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COMPARATIVE EVALUATION OF DEXMEDETOMIDINE VERSUS MIDAZOLAM ON QUALITY OF ANAESTHESIA AND REQUIREMENT OF KETAMINE - PROPOFOL (1:1) COMBINATION AMONG ADULT PATIENTS UNDERGOING VARIOUS SHORT SURGICAL PROCEDURE.

Anaesthesiology

Pravin B Kalsariya Third year post graduate resident, Department of Anesthesiology, Government medical college, surat, Gujarat, India.

Shweta A Patel Assistant professor, Department of Anesthesiology, Government medical college, surat, Gujarat, India.

Mitali K Ahir Assistant professor, Department of Anesthesiology, Government medical college, surat, Gujarat, India.

Geeta A Savani* Department of Anesthesiology, Government medical college, surat, Gujarat, India. *Corresponding Author

ABSTRACT

Background: patients who are posted for any type of short surgical procedures required good anesthesia in terms of adequate analgesia, anxiolysis and sedation with minimal adverse event. The aim of this study was to compare effectiveness and safety between intravenous dexmedetomidine and midazolam with ketamine-propofol combination for short surgical procedure. **Method:** we included total 60 patients of ASA grade I/II, 18-60 years of age posted for various short surgical procedure, divided into 2 groups. Both the group patients were received intravenous diclofenac sodium 75mgs/kg. Group DKP received intravenous dexmedetomidine 1µg/kg over 10 minutes, followed 0.4µg/kg/hr as continuous infusion and group MKP received intravenous midazolam 20mcg/kg over 10 minutes, followed by 20mcg/kg/hr as a continuous infusion. All patients were induced and maintained with intravenous ketamine-propofol combination 1 to 2 mg/kgs over 30-40 seconds and 0.5 to 1mg/kgs respectively. **Results:** Total mean requirement of ketamine-propofol combination was 96 ± 23.55 mg in DKP group and 144.5 ± 39.13mg in MKP group ($P<0.05$). Recovery time was early in DKP group (5.5 ± 1.52 minutes) than in MKP group (6.5 ± 2.33 minutes) ($p<0.05$). Emergence reaction was observed in 3.33% patient in DKP-Group and 6.66% patients in MKP-Group. 10% patients in DKP group and 6.66% patients in MKP group were experienced nausea. Visual analogue score was lower with DKP group than MKP group($p<0.05$). **Conclusion:** with this dose regime, both dexmedetomidine and midazolam with ketamine-propofol combination (1:1) provides adequate anesthesia during various short surgical procedure but dexmedetomidine with ketamine-propofol combination was superior in view of good hemodynamic profile, recovery profile and postoperative analgesia. Moreover, Dexmedetomidine Infusion reduced the requirement of ketamine-propofol combination.

KEYWORDS

Dexmedetomidine, Midazolam, ketamine propofol combination, short surgical procedure, Total intravenous anesthesia.

INTRODUCTION:

Patients who attend the hospital are anxious, physically or mentally disturbed due to illness or disease state. Moreover, other stressful conditions like surgical incision and anesthetic medications are also associated with hemodynamic instability. So, patients who are posted for any type of short surgical procedures also required adequate anesthesia in terms of analgesia, anxiolysis and sedation with minimal adverse event.

General anesthesia is maintained by intravenous infusion referred to as a total intravenous anesthesia.[1] Nowadays, there is increased trend of total intravenous anesthesia (TIVA) because of its many advantages like less operating room pollution, good recovery profile and better hemodynamic stability. So, total intravenous anesthesia is suitable for short surgical procedure. Ideal anesthetic agent provides adequate sedation, anxiolysis, analgesia, amnesia with smooth induction and rapid recovery with minimal side effects. Unfortunately, despite availability of numerous anesthetic agents, no single agent demonstrates superiority over others.

Ketamine is dissociative anesthetic agent with good sedo-analgesic property and it preserves spontaneous respiration which is desirable for procedural sedation.[2] It has sympathomimetic hemodynamic effects but its use is limited because of its propensity to cause emesis, psychomotor agitation and prolong recovery.

Propofol is short acting, rapid onset intravenous anesthetic agent and it suppresses sympathetic activity and inhibits baroreceptor reflex.[3] Propofol have no analgesic properties and excessive dose of propofol can causes cardiorespiratory depression.

A systemic review and meta-analysis by Ghojazadeh M et al[3] concluded that ketamine propofol mixture has less respiratory related adverse effect than propofol alone. Theoretically, ketamine-propofol combination can be used due to opposing physiological effect of ketamine and propofol. Propofol induced hemodynamic compromise may be compensated by ketamine and psychomimetic adverse effects of ketamine are reduced by use of propofol So, combination of both are useful in many clinical situation with better hemodynamic stability, analgesia and recovery.[4]

Dexmedetomidine being an alpha agonist and midazolam being a GABA agonist, both have sedative, hypnotic and anxiolytic properties with rapid onset, fast recovery and minimal hemodynamic variation. Barends et al[5] reviewed that titrated dose of dexmedetomidine and midazolam appear to have a similar cardio-respiratory safety profile.

