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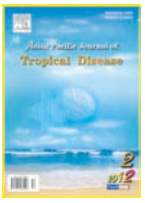

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A comparison study of Dexmedetomidine Vs Clonidine for sympathoadrenal response, perioperative drug requirements and cost analysis

Bijoy Kumar Panda[1], Priyanka Singh[1], Sourabh Marne[1], Atmaram Pawar[1*], Varshali Keniya[2], Sushma Ladi[2], Sarita Swami[2]

[1]*Department of Clinical Pharmacy, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune, India.*
[2] *Department of Anesthesiology, Bharati Hospital and Research Center, Bharati Vidyapeeth Deemed University, Pune, India.*

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ABSTRACT

Objective: To assess and compare the requirement of preanaesthetic agents to maintain anesthesia within the group of control and groups receiving Clonidine and Dexmedetomidine and reduction in cost due to reduced intraoperative anaesthetic and analgesics requirement. **Method:** Three groups of control, clonidine and dexmedetomidine were made. Twenty patients of American Society of Anesthesiologist´s grade I & II category for ⩾3 hours of surgery and >18 years of age were involved in the study of six months duration in each group. Hemodynamic variables of all patients were continuously recorded and maintained. Then, during surgery with anesthesiologists we have quantified the amount of drugs spared by use of these alpha2 agonists. **Results:** Dexmedetomidine and Clonidine were found hemodynamically stable during intubation compared to Control. Dexmedetomidine group showed 25% reduction in Isoflurane and 40% reduction in Diclofenac requirement compared to Clonidine group. The average Fentanyl dose was reduced by 33% and 44 % in Clonidine and Dexmedetomidine group respectively compared to Control group. Diclofenac and propofol requirement was found to be less in dexmedetomidine group than of clonidine. Thus, on average for surgery involving Clonidine INR 1065 per patient were charged while in Dexmedetomidine only INR 833. Significant cost benefit upto INR 463 per patient can be achieved with better hemodynamic control by Dexmedetomidine compared to Control requiring INR 1296. **Conclusions:** Intraoperatively dexmedetomidine showed significant cardiovascular stability compared to clonidine. Also, Dexmedetomidine group showed significant drug sparing effect of Isoflurane, Thiopentone and Fentanyl than Control group. A clinical pharmacist can assist anesthesiologist´s in apt selection of drugs.

1. Introduction

Anesthetic drugs do not save lives or do not even prolong lives, but they are responsible for approx 10% of most hospital's pharmacy budget[1]. Since sedation, anxiolytic and antisialogogue action are attractive attributes in a premedication agent prior to anaesthesia, administration of α2− agonist's suits this purpose well[2]. Clonidine, which was initially introduced as antihypertensive, is the most commonly used α2−agonist by anesthesiologist's[3] for its sympatholytic, sedative, anaesthetic sparing effects and haemodynamic stabilising properties[4,5,6,7]. Dexmedetomidine, is a highly specific and selective α2 adrenoreceptor agonist [8,9].

Dexmedetomidine exerted anesthetic−sparing effects, increased hemodynamic stability, and reduced unwarranted responses to endotracheal intubation[3]. The drug sparing effect of alpha−2 agonists is favored in few studies which concluded that by using α2−adrenoceptor agonists one can effectively and specifically decrease anesthetic and narcotic requirements and provide stable hemodynamic conditions during induction and intubation[10,11,12,13,14]. In recent studies, dexmedetomidine has been shown to have clinically significant effects on anaesthetic requirements, haemodynamic responses induced by anaesthesia and surgery in patients[15].

