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Use of Dexmedetomidine for Multimodal Analgesia in Head and Neck Cancer Surgeries- a Prospective Randomized Double Blind Control Study

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Abstract:

Introduction: *Patients with head and neck cancer are challenging not only in view of the airway management but also the secondary effects. Prior administration of radiotherapy, chemotherapy and opioids may also adversely affect the Intraoperative course and postoperative outcome. Thus there is always a need for safe & effective analgesia so as to provide better operative conditions and maintain stable hemodynamics not only intraoperatively but in postoperative period also for proper function of the reconstructive graft. Present study was aimed to study the role of dexmedetomidine as adjuvant in providing adequate perioperative analgesia and decreasing the dose of fentanyl postoperatively in head & neck cancer patients. To study the hemodynamic stability; and complications, if any.*

Methods: *Forty patients undergoing radical neck dissection were enrolled for the study after obtaining informed consent and approval from hospital ethical committee. They were randomly divided into two groups of twenty each. Group D received infusion of inj. dexmedetomidine 0.2mcg/kg/hr started just after premedication .Group S received inj. normal saline in similar doses. Hemodynamic variables were continuously monitored and recorded at regular intervals. Side effects if any were also studied. Transdermal fentanyl patch (25mcg/hr) was applied in both groups. The infusion was continued in the post operative period till 48 hrs till the patient was extubated. Pain and sedation scores were studied in postoperative period.*

Results and Conclusions: *Dexmedetomidine infusion@0.2 µg/kg/hr is useful adjuvant for multimodal analgesia and sedation (p=0); reduces the requirement of isoflurane (p<0.001) and neuromuscular blocking agents (p=0). It provides hemodynamic stability and reduces bleeding (p=0) in patients undergoing radical neck dissection.*

Keywords: *Perioperative analgesia, Opioids, Dexmedetomidine, Hemodynamics.*

I. Introduction

Malignancies are increasing in the modern era due to environmental and other factors besides the genetic ones. Previously thought to be commoner in older population, they are not uncommon in younger age groups. Widespread addiction of tobacco chewing in the adolescent Indian population leads to development of oral cancers early in thirties[1]. Besides this there may be malignancies of thyroid, larynx, parotid etc. which may require radical neck dissection. Airway is usually compromised in such patients either due to primary growth or secondarily due to preoperative radiotherapy, involvement of cervical lymph nodes etc .Airway maintenance is a challenge in such patients. Awake fibreoptic intubation is preferable and anesthetist managing such cases should be expert in other alternative techniques viz. retrograde intubation, high frequency jet ventilation, percutaneous tracheostomy etc. Whatever may be the case, surgical tracheostomy should always be kept as stand by. Besides this other important anesthetic considerations in such patients are sharing common field with the surgeon, presence of co morbidities viz. chronic bronchitis, COAD(chronic obstructive airway diseases), coronary artery disease, hypertension etc. Preoperative chemotherapy poses multiple problems for the anesthesiologist. The most common is thrombosis of peripheral veins making it difficult to establish a venous access. Individual agents have effects on various organs mainly affecting pulmonary, cardiac, renal and hematological systems. Paclitaxel and carboplatin cause decrease of more than 20% in diffusion capacity of carbon monoxide which may persist for upto5 months after stopping the drug. Methotrexate leads to oral mucositis, diarrhea, dyselectrolytaemias and myelosuppression leading to thrombocytopenia. Cisplatin has CNS toxicity, cyclophosphamide causes myocardial tissue injury and doxorubicin increases QT interval. In addition, preoperative radiotherapy leads to myelosuppression and dose dependent end myocardial fibrosis leading to restrictive cardiomyopathy.