So, different sedative, analgesic or dissociative agents have been used in varying combination to provide adequate anesthesia. Many studies are there which shows the effectiveness of ketamine –propofol combination but there are not many studies to evaluate the effect of dexmedetomidine and midazolam when given with ketamine-propofol combination in adult patient undergoing short surgical procedures. So, we want to know the quality of anesthesia and requirement of ketamine-propofol combination (1:1) when given with dexmedetomidine and midazolam infusion.

MATERIAL AND METHOD:-

After obtaining institutional ethical committee approval and written informed consent from the patients. A prospective observational study was conducted on 60 adult patients with 30 in each group, undergoing various routine or emergency short surgical procedures (<30 min).

Patients with 18-60 years of age of either sex who were posted for short surgical procedure like incision and drainage, wound debridement, excision biopsy, Split thickness graft, dilatation and evacuation, dilatation and curettage etc, belonging to ASA class I, II were included in our study. And patients who refused to participate in our study, had history of psychiatric illness, cardiovascular disease, acute alcohol intoxication, allergy to study drug and having bradycardia (less than 60/minute) were excluded from our study.

At the end of preanesthetic check-up, eligible patients were informed about our study and related procedure and who gave informed written consent were included in our study.

All the patients were premedicated with anticholinergic Injection Glycopyrrolate 0.2 mg and Inj. Diclofenac Sodium 75 mg intravenously. After shifting patient to operation theatre NIBP, pulse oximeter, ECG leads, ETCO2 monitor were attached and all parameters were noted that was considered as baseline value.

According to choice of consultant anaesthesiologist, patients received either Inj. dexmedetomidine 1mcg/kg iv slowly over 10 minutes, followed by continuous infusion of dexmedetomidine 0.4 mcg/kg/hr intravenously considered as DKP group or Inj. midazolam 20mcg/kg iv slowly over 10 minutes, followed by continuous infusion of midazolam 20mcg/kg/hr intravenously considered as MKP group.

All patients in both the group were induced with 1 to 2 mg/kg bolus dose of ketamine and propofol (1:1) combination intravenously over 30-40 second. After induction, transient side effect like presence or absence of pain on operating site (from facial expression, behaviour sign like facial grimaces and tears in eyes or withdrawal) and myoclonus noted. Patients were maintained on intermittent bolus dose of ketamine propofol combination (1:1) 0.5 to 1 mg/kg. Requirement of further dose was judged by variation of hemodynamic parameter (HR, BP) were more than 20% from baseline or sudden movement of the patients. Dexmedetomidine or midazolam infusion was discontinued at the end of surgical procedure.

We had judged quality of anesthesia by hemodynamic parameter noted intraoperatively at 5 minute interval till the end of surgery, total requirement of additional dose of ketamine-propofol combination during surgery, Occurrence of any side effects like tachycardia(≥20% from baseline value),bradycardia(≥20% from baseline), hypertension (≥20% from baseline value) and hypotension (≤20% from baseline value). Any airway or respiratory events like desaturation (spo2<90%), apnea (cessation of respiration >20 second).If hypotension occurred ,it was treated by intravenous fluid or injection ephedrine 6 mg and in case of bradycardia, injection atropine 0.6 mg intravenous bolus dose was given. Any increase in hemodynamic parameter >20% from baseline was considered as light plane of anesthesia and maintenance dose was supplemented, Occurrence of other non-respiratory adverse event like nausea, vomiting, emergence reaction or recovery agitation at the end of surgery, Recovery profile by modified alderete's score (MAS), analgesic effect was noted immediate post operative period by using VAS score.

At the end of surgery, time to achieve aldret's score ≥9 from stoppage of dexmedetomidine or midazolam infusion was noted. When we achieved aldrete score ≥9, patient was shifted to recovery room. In the recovery room, patient was observed for post operative adverse events like nausea, vomiting, emergence reaction, recovery agitation and pain up to 30 minutes, if any above side effects injection ondansetron 4mg iv, injection midazolam iv, injection paracetamol 1gm iv was given accordingly. After 30 minutes observation, patient was shifted to ward.

OBSERVATION AND RESULTS:

A comparative observational study was conducted to evaluate the effect of intravenous dexmedetomidine and midazolam on requirement of ketamine-propofol combination, intraoperative hemodynamic, recovery profile and postoperative analgesia.