Dexmedetomidine is increasingly being used as a sedative for monitored anaesthesia care (MAC) because of its analgesic properties, "cooperative sedation", and lack of respiratory depression. Few of the authors carried out the study to judge the efficacy and safety of dexmedetomidine during perioperative procedures and analyzed the anesthetic and other drug sparing effects. The result was

*Corresponding author: *Dr. A P Pawar. Mailing address: Professor and HOD, Department of Clinical Pharmacy, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune−411046, Maharashtra, India.
Telephone number: +91−9096800845
E−mail address: p_atmaram@rediffmail.com

found to be significant in attenuating sympathoadrenal response and producing a significant reduction in other drug requirements[16]. This study is an extension to the previous one taking clonidine as a comparator to dexmedetomidine as dexmedetomidine is found to be 10 times costlier than clonidine and both belong to the same class though dexmedetomidine is found to be more potent. Cost analysis was performed to compare the cost reduction while perioperative infusion of these α-2 agonists in terms of drug sparing effect. Thus, the study was undertaken to assess and compare the sympathoadrenal response attenuation to tracheal intubation during perioperative infusion of clonidine and dexmedetomidine and reduction in cost due to its sparing of intraoperative anaesthetic and analgesics.

2. Materials and methods

A prospective observational randomized control study for 6 months duration was carried out in Bharati Medical and Teaching Hospital, Pune, India after obtaining approval from Institutional Ethics Committee (Letter no. BVDU/MC/12).

The study population comprised of 60 patients with ASA physical status I and II, aged 18 to 65 years, scheduled for elective surgery of duration three hours or more. Written informed consent was taken from each patient. Pregnant and nursing woman, patient with morbid obesity, heart block, hypertensive patient on β blockers were excluded from the study. Patients with diabetes and renal disease were not included in the study. The patients were randomly assigned to one of the three groups, each containing 20 patients, using a "Drawing pieces of paper from a bag" technique (Figure 1). The subject's population was grouped into three groups as follows:

Group C =Control group: isoflurane, opioid, anesthetics agents

Group S =Standard group: clonidine, isoflurane, opioid, anesthetic agents

Group D =Test group: dexmedetomidine, isoflurane, opioid, anesthetic agents

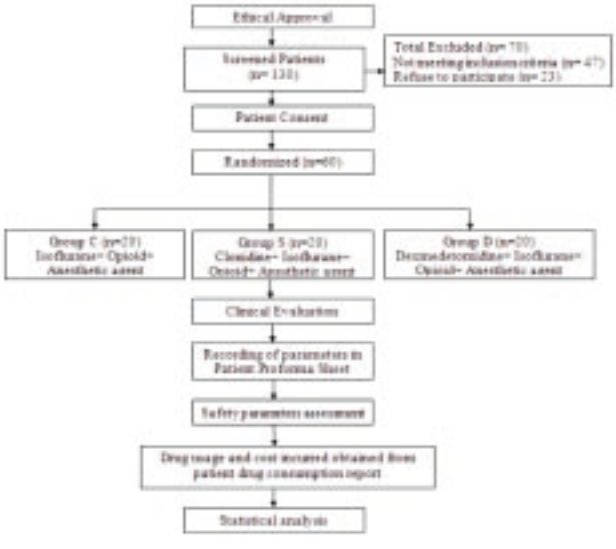

Figure 1: Flow diagram of the phases of a randomized study

All the patients were premedicated with injection glycopyrrolate 0.2 mg in 30 minutes prior to induction of anesthesia. On arrival of patient to the operating room, the patient's baseline HR, BP (SBP & DBP), SpO_2 and respiratory rate (RR) were recorded after 5 minutes settling in the operative room. All the patients in the group C and D received injection clonidine in the dose of 1 μg/kg and dexmedetomidine in the dose of 1 μg/kg respectively over a period of 10 minutes prior to induction of anesthetic agents through infusion pump. During the infusion HR, PR, systolic BP, diastolic BP, RR, oxygen saturation was recorded at 5 min interval and at 10 min (end of infusion). The entire patient received inj. ondansetron 4mg, Inj. fentanyl 1 μg/kg and inj. Midazolam 1mg intravenously, before induction of anesthesia. Then a dose of inj. thiopentone sufficient to abolish eyelash reflex was injected followed by inj. vecuronium 0.1mg/kg to facilitate laryngoscopy and tracheal intubation. The lungs were ventilated by mask for at least 3 min using 100% oxygen. Laryngoscopy was performed with a Macintosh laryngoscope and trachea was intubated with appropriate number endotracheal tube. Anesthesia was maintained with N2O in O2 (60:40), isoflurane, inj. fentanyl and inj. vecuronium. The isoflurane was used in lowest possible concentration necessary to keep blood pressure and heart rate within 20% limits of patient's preoperative baseline values. The inspiratory concentration of isoflurane was adjusted in steps of 0.2% when needed to keep the hemodynamic parameters to acceptable values. Inj. fentanyl in increments of 0.4 μg/kg was given when inspiratory isoflurane concentration exceeded by 1%. In all three groups, additional adjuvants were provided in the form of inj. diclofenac sodium or inj. propofol intravenously after inj. fentanyl exceeded 2 μg/kg. The clonidine and dexmedetomidine infusion was titrated in the respective group to keep the hemodynamic parameters in the acceptable range. Similarly, isoflurane was terminated at the start of skin closure and N_2O was discontinued after skin closure.

