Original Article

Recovery and post-operative analgesic efficacy from fentanyl- versus dexmedetomidine-based anesthesia in head and neck cancer surgery: A prospective comparative trial

ABSTRACT

Background: Opioids such as fentanyl are being used frequently in the management of postoperative period, whereas non-opioid drugs such as dexmedetomidine are now commonly being used as adjuvants during the perioperative period to hasten the fast recovery and better outcome in the post-operative period because of their anesthetic and analgesic property. The recovery profile was measured by the emergence of anesthesia and pain characteristics. We aimed to evaluate and compare the efficacy of dexmedetomidine and fentanyl in the surgery of head and neck cancer patients.

Methods: Prospective double-blind study on 60 patients with the American Society Anesthesiologists (ASA) grade I and II were randomly divided into two groups. Group DM received a loading dose of dexmedetomidine 1 μg/kg over 10 min followed by a maintenance dose of 0.5 μg/kg/h and Group FM received a loading dose of fentanyl 2 μg/kg/h for over 10 min followed by 1 μg/kg/h maintenance dose. Data were analyzed using a Chi-square test or Student's '*t* test.

Results: The group DM was hemodynamic stable as compared to group FM. The perturbation during extubation emergence was significantly lower in group DM as compared to that in group FM. A total of four patients were severely agitated in group FM, whereas it was absent in group DM. Severe agitation was significantly different between Group FM and Group DM. The visual analog scale (VAS) was lower among patients of Group DM as compared to Group FM at all times except at 4 h.

Conclusions: The infusion of dexmedetomidine was better in controlling emergence agitation, postoperative pain, and achieving peri-operative hemodynamic stability as compared to fentanyl.

Keywords: Analgesia, dexmedetomidine, emergence, fentanyl, head and neck surgery

INTRODUCTION

The head and neck are the sixth most common sites of cancer worldwide. Many factors such as lifestyle, habits, and demographic as well as genetic factors affect the geographic difference in the incidence of cancer.[1] It is the most common cancer in India in males and accounts for 35% of all newly diagnosed cancers in men. Head and neck cancer accounts for about 40% of tumors in the oral cavity, 15% in the pharynx, and 25% in the larynx, and histologically squamous cell carcinoma contributes to 90% of total cancer types.[2]

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Surgery is the most well-accepted method of initial definitive treatment for a majority of cancers over a century. Fear of pain is one of the most common causes of anxiety in the perioperative period. Pain control during this period is still the need of the hour, and also much research work is being conducted on this issue, particularly among head and neck patients. Pain remains one of the many cancer-related symptoms that leads to a poor quality of life (QoL) because pain alters physical functions and has an emotional impact.[3,4]

Many studies done previously showed that the nociceptive pain in the head and neck cancer is due to direct invasion and destruction of bones and soft tissue as well as also due to the inflammation and compression of the nervous tissue. A meta-analysis of almost 52 previous studies to measure the prevalence of cancer pain revealed the highest prevalence of head and neck cancer surpassing gastrointestinal, gynecological, breast, and lung tumors.[5]

Opioids are being used frequently for moderate to severe acute pain management in the perioperative period. However, in the last few decades, non-opioid drugs such as dexmedetomidine have become a favorite alternative for analgesia in the perioperative period to regain fast and early recovery postoperatively because of its anesthetic and analgesic-sparing effects.[6] The property of dexmedetomidine to diminish postoperative dynamic pain, free of any opioid-related side-effects such as respiratory depression, and gastrointestinal and bladder dysfunction, make it more suitable for the above purpose.[7] So, nowadays, narcotic-less or narcotic-free anesthetic drugs are being recommended for head and neck surgeries.

The newly introduced inhalation agents such as sevoflurane, desflurane, and enflurane are commonly used because of having rapid induction, pleasant smell, minimal side effects, and rapid postoperative recovery. Despite better properties, their use frequently causes emergence agitation in the recovery phase from general anesthesia. Various induction agents including propofol, ketamine, opioids, clonidine, have been used to avoid emergence agitation but may have some side effects such as sedation, nausea, and vomiting.

