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Comparison of Hypotension Caused By Dexmedetomidine–Fentanyl Combination with that of Midazolam–Fentanyl Combination in Hypertensive Patients Undergoing Tympanoplasty Surgery under MAC.

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ABSTRACT

Background: During middle ear surgeries done under local anaesthesia, patients may feel discomfort. A bloodless microscopic field is also essential to facilitate surgical exposure. Hypertensive patients pose additional problem in that they show a high blood pressure recording in the intraoperative period. Various combinations of analgesics and sedatives have been used to achieve hypotension, sedation and analgesia so as to improve the visibility of surgical field and provide comfort to patient and surgeon. **Methods**: Hundred ASA grade II patients above 30yrs of age with history of uncomplicated hypertension were selected. Baseline heart rate(HR), systolic & diastolic blood pressure, oxygen saturation and level of sedation were recorded at baseline and at every 5mins. ECG was monitored while supplemental oxygen was administered. Patients were divided into two groups, Group M and Group D, each consisting of 50 patients. Group M received intravenous midazolam 0.06mg/kg with a ceiling dose of 3 mg along with intravenous Fentanyl 2µg/kg with a ceiling dose of 100 µg over a period of 10 minutes. Group D received intravenous infusion of Dexmedetomidine 1µg/kg in 100 ml of normal saline with a ceiling dose of 50 µg along with intravenous bolus dose of Fentanyl 2 µg/kg with a ceiling dose of 100µg over a period of 10 minutes. **Results:** Fall in MAP was significantly more in group D as compared to that of group M. Level of sedation was better and the requirement of rescue analgesia was less in group D. **Conclusion**: Dexmedetomidine-fentanyl combination is superior and an excellent alternative to midazolam-fentanyl combination.

Keywords: Monitored Anaesthesia Care, Dexmedetomidine, Fentanyl, Midazolam.

INTRODUCTION

Middle ear diseases affect patients of all ages. Common middle ear pathological conditions requiring surgery in adults include tympanoplasty, stapedectomy, ossiculoplasty for otosclerosis, mastoidectomy and removal of cholesteatoma.[1] Tympanoplasty consists of reconstruction of perforated tympanic membrane with or without ossiculoplasty.[2]

Tympanoplasty can be performed under either local or general anaesthesia. Local anaesthesia technique has many advantages such as less bleeding, cost effectiveness, early recovery, ability to test the hearing of the patient, ability to diagnose iatrogenic facial palsy and postoperative analgesia.[3,4]

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Despite these advantages, tympanoplasty is still done under general anaesthesia due to concerns related to patient's anxiety, surgeon's comfort with hypotensive general anaesthetic technique and fear of sudden patient movement during operation under local anaesthesia.[1,3,4-7] The most common discomforts reported by patients during tympanoplasty under local anaesthesia were anxiety caused by noise of suction during surgery, discomfort due to positioning of head and neck and pain during surgery near stapes.[3,4] Hypertensive patients posted for tympanoplasty under local anaethesia pose an additional problem of increased blood pressure in the perioperative period. This leads to increased bleeding, poor visualization of structures at the surgical site, obscuring surgeon's view under microscope and thus, hinders surgical procedure leading to prolongation of surgical time & iatrogenic complications.[1]

According to previous literature, general anaesthesia with hypotensive anaesthesia was administered to overcome intraoperative hypertension.[5-10] General anaesthesia has the disadvantages of increased cost, delayed recovery, prolonged hypotension in the post-

operative period, post-operative nausea, vomiting and immediate post-operative pain.[11]

In view of advantages of local anaesthesia over general anaesthesia,[11] medications and combination of medications have been used to provide intraoperative hypotension, sedation, anxiolysis and analgesia during tympanoplasty surgery done under local anaesthesia so as to provide comfort to both surgeon and patient. This technique is called Monitored Anaesthesia Care (MAC).[12]

Medications commonly used for MAC include Ketamine,[13] Propofol,[14,15] Pentazocine,[16] combination of Midazolam-Fentanyl,[16-20] Midazolam as single agent,[21-23] Dexmedetomidine as a single agent and combination of Dexmedetomidine-Fentanyl.[20]

Combination of Dexmedetomidine with Fentanyl leads to potentiation of all actions of Dexmedetomidine resulting in excellent hypotension, sedation and analgesia during the intraoperative period.[20]

In the present study, the efficacy of Dexmedetomidine-Fentanyl combination has been compared with the time tested Midazolan-Fentanyl combination in providing hypotension in hypertensive patients undergoing tympanoplasty surgery under MAC.