The mean age, weight, duration of surgery, gender, ASA grade of the patients in DKP group and MKP group were comparable(p>0.05) (Table 1).

Table 1:

	DKP group (n=30)	MKP group (n=30)
Mean Age(years) (mean ± SD)	28.23 ± 8.45	32.33 ± 9.22
Gender: Male	6(20%)	12(40%)
Female	24(80%)	18(60%)
Mean weight(kgs)(mean ± SD)	49.16 ± 9.29	53.16 ± 8.34
ASA Grade I	5(17%)	5(17%)
Garde II	25(83%)	25(83%)
Duration of surgery(min)(mean ± SD)	27 ± 4.47	27 ± 4.00

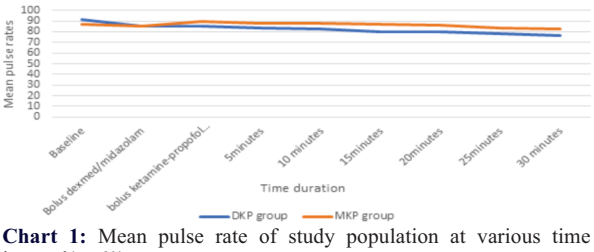

Chart 1: Mean pulse rate of study population at various time interval(n=60).

Chart 1 shows the trend of mean pulse rate of DKP-Group and MKP-Group. Mean baseline pulse rate of DKP-Group was 91.03 ± 13.97 per minutes and MKP-group was 87.33 ± 14.34 per minutes which was comparable(P>0.05). Significant reduction of mean pulse rate was found in DKP group than MKP group(p<0.05).

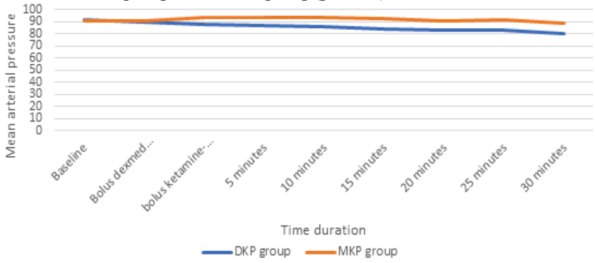

Chart 2. Mean Arterial blood pressure of study population at various time interval(n=60).

Chart 2 shows trend of mean arterial pressure in both groups. Significant reduction of mean arterial pressure was found at 5, 10 and 15 minutes of surgery in DKP group compared to MKP group(P<0.05) and thereafter up to 30 minute this reduction was very significant (P<0.001).

There was significant difference in mean RR and mean ETCO2 during 15 min, 25min and 30 minute in DKP Group, but mean RR and mean ETCO2 remained within normal range 18 to 24 per minute and 35 to 45 cmH_2O respectively.

There was not significant difference of RR, Saturation and Etco2 between both groups(P>0.05).

Table -2 Total Ketofol (ketamine-propofol) Requirments And Mean Modified Aldrete's Score(MAS) (n=60).

Group	DKP-Group	MKP-Group	P value
Total ketofol requirement(mg) overall. (Mean ± SD)	96±23.55	144.5±39.13	P<0.05(0.0019)
Total ketofol requirement(mg) for maintenance. (Mean ± SD)	49.65±19.68	87.3±35.97	P<0.05(0.0017)
Mean MAS (Mean ± SD)	5.5±1.52	6.5 ± 2.33	(p<0.05)0.0025

During induction, Pain on injection site was present only in 5(17%) patients in MKP group. During post operative periods, Nausea was observed in 3(10%) patients in DKP-Group while 2(6.66%) patients in MKP-Group and emergence reaction was observed 1(3.33%) patient in DKP-Group and 2(6.66%) patients in MKP-Group. (p>0.05).

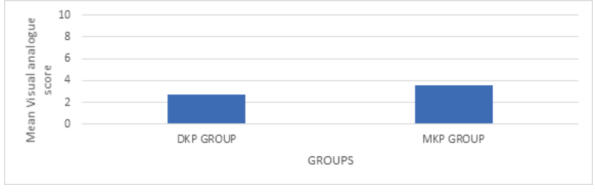

Chart 3: VAS Score Of The Patient.

Mean visual analogue score (2.733 ± 0.85) of DKP group was lower than MKP group(3.57 ± 0.75) which was statistically highly significant. (p<0.01)

DISCUSSION:

We used ketamine-propofol 1:1 concentration (5mg/ml ketamine + 5mg/ml propofol) for induction and maintenance of anesthesia, considering the dose and ratio of mixture which decides safety and efficacy of ketamine-propofol combination. And it also has several benefits like hemodynamic stability, lack of respiratory depression, good recovery and post procedural analgesia. Our dose regime is similar with the dose regime of Kayhan GE et al[6] and Miner et al[7].