Finally, during the post-operative course, the patients were observed for 24 hours by one of the investigators in the post anesthetic care unit till they were shifted to the ward.

2.1. Hemodynamic parameters studied

All the parameters and results from all the three groups were entered in a predesigned patient proforma sheet. Heart rate, systolic blood pressure, diastolic blood pressure at 5 min, 10 min, and after clonidine and dexmedetomidine administration in the respective groups were recorded. Pre-induction, induction 0 min, 1 min, 5 min, after intubation, hemodynamic parameters during pre-induction, post-induction, induction and intraoperative were taken into account for recording.

2.2. Drug sparing parameters studied

The consumption of the study drugs, anesthetics and other adjuvants were recorded in the self predesigned patient drug consumption report. The total isoflurane requirement during the procedure is calculated as follows:

Isoflurane requirement (ml/hr) = 3 X Total air flow X Average dial concentration

Where,

Total air flow = 8 liters

concentration 'A' of Isoflurane × duration (min) + concentration 'B' of Isoflurane × duration (min) + concentration 'C' of Isoflurane × duration (min) +... upto concentration 'n' of Isoflurane × duration (min)

$$\text{Average dial concentration} = \frac{\begin{array}{l}\text{concentration 'A' of Isoflurane} \times \text{duration (min)} + \\ \text{concentration 'B' of Isoflurane} \times \text{duration (min)} + \\ \text{concentration 'C' of Isoflurane} \times \text{duration (min)} + \ldots \text{ upto} \\ \text{concentration 'n' of Isoflurane} \times \text{duration (min)}\end{array}}{\text{Total duration for which Isoflurane is given (min)}}$$

Total Isoflurane requirement = Isoflurane Req.(ml/hr) X duration of surgery (hrs)

The drug usage requirements for each patient were studied and reported in the following aspects:

a) Total average isoflurane concentration required per patient.

b) The average dose of injection thiopentone for induction of anesthesia.

c) Total average fentanyl requirements throughout the operative procedure.

d) The intra-operative need for adjuvants such as inj. diclofenac sodium and inj. propofol were also calculated in each group and expressed as an avg. requirement.

2.3. Cost parameters studied

To determine the costs of drugs consumed in each group during the surgical procedure, the direct costs of drugs that were charged from the patient by the anesthetics satellite pharmacy department was taken into account for the pharmacoeconomic study. The cost conversion was done where costs charged from the patient were converted into the actual quantity of the drug consumed during the complete surgery procedure. The reduction in the requirement of drugs and cost associated, within the groups were analyzed and reported as mean±SD (standard deviation).

2.4. Safety

Safety was assessed by monitoring of vital signs and detecting adverse events for 24 hours on PACU such as bradycardia (heart frequency < 45 beats/min), respiratory depression (RR < 9 breaths/ min), hypertension (BP level >30% over baseline levels), and hypotension (BP level < 30% lower than baseline levels).