Dexmedetomidine, a 2-adrenergic receptor agonist, possesses anxiolytic sedative and hypnotic properties without significant respiratory depression. Previous studies conducted to evaluate the efficacy of dexmedetomidine for inhibition of emergence agitation in adult patients undergoing head and neck surgery are insufficient.

A comparative study of dexmedetomidine with fentanyl has been done previously successfully in various surgical procedures; however, there is limited literature on the intraoperative use of dexmedetomidine and fentanyl anesthesia for comprehensive comparison in head and neck surgery.

Therefore, we planned a comparative study on head and neck cancer patients and aimed to assess the efficacy of dexmedetomidine as a suitable alternative to improve-opioids such as fentanyl. We compared both these drugs for their effects on hemodynamic parameters, emergence from anesthesia, recovery characteristics and postoperative analgesic requirements.

MATERIALS AND METHODS

A randomized double-blind prospective study was performed after getting clearance from the institutional ethics committee research cell with (Ref no: 93rd ECM II B-Thesis/P14) dated 08.03.2019. A total of 60 patients of either sex, American Society Anesthesiologists (ASA) grade I or II within the age range of 20–60 years undergoing elective head and neck surgery under general anesthesia were allocated into two groups of 30 patients each.

Surgery were included different site of head and neck region like; alveolus, buccal mucosa, tongue and thyroid.

Randomization was done using a computer-generated random number. Patients having chronic analgesic therapy, chronic pain, pregnancy, history of any drug abuse or dependent on opioid drugs, and severe cardiac, pulmonary, liver, renal or neurological disease were excluded from the study. Patients with previous head and neck surgery, restricted mouth opening (<5 cm), Mallampati grading ≥ 3, and those patients who need postoperative ventilatory support were also excluded from the study. Patients who had a major defect and needed flap reconstruction surgery were also excluded from the study as such patients need different intensive care unit management; so, they could not be followed up for our study.

In preanesthetic evaluation, all patients were completely examined and their airways assessed. They were explained about the study and the possibility of being randomly allocated into any study group and included only after taking consent.

Patients were randomly divided into two groups.
- **Group DM** received a loading dose of dexmedetomidine 1 μg/kg over 10 min followed by a maintenance dose of 0.5 μg/kg/h.

- **Group FM** received a loading dose of fentanyl 2 µg/kg over 10 min followed by maintenance dose of 1 µg/kg/h.

All patients were premedicated orally with 150 mg ranitidine, 10 mg metoclopramide and 0.25 mg alprazolam orally on the night day before surgery and kept overnight fasting. On the day of surgery, all patients were shifted to the operation room and two peripheral intravenous lines were secured using an 18G intravenous cannula. All monitors for measuring oxygen saturation (SpO2), noninvasive blood pressure (NIBP), electrocardiogram (ECG), and temperature were attached. After obtaining the baseline heart rate (HR), oxygen saturation, and mean blood pressure, infusion of the study drugs (dexmedetomidine/fentanyl) for loading was commenced according to weight-adjusted doses taking the patient's actual weight.

Patients received a loading dose of dexmedetomidine 1 µg/kg or fentanyl 2 µg/kg over 10 min just before induction. Study drugs were administered by a third person not involved in any study procedure. All patients were planned for nasal intubation with a flexometallic tube as surgery mainly involved oral cancer. Patients were preoxygenated with 100% oxygen for 3 min and then induced by Inj. propofol 2 mg/kg. Nasal intubation was facilitated with vecuronium 0.1 mg/kg as intubating dose followed by throat packing. Anesthesia was maintained by 0.02 mg/kg vecuronium every 20 min with $O_2 + N_2O$ at a 50:50 ratio and inhalational agent sevoflurane at one minimal alveolar concentration (MAC). Continuous infusion of dexmedetomidine at 0.5 µg/kg/h or fentanyl at 1 µg/kg/h was given during the intraoperative period up to 10 min before extubation when skin closure started.