We found more stable hemodynamic in DKP group than MKP group throughout the surgery without any significant side effects.

We found lower heart rate in dexmedetomidine group than midazolam group of the patients which are similar with the study of Sundar S et al[8], Sethi P et al[9] and Dere k et al[10]. Contrast to our study, Delmade et al[11] found significant bradycardia in dexmedetomidine group and they did not found significant heart rate difference in dexmedetomidine group and midazolam group. Fentanyl supplementation in both groups and higher dose of midazolam might be the reason.

Similar to our study Sunder S et al[8] found significant attenuation of the mean arterial pressure in dexmedetomidine group when compared to baseline and midazolam group although they found higher mean blood pressure in midazolam group due to local anesthesia infiltration. Delmade et al[11] also observed similar changes of mean blood pressure in their study. Apan et al[12] observed mean blood pressure were comparable in dexmedetomidine and midazolam group which is not consistent with our study. These may be due to direct infusion of minimal dose without bolus dose of dexmedetomidine and midazolam and their all patients were preloaded with crystalloid solutions.

None of the patients developed hypertension or hypotension and tachycardia or bradycardia in both the groups that might be due to careful dose titration via infusion pump, loading dose of both study drug infused slowly and we used diclofenac as premedication and ketofol as maintenance agent with vigilant monitoring.

These finding suggest that dexmedetomidine has clinical advantages when used with ketofol over midazolam in view of hemodynamic stability.

We observed transient fall in spo_2 < 90% in 3 patients in MKP Group, which was mostly due to upper airway obstruction. Out of 3 patients ,2 patients recovered after airway repositioning (chin lift manoeuvre) and 1 patient recovered after jaw thrust manoeuvre. Contrary to our study, Dere K et al[10] found significant fall of saturation at 5th and 10th minute intraoperatively in midazolam groups(P<0.05). Higher dose of midazolam and fentanyl were the possible reason.

Ravipati p et al[13] have proved that dexmedetomidine reduced the requirement of propofol and ketamine with more intraoperatively hemodynamic stability**.** Similarly, in our study, Dexmedetomidine reduced requirement of ketamine propofol combination than midazolam.

In our study, MKP Group patients experienced pain while patient treated with dexmedetomidine were free of pain at injection site. L He et al[14] demonstrated lower dose (0.25mcg/kg and 0.5mcg/kg) of dexmedetomidine could not reduce incidence and severity of propofol induced pain than higher dose(1mcg/kg). In our study, additive analgesic effect of dexmedetomidine infusion with ketamine-propofol combination might have worked to reduce the incidence of pain at injection site.

In our study, we observed nausea in 3(10%) patients in DKP group and 2(6.66%) patients in MKP group was treated by inj.ondensetron 0.1-0.2mg/kg iv. In recovery room (3.33%) patients in DKP Group and 3(13.33%) patients in MKP Group had pain on surgical site which was treated by inj. paracetamol.

We observed emergence reaction in 1(3.33%) and 2(6.66%) patients in DKP group and MKP group respectively which was treated by additional dose of midazolam. Ketamine causes depression of auditory and visual relay nuclei leading to misinterpretation of auditory and visual stimuli. This mechanism is responsible for emergence reaction of ketamine. In our study, It may be due to ketamine in ketamine propofol combination(1:1), young age group, higher preoperative anxiety and postoperative pain (out of 60 , all three patients postoperative VAS score was 5 in recovery room). Our findings are similar to Kurhekar P et al[15] who observed dexmedetomidine infusion was effective in prevention of emergence reaction in nasal surgeries than midazolam infusion.Dexmedetomidine group showed Faster recovery, similar recovery profile were observed by sethi p et al[9] and Ravipati p et al[13].

In our study, VAS score was significantly lower in DKP group because analgesic property of dexmedetomidine along with ketamine-propofol combination. Midazolam has no analgesic effect. Average VAS score was less than 4 in both the groups that was because we used ketamine-propofol combination for induction and maintenance of anesthesia. Ketamine has analgesic effect while propofol does not have such property. Addition of ketamine to propofol has synergistic effect , theoretically ketamine-propofol combination potentiates sedative activity of propofol and analgesic activity of ketamine resulting in enough analgesia.

CONCLUSION:

It is concluded that with this dose regime, both dexmedetomidine with ketamine –propofol combination(1:1) and midazolam with ketamine-propofol combination(1:1) provides adequate anesthesia during various short surgical procedure among adult patients. But dexmedetomidine with ketamine-propofol combination was superior to midazolam with ketamine-propofol combination(1:1)in view of good hemodynamic profile, recovery profile and postoperative analgesia. Moreover, Dexmedetomidine infusion reduced the requirement of ketamine-propofol combination(1:1).

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