2.5. Statistical analysis

One-way analysis of variance was used to compare the continuous variables among the three different groups. If a significant difference was noted, a Newman-Keuls multiple comparison test was used to determine the intergroup differences. A P value <0.05 was considered statistically significant. Data are presented as mean values±SD, numbers, or percentages. All the statistical tests were conducted using SPSS (version 10, 2010) for Windows statistical package.

3. Results

There were no significant differences between the three groups with respect to gender distribution, weight, age, pre-operative HR, duration of surgery (Table 1). In ward systolic and diastolic BP was 120±11/ 78±9 mmHg in group C, 123±11/80±7 mmHg in group S and 120±11/77±7 mmHg in group D. These differences were not statistically significant.

No signs of excessive sympathetic drive (i.e. hypertension, tachycardia, and irritability) that could be attributed to clonidine withdrawal were observed in group S before being discharged from the post-operative care unit. Whereas, dexmedetomidine was well tolerated and no drug related adverse effects were observed in group D.

Table 1

Patient Characteristics (Mean±SD, with Range in Parenthesis)

	Group C	Group S	Group D
Age (yrs.)	44±13 (26-65)	40±10 (19-60)	41±13 (21-65)
Sex			
Male	N=9	N=9	N=12
Female	N=11	N=11	N=8
Weight (kg)	52±8 (33-65)	51±7 (40-61)	56±12 (40-78)
ASA physical status			
I	N=14	N=13	N=13
II	N=6	N=7	N=7
Type of surgery			
Head and Neck	N=10	N=06	N=09
Abdominal	N=10	N=14	N=11
Surgery duration (min)	279±68 (195-450)	252±68 (180-450)	277±116 (180-645)
RR/min	15±2	15±2	16±2

3.1. Hemodynamics

In the present study, the addition of Clonidine and Dexmedetomidine to the anesthetic regimen reduced the fluctuation of BP (SBP) and HR effectively during tracheal intubation. There was a significant reduction seen in the SBP, DBP and HR as shown in Figure 2,3,4. Dexmedetomidine

(Group D) compared to Clonidine (Group S) to the anesthetic regimen, showed a significant reduction in myocardial contractility during tracheal intubation procedure. Even, during the intra-operative period the Dexmedetomidine compared to Clonidine showed a significant control of SBP and HR within a normal range (Figure 2, 4).

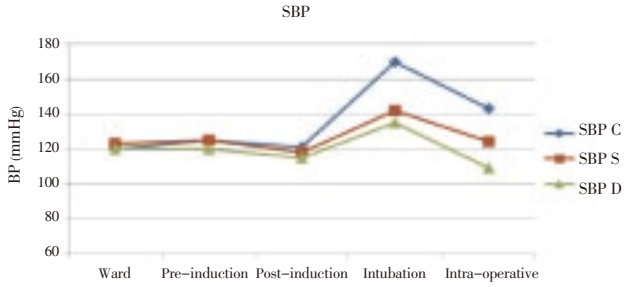

Figure 2: SBP (mean) during study period

Where,

SBP C: Systolic blood pressure for Control group

SBP S: Systolic blood pressure for Standard group (Clonidine)

SBP D: Systolic blood pressure for Test group (Dexmedetomidine)

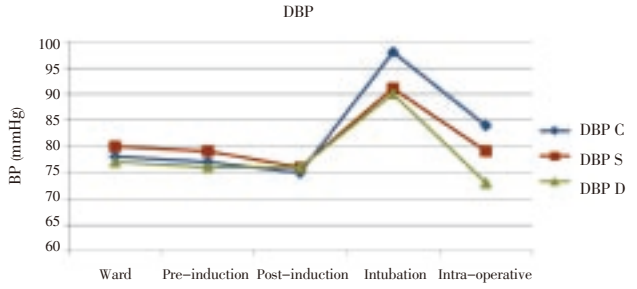

Figure 3: DBP (mean) during study period

Where,

DBP C: Diastolic blood pressure for Control group

DBP S: Diastolic blood pressure for Standard group (Clonidine)

DBP D: Diastolic blood pressure for Test group (Dexmedetomidine)

