, nausea, vomiting and shivering were not statistically

Table 6: Patients satisfaction score represented by n (%)

Variables	Group KL	Group DX	p value
Patient satisfaction score of 5	16(32)	0	0.002
Patient satisfaction score of 6	11 (22)	20(40)	0.001
Patient satisfaction score of 7	23 (46)	30(60)	0.01

significant among the groups (Table 5).

The patient's satisfaction scores were higher in dexmedetomidine group, which were statistically significant. ($p < 0.05$) (Table 6).

DISCUSSION

The aim of this study was to compare intravenous dexmedetomidine and ketorolac, for their effect on attenuating tourniquet induced cardiovascular responses in patients undergoing lower limb surgery under general anesthesia. We also compared the time to first analgesic request after surgery and the degree of comfort experienced by patients in both the groups. Doses of dexmedetomidine and ketorolac used in our study were the same used widely in previous studies.[15,16]

Dexmedetomidine produces nociception by inhibiting the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. The presynaptic activation of the

α_2-adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals and postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate.[17, 18]

Ketorolac, being a NSAID, may have the potential to attenuate release of inflammatory mediators that in turn may cause tourniquet pain. Ketorolac also has a direct action by blocking hyperalgesia caused by substance P and stimulation of NMDA receptors.[19,20] These actions of ketorolac along with its analgesic effects might prove it to be an effective agent for prevention of tourniquet induced cardiovascular responses.[21]

In our study adequate depth of anesthesia (BIS of 40-60) was maintained by adjustment of isoflurane concentration, to exclude inadequacy, as the cause of intraoperative hypertension and tachycardia.

An equal reduction in incidence of tourniquet induced cardiovascular responses was expected in both the groups. However, we found that ketorolac was significantly less effective to attenuate increases in blood pressure and heart rate associated with tourniquet inflation compared to dexmedetomidine. The overall incidences of tourniquet induced hypertension were 74% in the ketorolac group compared to 18% in the dexmedetomidine group ($p = 0.01$) It proves that dexmedetomidine has clinical advantages over ketorolac in attenuating tourniquet induced increases in blood pressure and heart rate.

Zaidi R et al. also found statistically significant higher incidences of tourniquet induced hypertension in the ketorolac group (30 mg) when compared with low dose ketamine group (0.25 mg/kg) during elective knee surgery under general anesthesia.[22] Yao Lu *et al*. obtained lower incidences of tourniquet induced hypertension in a placebo controlled study with intravenous dexmedetomidine (0.5 μg/kg) given before tourniquet inflation, to patients undergoing lower limb surgery under general anesthesia.[15] Lao, et *al*. found similar results with a loading dose of dexmedetomidine (0.8 μg/kg) over 10 min followed by continuous infusion of dexmedetomidine (0.4 μg/kg/h) until tourniquet deflation.[23]

On comparing the time of the first dose of postoperative analgesic request between the two groups in our study, there was statistically significant increase in the time to request of the first dose of postoperative analgesia by patients in ketorolac group as compared to dexmedetomidine group. Similarly, postoperative diclofenac requirements during first 6 h were significantly less in patients who received ketorolac. This was probably due to the difference in mechanism of action of both the drugs.

When intravenous ketorolac was compared in a placebo controlled study following lumbar decompression laminectomy, lower morphine requirements and better pain scores were found in ketorolac group during postoperative period.[24] Mirkheshti A et al compared the effects of adding dexmedetomidine and ketorolac to lidocaine in infraclavicular brachial plexus block and reported that adding ketorolac had statistically significant increased the time to first postoperative analgesic request as compared to dexmedetomidine.[25]

The incidences of hypotension and bradycardia

were higher in dexmedetomidine group as compared to ketorolac group but not statistically significant. These hemodynamic changes were due to decrease in central sympathetic outflow and decreased circulating levels of nor epinephrine.

In present study, sedation score of more than 3 was observed in three patients of the dexmedetomidine group compared with no patients in the ketorolac group. Dexmedetomidine is use as sedative agent owing to its short elimination half-life and keeps the patients calm, arousable and cooperative.[18] It's effect can be reversed by a α_2 antagonist named 'atipamezole'. Dexmedetomidine does not have depressant effects on respiratory function even at higher doses,[26] similarly no patient from both the group suffered from respiratory depression in our study.

Patient's satisfaction scores were compared and there was a statistically significant difference between two groups. Dexmedetomidine group had higher patient's satisfaction scores. This may be due to the sedative effect of dexmedetomidine.

The limitations of our study are that we could not follow the placebo controlled study design and unable to estimate the level of stress hormones during surgery which would have given a better idea of changes in hemodynamic response. Moreover, further multicenter trials on large scale are needed to yield newer aspects of observation.

We conclude that intravenous dexmedetomidine 0.5 μg/kg, administered before inflation of tourniquet is more effective in attenuating tourniquet induced cardiovascular effect as compared to intravenous ketorolac 30 mg, in patients undergoing lower limb surgery under general anesthesia. However, the first time to postoperative analgesic request is longer in patients receiving intravenous ketorolac.

Acknowledgement: Nil

Conflict of interest: Nil declared by the authors

Author contribution: All of the authors took part in the conduct of the study, literature search and in manuscript preparation

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