The target point hypotension in this study was chosen at a mean arterial pressure between 80-90 mmHg.

MATERIALS AND METHODS

This prospective study was undertaken after Institutional Ethical Committee approval. Hundred ASA grade II patients above 30yrs of age with history of uncomplicated hypertension, taking regular antihypertensive drugs, scheduled for Tympanoplasty surgery were selected. Uncomplicated hypertension implies normal 2D-Echocardiography and normal ECG without any peripheral complications of hypertension. Informed consent was taken from all patients. All patients were counselled regarding sedation, local anaesthesia and operative procedure.

Patients with preexisting bradycardia and drug induced bradycardia due to chronic use of β-blockers & calcium channel blockers were excluded from the study because dexmedetomidine aggravates bradycardia. Patients with known allergy to local anaesthetics, pregnant and lactating females were also excluded from the study.

A preoperative assessment of all patients was done and those patients with normal values were selected for the study. Age, sex and weight of all patients were recorded. Thorough systemic examination of all patients was done preoperatively.

On the day of surgery, all patients were asked to take their regular morning dose of oral antihypertensive drug 2 hrs before surgery with sips of water. After taking the patient inside the operation theatre, patient was premedicated. Baseline heart rate(HR), systolic & diastolic blood pressure, oxygen saturation and level of sedation were recorded in all patients. ECG was monitored while supplemental oxygen 6l/min. via nasal cannula was administered to all patients. The level of sedation was assessed by Ramsay sedation score which is graded as:-

1. Agitated, restless
2. Cooperative, tranquil
3. Responds to verbal commands while sleeping
4. Brisk response to glabellar tap(or) loud voice while sleeping
5. Sluggish response to glabellar tap(or) loud voice while sleeping
6. No response to glabellar tap

Preoperative Mean Arterial Pressure (MAP) and Rate Pressure Product (RPP) were calculated from the recordings of heart rate, systolic and diastolic blood pressure of all patients.

The hundred patients were divided into two groups, Group M and Group D, each consisting of 50 patients. Group M received intravenous midazolam 0.06mg/kg with a ceiling dose of 3 mg along with intravenous Fentanyl 2µg/kg with a ceiling dose of 100 µg over a period of 10 minutes. Group D received intravenous infusion of Dexmedetomidine 1µg/kg in 100 ml of normal saline with a ceiling dose of 50 µg along with intravenous bolus dose of Fentanyl 2 µg/kg with a ceiling dose of 100µg over a period of 10 minutes. During this 10 minutes, the surgeon was asked to give local infiltration at the site of surgery with plain 2% xylocaine. Adrenaline was avoided in the local infiltration in view of hypertensive status of all patients. Surgery was commenced after confirmation of adequate analgesia.

At the end of 10 minutes, the heart rate, systolic and diastolic blood pressure, oxygen saturation and Ramsay sedation score of all patients in both the groups were recorded at every five minute interval for forty five minutes during the intraoperative period. The study ended at forty five minute interval because most middle ear surgery is over by forty five minutes after which closure begins and hypotensive anesthesia is no longer required.

Rescue analgesia in the intraoperative period was given in the form of nitrous oxide inhalation along with oxygen via the nasal cannula in the ratio of 60:40. The number of patients requiring rescue analgesia was recorded in both groups.

Occurrence of adverse effects like bradycardia oxygen desaturation, severe hypotension and vomiting was also recorded.

RESULTS

The demographic and baseline characteristics were comparable between the two groups [Table 1 & 2]

with P>0.05. At 5 minute interval itself [Table 2], there was significant fall in heart rate (HR) resulting in fall in rate pressure product (RPP) in group D (mean HR < 80/min and mean RPP < 7000) from the baseline values and from corresponding values in group M (mean HR>80/min and mean RPP>7500) with P<0.05. This low HR and RPP continued till the end of the study in group D whereas in group M the HR and RPP showed a slow decrease upto 25 minutes interval followed by slow increase [to > 85/min and > 8500 respectively] towards the end of the study.

Table 1: Demographic Characteristics

	Group D		Group M		P Value
	Mean	SD	Mean	SD	
Age	45.6	9.541711	42.88	10.10572	0.274742
Weight	70.12	12.69619	68.16	11.53863	0.570513

Table 2: Mean values of all parameters in both groups at various interval.