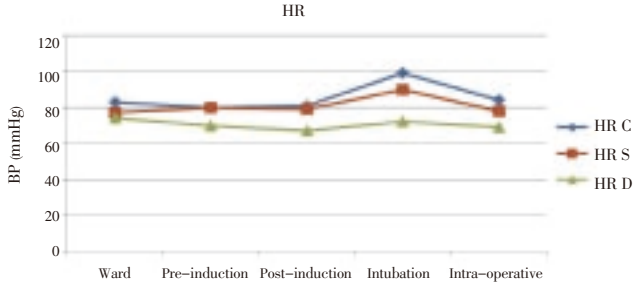

Figure 4: HR (mean) during study period

Where,

HR C: Heart rate for Control group

HR S: Heart rate for Standard group (Clonidine)

HR D: Heart rate for Test group (Dexmedetomidine)

3.2. Anesthetic and Analgesic Requirements

The average dose of various drugs requirements in surgery per patient in each group are presented in Table 2a,2b,2c. The average dose of thiopentone required per patient in respective groups were found to be significant as reported in Table 2a,2b. Total requirement of Fentanyl dose was 73±37 μg and 65±22 μg which in Group S and Group D compared to Group C ($P < 0.01$) (Table 2a,2b,2c). The average dose of Fentanyl was reduced by 33% in Clonidine and 44 % in Dexmedetomidine group compared to control group.

Table 2a

Average drug requirements per patient within groups C and S (Mean± SD)

Group	Isoflurane(ml)	Fentanyl(μg)	Thiopentone(mg)
C	83±27	102±17	352±64
S*	71±26	73±37	298±56
P-value	NS	0.003	0.006

*Average requirement of Clonidine per patient = 51.6 μg

Table 2b

Average drug requirements per patient within groups C and D (Mean± SD)

Group	Isoflurane(ml)	Fentanyl(μg)	Thiopentone(mg)
C	83±27	102±17	352±64
D#	55±26	65±22	294±87
P-value	0.002	<0.001	0.01

Average requirement of Dexmedetomidine per patient = 56 μg

Table 2c

Average drug requirements per patient within groups S and D (Mean± SD)

Group	Isoflurane(ml)	Fentanyl(μg)	Thiopentone(mg)
S*	71±26	73±37	298±56
D#	55±26	65±22	294±87
P-value	NS	NS	NS

*Average requirement of Clonidine per patient = 51.6 μg

Average requirement of Dexmedetomidine per patient = 56 μg

There was significant difference observed in the reduction of analgesic requirement in the three groups. Diclofenac requirement was 40 % more in Group S compared to the Group D as reported in Figure 5. Propofol utilization as reported in Figure 6 was found more in Group C compared to Group S and Group D.

3.3. Pharmacoeconomic assessment

The costs of inhaled anesthetics and i.v. adjuvants differ significantly within the groups as shown in Table 3a,3b,3c. Group D shows significant reduction in the cost of isoflurane, thiopentone, fentanyl than the Group C but there was no significant difference observed compared with Group S (Table 3a). This cost difference would have been more pronounced had the costs of wasted drugs being considered in overall costs.

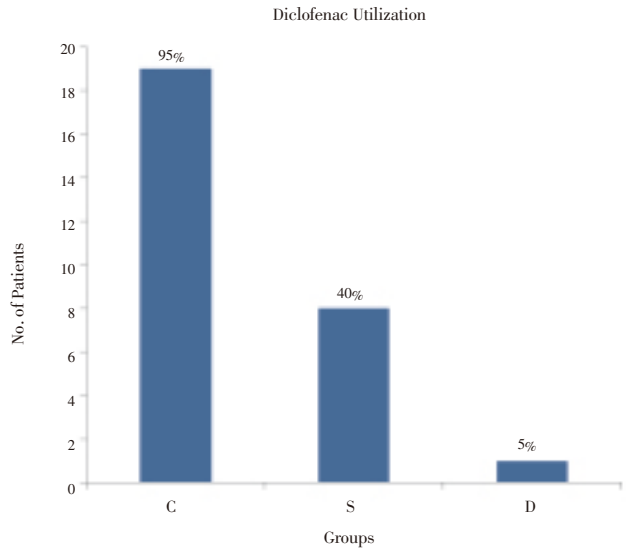

Figure 5: Diclofenac utilization during the intra-operative period within the groups