HR and mean arterial pressure (MAP) were noted in the preoperative period before induction, after intubation, and every 20 min during the intraoperative period, before and after extubation. During the surgical procedure, patients received intravenous crystalloid solutions as per standard calculation, and ondansetron 0.1 mg/kg intravenous was given for the prevention of postoperative nausea and vomiting at the end of surgery. The maximum allowable blood loss (MABL) was calculated for all patients and intraoperatively blood loss was measured during surgery. Packed red blood cells were transfused to those patients whose blood loss exceeded the MABL.

After wound closure, reversal of residual neuromuscular blockade was done with inj. neostigmine 0.04 mg/kg intravenous and inj. glycopyrrolate 0.01 mg/kg intravenous. When spontaneous respiration was adequate and patients were able to obey simple commands, oropharyngeal suctioning was done and tracheal extubation was performed. The emergence from anesthesia was measured on the Riker Sedation Agitation scale (RSAS) just after extubation and pain on the visual analogue scale (VAS) was measured at 0 h, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h after extubation. Rescue analgesia was covered with infusion of paracetamol (PCM) 15 mg/kg and second rescue analgesia inj. tramadol with a dose of 2 mg/kg weight when VAS score was ≥4 postoperatively.

The statistical analysis was done using the SPSS (Statistical Package for Social Sciences) Version 21.0 Statistical Analysis Software. The sample size was calculated, based on a α risk of 0.05 and β risk of 0.20 (80% power of study). The values are represented in number (%) and mean ± standard deviation (SD). Comparisons between groups at different time intervals and mean were assessed using Student's "*t*" test. All categorical data were compared using a Chi-square test. The '*P*' ≤0.05 were taken as statistically significant.

Riker Sedation-Agitation Scale

Score	Description	Explanation
7	Dangerous agitation	Tries to remove monitors and devices or climb out of bed; tosses and turns; lashes out at staff
6	Very agitated	Remains restless despite frequent verbal reassurance; bites endotracheal tube; requires restraint
5	Agitated	Anxious or restless; attempts to move; calms down with reassurance
4	Calm and cooperative	Calm; easy to arouse; able to follow instructions
3	Sedated	Difficult to awaken; responds to verbal prompts or gentle shaking but drifts off again
2	Very sedated	Incommunicative; responds to physical stimuli but not verbal instructions; may move spontaneously
1	Unarousable	Incommunicative; little or no response to painful stimuli

RESULTS

The demographic profile such as age, sex, weight, height, ASA grade, and duration of surgery are shown in Table 1. The mean age of patients of group FM and group DM were 42.90 ± 11.15 years and 48.40 ± 10.25 years, respectively. A total of 21 (70%) males and 9 (30%) females in group FM and 22 (73.33%) males and 8 (26.67%) females in group DM. A total of 10 (33.33%) ASA grade I, and 20 (66.67%) ASA grade II in group FM and 7 (23.33%) ASA grade I and 23 (76.67%) ASA grade II in group DM. The mean weight (kg) and mean height (cm) of patients of group FM and group DM were 63.60 ± 8.92 kg and 61.37 ± 7.86 kg and 166. 67 ± 7.cm and 165.10 ± 7.88 cm, respectively. The mean duration of surgery for group FM and group DM were 14.87 ± 0.98 and 14.63 ± 0.90, respectively. The

demographic characteristics such as age, sex, weight, height, ASA grade, and duration of surgery were comparable between group DM and group FM.

The HR was comparable at the preoperative, at intubation, and at skin incision at 160 min and 180 min ($P > 0.05$). The HR was significantly lower just ($P < 0.05$) before intubation, from 20 min to 140 min, and extubation in Group DM as compared to Group FM as shown in Figure 1.