Time interval	Parameter	Group D		Group M		P Value
		Mean	SD	Mean	SD	
Pre-Operative	HR	88.72	14.03721	91.6	16.23525	0.505537
	MAP	114.8	6.350853	114.12	6.04373	0.699869
	RPP	10249.24	1928.421	10511.52	2051.22	0.643473
	SaO2	98.24	1.3	98.52	0.962635	0.391449
05 Min	HR	76.88	12.454	87.4	12.981	0.005264
	MAP	96.72	9.4142	99.04	7.4525	0.339087
	RPP	7491.9	1600	8727.3	1664	0.010169
	SaO2	95.04	2.508	95.84	1.8184	0.203406
10 Min	HR	75.04	10.772	86.24	12.768	0.001597
	MAP	90.28	9.1356	93.32	7.8619	0.213496
	RPP	6813.3	1332.7	8116.3	1603.5	0.003065
	SaO2	96.08	2.2898	96.48	1.8055	0.49628
15 Min	HR	72.84	10.036	84.68	12.362	0.000543
	MAP	85	8.4063	90.08	7.2106	0.026351
	RPP	6210.4	1059.5	7702.8	1572.4	0.000306
	SaO2	97.12	1.7156	97.92	1.579	0.092745
20 Min	HR	72.8	9.583	82.76	12.567	0.002896
	MAP	82.24	8.8189	88.92	5.8731	0.002995
	RPP	6009.6	1075.2	7431.3	1540.3	0.000473
	SaO2	97.96	1.7436	98.52	1.5308	0.233525
25 Min	HR	73	9.6003	81.76	11.204	0.0047
	MAP	81.32	7.553	89	4.813	0.000
			8		2	108
	RPP	5938.9	1161.8	7322.6	1259.9	0.000195
	SaO2	98.44	1.6093	98.92	1.222	0.241218
30 Min	HR	73.92	8.4947	82.76	10.698	0.00226
	MAP	82.36	8.5872	89.88	4.4283	0.000414
	RPP	6117.9	1007.7	7484.8	1168.1	<0.0001
	SaO2	98.72	1.1733	99.48	0.7703	0.009808
35 Min	HR	73.76	7.3046	83.76	11.137	0.000535
	MAP	82.76	6.3	91.68	5.305	<0.0001
	RPP	6134.4	775.7	7744.2	1274.2	<0.0001
	SaO2	98.92	1.115	99.52	0.7141	0.028841
40 Min	HR	74.44	8.6654	85.88	10.91	0.000165
	MAP	83.8	7.0711	94.72	4.5782	<0.0001
	RPP	6286.4	1070.5	8180.9	1167.9	<0.0001
	SaO2	99.12	0.9713	99.68	0.6904	0.023413
45 Min	HR	75.2	9.0323	87.08	12.086	0.000287
	MAP	85.28	7.1328	98.68	3.8267	<0.0001
	RPP	6446.7	1156.4	8610	1191.8	<0.0001
	SaO2	99.16	0.9434	99.68	0.6904	0.031328

At 10 min interval [Table 2] the diastolic pressure in group D showed significant fall from the baseline value and corresponding value in group M with P<0.05. In both groups the systolic pressure showed fall from baseline value from the beginning till the end of the study with maximum fall at 25 min interval in group D (113 mmHg) which is less than the corresponding value in group M (121 mmHg) with P<0.05. Both the groups showed fall in the MAP from the baseline values from the beginning of the study but the fall was significantly more in group D compared to that of group M.The target point MAP (between 80-90 mmHg) was attained at 15 min. interval in group D (mean MAP-85 mmHg) which is lower than the corresponding value in group M (mean MAP-90.08 mmHg) [Table 2]. The target point MAP was maintained between 80-85 mmHg in group D till the end of the study with p<0.005 [Table 2] as compared to that of group M in which it increased to >90 mmHg at the end of the study.

The number of patients attaining target point MAP was significantly more in group D as compared to that of group M at each interval [Table 3]. At the end of the study, the MAP was maintained within target point in 40 patients of group D while in group M the MAP increased above target point in all the patients.

Table 3: No. of patients achieving target point MAP in both the groups at each interval.