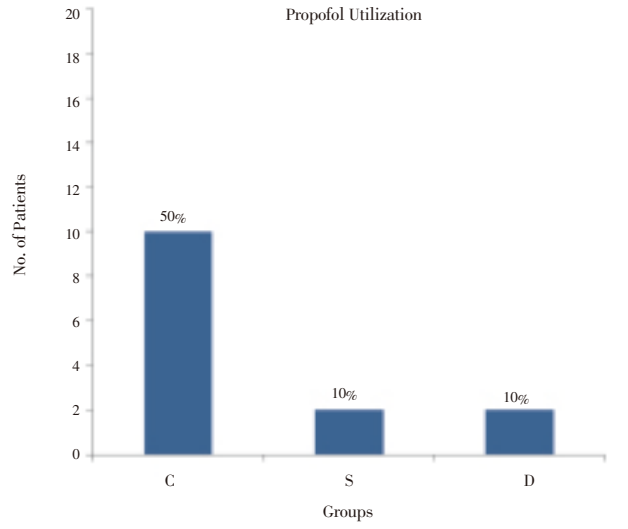

Figure 6: Propofol utilization during the intra-operative period within the groups

Table 3a

Average drug costs per patient within groups C and S (Mean±SD)

Group	Isoflurane(INR)	Fentanyl(INR)	Thiopentone(INR))
C	1156±381	39±7	40±6
S*	987±360	28±14	34±6
P-value	NS	0.0032	0.003

S* = Average cost of Clonidine incurred per patient = INR169

Table 3b

Average drug costs per patient within groups C and D (Mean±SD)

Group	Isoflurane(INR)	Fentanyl(INR)	Thiopentone(INR)
C	1156±381	39±7	40±6
D#	775±361	25±9	33±10
P-value	0.002	0.0001	0.01

D# = Average cost of Dexmedetomidine incurred per patient = INR 15

Table 3c

Average drug costs per patient within groups S and D (Mean±SD)

Group	Isoflurane(INR)	Fentanyl(INR)	Thiopentone(INR)
S*	987±360	28±14	34±6
D#	775±361	25±9	33±10
P-value	NS	NS	NS

S* = Average cost of Clonidine incurred per patient = INR169

D# = Average cost of Dexmedetomidine incurred per patient = INR 15

Note:

1. Cost of Dexmedetomidine is 10 times of Clonidine on the basis of acquisition.
2. Cost of study drug and all other drugs taken as per the amount consumed by each patient.

3.4. Safety

No patient was found in our study with bradycardia (heart frequency < 45 beats/min), respiratory depression (RR < 9 breaths/ min), hypertension (BP level >30% over baseline levels), and hypotension (BP level < 30% lower than baseline levels). And vitals were also stable in post anesthesia care unit.

4. Discussion

4.1. Hemodynamics

Clonidine, an α-2 adrenergic agonist interacts with the catecholaminergic neuronal system which modulates tonic and phasic (reflux) BP control , and reduces the release of nor-epinephrine from nerve endings both centrally and peripherally [7]. In the present study, clonidine was administered 10 minutes prior to induction of anesthesia which resulted in significant decrease in SBP and myocardial contractility during tracheal intubation period and thereafter also. These observations were consistent with previous results.

Dexmedetomidine (Group D) showed a significant decrease about 13% in SBP and HR compared to Clonidine (Group S) and dexmedetomidine was well tolerated and no serious side effects or adverse reactions occurred in the present study. It causes a dose dependant decrease in arterial blood pressure and heart rate associated with decrease in serum nor-epinephrine concentration [17,18].