The mean arterial pressure (MAP) was comparable at the preoperative, before intubation, at intubation, at skin incision, at 40 min, 60 min, and at 160 min ($P > 0.05$). The MAP was significantly lower ($P < 0.05$) at 20 min, 80 min to 140 min, 180 min, and extubation in Group DM as compared to Group FM as shown in Figure 2.

The extubation emergence was significantly lower in group DM (3.90 ± 0.48) as compared to that of group FM (4.83 ± 0.65). A total of four (13.33%) patients were severely agitated in group FM, which was significantly higher than in group DM [Table 2].

The VAS was a significant difference between groups at extubation (0 h), 4 h, 8 h, and 12 h. The VAS was lower among the patients of Group DM as compared to Group FM at all periods except at 4 h [Table 3].

The requirements of rescue analgesics were observed at extubation, and between 1 and 8 h after extubation, as shown in Table 4. Paracetamol was required in 16.67% of patients at extubation (0 h), 50.0% of patients at 1 h, 23.33% of patients at 2 h, and 6.67% of patients at 4 h in group FM, and 30.0% of patients at 1 h, 36.67% of patients at 2 h, 23.33% of patients at 3 h, and 3.33% at 4, 5, and 8 h in group DM. Paracetamol was more required at extubation (0 h, 1 h, and 4 h in group FM whereas that at 2 h, 3 h, 5 h, and 8 h in group DM.

Tramadol was required in 13.33% of patients at 1 h, 33.33% of patients at 2 h, 30.0% of patients at 3 h, 10.0% of patients

at 4 h, 6.67% of patients at 6 h, and 10.0% of patients at 8 h in group FM, whereas it was required in 6.67% of patients at 2 h, 26.67% of patients at 3 h, 33.3% of patients at 4 h, 23.33% of patients at 5 h, and 3.33% of patients at 6 and 8 h in group DM. The requirement for tramadol was more at 1 h, 2 h, 3 h, 6 h, and 8 h in group FM, whereas the requirement of tramadol was more at 4 h and 5 h in group DM.

Table 1: Demographic characteristics

	Group FM		Group DM		P
	Mean/*n*	±SD/%	Mean/*n*	±SD/%	
Age (years)	42.90	11.15	48.40	10.25	0.051
Sex					
Male	21	70.0%	22	73.33%	
Female	9	30.0	8	26.67	0.779
Weight (kg)	63.60	8.92	61.37	7.86	0.308
Height (cm)	166.67	7.09	165.10	7.88	0.421
ASA grade					
I	10	33.33%	7	23.33%	0.399
II	20	66.67%	23	76.67%	
Duration of surgery (min)	137.00	21.03	143.33	22.94	0.270

Table 2: Extubation emergence and severely agitated (>5) in between groups

	Group FM		Group DM		P
	Mean	±SD	Mean	±SD	
Extubation emergence	4.83	0.65	3.90	0.48	<0.001*
Severely agitated (>5)	4	13.33%	0	0.0%	0.039*

Table 3: Comparison of VAS scores in groups

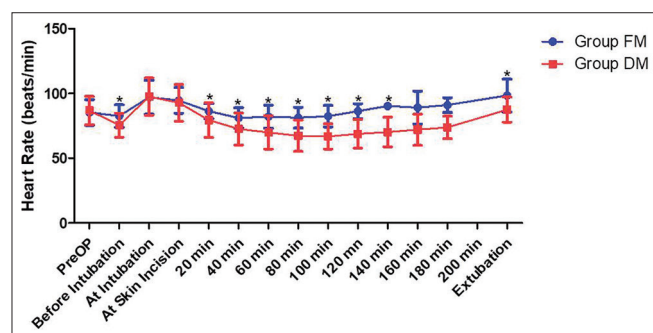|	Group FM			Group DM			P
	n	Mean	±SD	*n*	Mean	±SD	
0 h (at extubation)	30	4.43	1.10	30	0.40	0.89	<0.001*
2 h	30	4.83	1.53	30	4.33	1.37	0.189
4 h	30	3.33	0.99	30	4.50	1.48	0.001*
8 h	30	1.97	0.67	30	1.33	0.96	0.004*
12 h	30	1.13	0.63	30	0.20	0.48	<0.001*
24 h	30	0.13	0.35	29	0.03	0.19	0.179