	No. of patients achieving target point MAP in both the groups at each interval		Number of patients showing RSS 3 in both groups	
Time interval	Group M	Group D	Group M	Group D
5 min	10	10	50	50
10 min	22	30	50	50
15 min	28	36	48	50
20 min	34	40	47	50
25 min	30	44	46	50
30 min	26	46	28	49
35 min	20	44	1	48
40 min	10	42	-	24
45 min	-	40	-	16
5 min	10	10	50	50

In the present study, the target point for sedation was chosen at Ramsay sedation score (RSS)-3 which was achieved at 5 min interval itself in all patients of both the groups [Table 3] but after 15 min interval the number of patients showing RSS-3 decreased in group M as compared to that of group D at each interval. At the end of study, no patient in group M showed RSS-3 while in group D RSS was maintained at 3 in 30 patients. This shows that sedation was maintained for longer duration and in more number of patients in group D compared to that of group M.

Since supplemental oxygen of 6l/min was administered to all patients of both groups, oxygen desaturation i.e., SaO2<92 was not encountered in any patient. But mild fall in oxygen saturation was seen during the initial 10-15 minutes in both groups. This fall was seen more in group D compared to that of group M [Table 2].

The requirement of rescue analgesia was seen more in group M as against group D [Table 4].

Table 4: Requirement of rescue analgesia in both groups

No. of Patients	Group M	Group D
	26	6

In the present study, adverse effects eg. bradycardia, severe hypotension & oxygen desaturation were not encountered in any patient. Also, no post-operative nausea-vomiting was encountered in any patient.

DISCUSSION

Middle ear surgeries like Tympanoplasty pose a different set of challenges for the patient, surgeon and anaesthesiologist. Hypertensive patients pose an additional problem of high blood pressure in the perioperative period.Sympathetic stimulation due to perioperative stress and movements of an anxious patient causes increased bleeding and disturbs the visualization of fine structures under microscope during Tympanoplasty surgery leading to graft failure.[3,4] Therefore, maintenance of hypotension throughout the surgery is crucial for the success of surgery.

According to previous literature, Tympanoplasty surgeries were done under general anaesthesia with hypotensive anaesthesia for the comfort of surgeon.[5-7,9,11] Controlled hypotension is defined as drug induced reduction in systolic blood pressure up to 80 mmHg and MAP to 50 mmHg.[6] Pharmacological agents used for controlled hypotension include inhalational anaesthetics, vasodilators, β blockers, opioids, α2-agonists. Tympanoplasty under local anaesthesia has many advantages compared to that of general anaesthesia. Good patient selection, pre-operative counselling and use of appropriate sedation are important factors for the success of surgery under local anaesthesia.[3,4] The ability to deliver safe & effective sedation, analgesia and hypotension throughout the intraoperative period is crucial for the success of middle ear surgeries under local anesthesia. This can be achieved by Monitored Anaesthesia Care (MAC), a term used for short procedures performed under local anaesthesia along with intravenous sedation titrated to a level that preserves spontaneous respiration and airway reflexes.[12] The drugs used to provide sedation, analgesia and hypotension should have quick onset, short duration of action, rapid and clear headed recovery with no postoperative complications and should be easy to administer and monitor.

Dexmedetomidine is a selective α2 agonist with potent hypotensive effect and mild analgesic and sedative effect. The onset of action of intravenous infusion is 5-10 minutes with peak effect at 15-30 minutes and duration of action is 1-2 hours which is dose dependent.[13,24]

Fentanyl is a short acting opioid with potent analgesic effect in addition to mild sedative and mild hypotensive effect. The onset of action of intravenous bolus dose of 100 µg is immediate with peak effect at 3-5 minutes and duration of action 30-60 minutes.[25]

Midazolam is a benzodiazepine that induces sleep, decreases anxiety and produces anterograde amnesia. It acts as GABAA receptors and enhances the effect of neurotransmitter GABA on GABAA receptors resulting in neural inhibition. The onset of action of intravenous bolus dose is 2-3 min with peak effect at 5-10 minutes and duration of action 45-60 minutes.