In our study, two patients were of craniotomies for supratentorial tumours. The perioperative hemodynamic stability is of utmost importance in such surgeries. Increase or decrease in blood pressure may cause bleeding or edema or predispose the patient to cerebral ischaemia. The hemodynamic responses to emergence from anesthesia and extubation were blunted with dexmedetomidine [19] and the centrally mediated sympatholytic effect was

continued well in post op-period, which was advantageous in these patients. Tanskanen PE and co-workers, in their study (using dexmedetomidine as an anesthetic adjuvant for intracranial tumor) concluded to have increased perioperative hemodynamic stability in patients undergoing brain tumor surgery without postoperative respiratory depression [20]. Also, dexmedetomidine have been studied as a supplement to isoflurane for vitreoretinal surgeries without causing undue hemodynamic fluctuation and shown to decrease the excitatory response during extubation with acceptable reduction in intraocular pressure [21].

Measurement of QT interval and plasma catecholamine levels; more objective means of hemodynamic response[22] were not measured because of practical difficulty. Studies of post-operative requirement of analgesics were not taken into consideration.

4.2. Pharmacoeconomics

The dose of thiopentone needed for the induction was reduced significantly (18%) in the patients receiving Clonidine[11] and dexmedetomidine, as found also by Aantaa and co-workers, demonstrating the anesthesia potentiating effects of drugs [17,23]. Similarly, propofol requirement was seen only in 10% of the patients in groups taking clonidine and dexmedetomidine (Figure 6) as compared to 50% of patients in group C. It has also been shown that dexmedetomidine potentiates analgesia caused by fentanyl and reduces its dose requirements in human during surgery[17]. The fentanyl dose in the control group was almost twice that given in the dexmedetomidine group. The requirement of fentanyl was reduced by 44% in the dexmedetomidine group in our study.

Both the study drugs have significant opioid and analgesic (diclofenac) and thiopentone sparing property as compared with control but only dexmedetomidine showed a significant anesthetic (isoflurane) sparing effect compared to clonidine as and when compared with the control group. As such no significant difference was observed in opioid and anesthetic sparing effect within the two study drug groups (Group S vs. Group D) but the requirement of diclofenac as an analgesic during intra-operative period was negligible in dexmedetomidine study group.

Clonidine administration (INR 15 avg. cost per patient) during surgery for a patient will have to incur only INR 1065 as compared to control requiring INR 1296, whereas, Dexmedetomidine group has to bear an avg. cost of INR 833 on the expense of INR 169 (avg. dexmedetomidine cost per patient). This shows that there is a significant cost benefit of two study drugs when compared to control group. But cost benefit of upto INR 463 or more (avg. cost per patient) can be achieved along with better hemodynamic control by dexmedetomidine infusion compared to clonidine.

A clinical pharmacist of requisite qualification and experience can act as a formulary think tank as well as identify and supervise in the wastage of narcotics and controlled substances. He/ she can also act upon cost avoidance in anesthesia during the whole operation procedures and provide a cost benefit in terms of institutional or social perspective by application of pharmacoeconomic principles[24].

The present study findings corroborate with previous studies. No adverse cardiovascular effects from the drug were seen in present study. Bradycardia, a possible consequence of administration of $\alpha 2$ agonist was counteracted by the use of atropine.

The absence of a double blind study design represents a limitation of our present study, since observer's bias could have been introduced with respect to anesthetic drugs administration. Solely drug's cost was taken into account for cost analysis, other direct costs were not considered like bed charges, nursing charges etc. Small study population and short study duration are other limitations. If the population and duration would have been more, than more prominent outcomes could be observed and quantified.

In conclusion, Dexmedetomidine as preanaesthetic medication and intraoperative infusion significantly attenuates sympathoadrenal response to tracheal intubation compared to clonidine. Also it has noteworthy hemodynamically stability with opioid and anesthetic sparing property when analyzed against clonidine. Thus, dexmedetomidine should be introduced into hospital formulary considering patient's benefits based on clinical and pharmacoeconomic outcomes. Also this study shows dynamic participation of clinical pharmacists with anesthesiologists in suitable drug selection.

Conflict of interest statement

We declare that we have no conflict of interest.

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