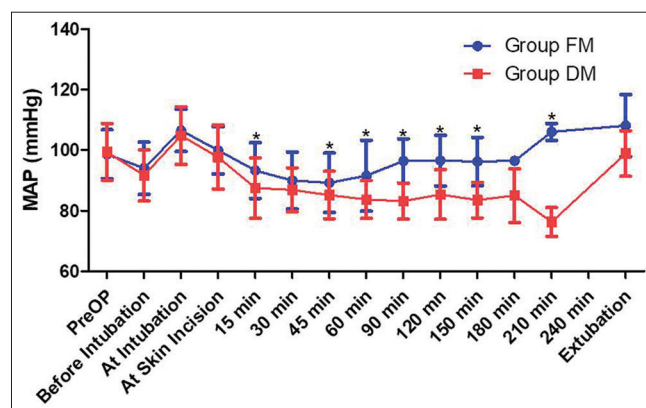Figure 1: Heart rate (pulse/min) in between groups

Figure 2: Mean arterial pressure (MAP) mm Hg in between groups

Table 4: Requirements for rescue analgesia

	Paracetamol (PCM)			Tramadol		
	Group FM	Group DM	[1]P	Group FM	Group DM	[1]P
0 h	5 (16.67%)	0 (0.0%)	0.019*	0 (0.0%)	0 (0.0%)	-
1 h	15 (50.0%)	9 (30.0%)	0.112	4 (13.33%)	0 (0.0%)	0.039*
2 h	7 (23.33%)	11 (36.67%)	0.399	10 (33.3%)	2 (6.67%)	0.019*
3 h	0 (0.0%)	7 (23.33%)	0.073	9 (30.0%)	8 (26.67%)	0.567
4 h	2 (6.67%)	1 (3.33%)	0.321	3 (10.0%)	10 (33.3%)	0.028*
5 h	0 (0.0%)	1 (3.33%)	0.321	0 (0.0%)	7 (23.33%)	0.004*
6 h	0 (0.0%)	0 (0.0%)	-	2 (6.67%)	1 (3.33%)	0.561
7 h	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
8 h	0 (0.0%)	1 (3.33%)	0.321	3 (10.0%)	1 (3.33%)	0.309

DISCUSSION

Major surgery is usually associated with postoperative pain that should be managed with a well-planned multimodal analgesic technique. We have done our study with non-opioid drug dexmedetomidine in view of better postoperative recovery profile and analgesic efficacy and compared it to fentanyl, an opioid-based anesthetic.

General anesthesia is usually proceeded with combining intravenous and inhalational agents and is the technique commonly used for head and neck cancer surgeries. An infusion pump is commonly used for administrating intravenous anesthetics and analgesic drugs in every controlled way and for better action (White *et al.* 1989).[8]

Previous literature showed that there is no conclusive study on equipotent doses of dexmedetomidine and fentanyl regarding their use for anesthesia and analgesia. Fentanyl was used with 2–6 μg/kg as the loading dose followed by the maintenance dose with an infusion of 0.5–5 μg/kg/h, whereas dexmedetomidine was used with 1 μg/kg as the loading dose followed by infusion of 0.2 to 0.7 μg/kg/h as the maintenance dose for anesthesia and analgesia (Hall *et al.*, 2000).[9]

Hence, in our study, we advocated using the minimum dose of fentanyl (2 μg/kg loading dose followed by 1 μg/kg/h as the maintenance dose) and dexmedetomidine (1 μg/kg loading dose followed by 0.5 μg/kg/h as the maintenance dose) with constant rate throughout the intraoperative period.