Literature suggests that combining a sedative with an opioid potentiates the sedative effect. Commonly, midazolam is given in combination with fentanyl in MAC.[16-20] This combination has the advantage of potentiating both hypotensive and sedative effect. It has minimal effect on heart rate as midazolam causes mild tachycardia and fentanyl causes mild bradycardia.[25,26] But the side effect of this combination is increased respiratory depression &

oxygen desaturation at the peak effect of both drugs.[17]

When dexmedetomidine is combined with fentanyl all its actions of hypotension, bradycardia, sedation and analgesia are potentiated, thus increasing its efficacy in MAC.[20]

In the present study, we have chosen to compare the hypotensive effect of dexmedetomidine-fentanyl combination with that caused by midazolam-fentanyl combination in hypertensive patients undergoing tympanoplasty surgery under MAC.

In hypertensive patients, due to alteration in the sympathetic autoregulation of blood pressure and resetting of arterial baroreceptors, MAP of <80mmHg may cause severe tissue hypoxia.[27-30] Therefore, in the present study we have chosen the target point MAP between 80-90 mmHg. With this MAP, visibility of surgical field was significantly better. The target point MAP was achieved faster and maintained throughout the end of the study with dexmedetomidine – fentanyl combination (group D) compared to that of midazolam-fentanyl combination (group M).

The lower heart rate and MAP in group D as compared to group M can be explained by decreased sympathetic activity caused by dexmedetomidine by virtue of its α2 agonist effect. Our findings were similar to other studies where lower heart rate and MAP were observed with dexmedetomidine.[24,31-34]

The low heart rate and MAP was maintained for longer duration in group D compared to that of group M which can be explained by longer duration of action of dexmedetomidine,[24,30] as compared to that of midazolam.[18,26] These results suggest that dexmedetomidine has clinical advantage over midazolam in providing a better operative field for microscopic surgery and therefore better surgeon satisfaction.

Over sedation leading to respiratory depression is an important complication during MAC.[17,35] In the present study, the doses of dexmedetomidine 1µg/kg,[16,19,20] midazolam 0.06 mg/kg,[16,17,19,20] and fentanyl 2µg/kg,[16,19,20] was chosen based on previous studies. The dose of midazolam 0.06 mg/kg is comparable to that of dexmedetomidine 1µg/kg in term of sedation.[21-23] The doses of all three drugs were limited to a ceiling dose in the present study to prevent oversedation and respiratory depression. In spite of supplemental oxygen, mild fall in oxygen saturation was encountered in both groups during the first 15 min due to the peak sedative effect of drugs. This fall was more in group D compared to that of group M at all intervals in the study This may be due to increased hypotensive & sedative effect caused by dexmedetomidine compared to that of midazolam at all intervals.[21-23]

In the present study, another reason for no evidence of severe oxygen desaturation & bradyapnea in any patient was the use of only single bolus dose of sedative drugs which were not followed by any maintenance doses.

In the present study, the level of sedation was measured according to Ramsay Sedation Score1. An RSS of 3 was chosen as appropriate for MAC based on previous studies.[16,19,20] In both the groups at 5 min interval itself, RSS of 3 was achieved. This shows that both dexmedetomidine & midazolam cause good sedation in combination with fentanyl.[16,19,20] But in group M the RSS was maintained at 3 only for a short duration compared to that of group D where it was maintained at 3 throughout the end of the study. These results are in accordance with those obtained in previous studies.[16,19,20,22,23] This proves that dexmedetomidine is a better sedative agent compared to that of midazolam and its duration of action is longer than that of midazolam.[18]

In the present study, all patients were administered an antiemetic ondansetron before surgery to overcome the emetic effect of fentanyl.[25] Therefore, there was no incidence of intraoperative and post-operative nausea-vomiting in both the groups. In addition, dexmedetomidine is known to have antiemetic properties.[11,24]

Less number of patients in group D demanded rescue analgesia as compared to group M. This is attributable to analgesic effect of dexmedetomidine whereas midazolam has no analgesic effect.[21,22,36]

A possible limitation of this study could be that surgeon & patient satisfaction scores were not studied & amnesia scoring and cognitive function testing for psychomotor impairment was not done as early discharge of the patient was not a concern of this study. Another limitation of this study could be that the effects of the drugs were studied only in uncomplicated hypertensive patients. The effects of α2 agonist on the cardiovascular system may be beneficial in high risk patients.[31] Further studies need to be carried out recruiting high-risk patients.

CONCLUSION

Dexmedetomidine-fentanyl combination is superior and an excellent alternative to midazolam-fentanyl combination in providing hypotension, sedation and analgesia in hypertensive patients undergoing Tympanoplasty surgery under MAC. It is associated with better patient and surgeon satisfaction.

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