In our study, the HR and MAP were decreased following a loading dose of dexmedetomidine but later stabilized during the intraoperative period. There was an insignificant fluctuation in HR and MAP in the DM group as compared to the FM group in response to intubation and skin incision. These effects are probably caused by an inhibition of central sympathetic outflow that overrides the direct effects of dexmedetomidine on the vasculature, thus attenuating the stress-induced sympathoadrenal response to intubation, during skin excision, extubation, and during emergence from anesthesia.

These effects and responses are supported by a study by Uysal *et al.*[10] who compared dexmedetomidine with esmolol and sufentanil in hypertensive patients and demonstrated that dexmedetomidine administration before induction of anesthesia decreased the HR and systolic and diastolic blood pressure.

Goyal *et al.*[11] and Talke *et al.*[12] further supported our study where they showed that dexmedetomidine mitigated sympathetically induced rise in HR and nor-epinephrine levels during emergence from anesthesia but in the FM group, a significant rise in HR and MAP was observed in response to intubation and extubation ($P < 0.001$). The findings were favored by numerous studies conducted previously that revealed that dexmedetomidine attenuated hemodynamic pressor responses to laryngoscopy, intubation, and extubation (Bajwa *et al.*, 2012, Bekker *et al.*, 2008, Aksu *et al.*, 2009, Bindu *et al.* 2013, Kataria *et al.*, 2016).[6,13-16]

In our study, postoperative VAS was significantly lower in the DM group as compared to the FM group. Our study also showed that the consumption of rescue analgesia was higher in the FM group than in the DM group.

Various studies have shown that increased use of dexmedetomidine for pain management leads to decreasing trends of narcotic use and subsequently insignificant or no respiratory suppression. The use of dexmedetomidine leads to less use of inhalational agents intraoperatively, and a lower total dose of self-administered patient-controlled analgesia postoperatively showed its narcotic-sparing effect. This observation of the opioid-sparing effect of dexmedetomidine is supported by previous studies comparing the two drugs (Bajwa *et al.*, Blaudszun *et al.*, Khalil *et al.*,).[6,17,18] This opioid-sparing property of dexmedetomidine recommends its use to avoid side effects of opioids, such as nausea and vomiting, respiratory depression, pruritus, postoperative ileus, and urinary retention.

Manaa *et al.*[19] has shown in his study that the need for the first analgesic dose was significant earlier in the placebo group compared with FM and DM groups, where it was similar. Goyal *et al.*[11] also demonstrated that the time to first rescue analgesic and postoperative pain scores was comparable in both the FM and DM groups.

In current study, in the aspect of extubation emergence and recovery characteristics, the DM group has an advantage over fentanyl. The time to respond to verbal commands,

time to extubation, and time for orientation were lower in the DM group and it might be because of lower volatile anesthetic agent requirement. Our studies were supported by various previous studies (Goyal *et al.*, Turgut *et al.,* and Kim *et al.*)[11,20,21] where they found better recovery profiles and faster recovery in the DM group. Gupta *et al.*[22] and Richa *et al.*[23] reported a significantly slower extubation time in patients receiving dexmedetomidine compared with those receiving remifentanil for controlled hypotension. Turan *et al.*[24] observed that the DM group had a slower but smooth emergence from anesthesia compared with the control group.

CONCLUSION

It was concluded from current study that intravenous infusion of dexmedetomidine was better in controlling emergence agitation and postoperative analgesia, minimizing rescue analgesics consumption, and achieving perioperative hemodynamic stability as compared to intravenous infusion of fentanyl in patients undergoing head and neck surgeries.

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Conflicts of interest
There are no conflicts of interest.

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