Thus these patients are always at risk of noncardiogenic pulmonary edemas, hypersensitive pnuemonitis, pulmonary fibrosis and hemodynamic catastrophes[2]. Opioids are frequently used preoperatively for the management of cancer pain and may lead to cognitive dysfunction varying from delirium , sedation to even unconsciousness [3].Hypotension is usually demanded by the surgeons for better surgical field. Dexmedetomidine, a newer alpha 2 adrenergic agonist, is a suitable agent. It helps in maintaining stable hemodynamics thus reduces blood loss[4].It provides perioperative analgesia and sedation without causing respiratory depression[5].It has been used in loading doses upto1mcg/kg followed by maintenance infusions of 0.2-0.6 mcg/kg/hr. Higher doses are found to be associated with severe hypotension and bradycardia sometimes requiring pharmacological intervention. It is usually not seen with lower doses [6]. Loading doses may lead to initial hypertension followed by hypotension. Hence we avoided loading doses and used low dose maintenance infusions. Moreover it is essential to maintain stable hemodynamics in the perioperative period for better graft acceptance. Hence we continued the infusion in the postoperative period also.

II. Methods

This prospective randomized double blind placebo controlled study was conducted in forty patients undergoing radical neck dissection. Informed patient consent and approval from the institutional ethical committee was obtained before commencement of the study. The patients were randomly divided into two groups of twenty each using computer generated method. Group D received infusion of dexmedetomidine 0.2mcg/kg/hr started just after premedication and group S received normal saline in similar doses. The infusion of the study drug was continued in the postoperative period till 48 hours.

Preoperative indirect laryngoscopy was done to assess the airway and to have information about the extent of the tumor. After receiving the patient in the operation room routine monitoring was started viz. heart rate, non invasive blood pressure, ECG(electrocardiogram), SpO2(pulse oximetry), temperature etc. After performing allen test, intrarterial canula was inserted in radial artery for monitoring of invasive blood pressure; and central venous catheter for CVP (central venous pressure) monitoring. Intraoperative ventilation was monitored via flow volume, pressure volume loops and $EtCO_2$ (end tidal carbon di oxide).All patients were co loaded with 500 ml of hydroxyethyl starch. Administration of intravenous fluids was guided by central venous pressure and secondarily by urine output. Target was to maintain CVP 6-8 cm H2O and mean arterial blood pressure of 60-65 mmHg.Heart rate less than 20% of baseline values was considered as bradycardia. Hemodynamic variables were recorded at baseline and frequent intervals throughout the surgery and in the postoperative period. All patients were given inj glycopyrrolate0.2mg iv and inj. fentanyl 50mcg iv as premedication. Awake fibreoptic intubation was done with well lubricated reinforced cuffed endotracheal tube of appropriate size, after properly topicalising the patient. Anesthesia was maintained with N_2O:O_2:Isoflurane.Neuromuscular blockade was attained using inj vecuronium bromide given as guided by peripheral nerve stimulator to achieve TOF ratio of 4.

In cases of disproportionate rise in blood pressure, bolus doses of inj propofol 30mg were given. NTG infusion was kept as stand by to be used in case target blood pressure was not achieved even with propofol boluses. Transdermal patch releasing 25mcg/hr fentanyl was applied on non greasy non hairy skin just after induction of anesthesia in both the groups. Intraoperative blood loss was estimated via weighing the soaked gauges and amount of blood in suction bottle. Requirement of isoflurane was also noted. Surgeon satisfaction was assessed on a 7 point Likert scale.

After the completion of surgery, patients were shifted to intensive care unit and kept on elective mechanical ventilation for48hrs.Monitoring and drug infusion was continued in postoperative period. Sedation and pain scores were assessed in the postoperative period .If VAS score was more than 3 supplemental doses of inj fentanyl were given as boluses of 50 mcg. After 48 hrs patients were weaned and extubated. Postoperative blood loss was also assessed.

The primary end point was the ease of achieving adequate analgesia and sedation in the postoperative period. The secondary end points were maintaining mean arterial pressure within the desired range of 60-65mmHg. Inclusion criteria: Patients of age group 30-70 yrs of ASA status II/III scheduled for radical neck dissection. Exclusion criteria: Patients having heart block or arrhythmias, sensitive to opioids, those unwilling to participate in the study. Since radical neck dissection is a specialized surgery, all the subjects undergoing this surgery during the study period were taken as sample size. Normally distributed data were presented as mean and standard deviation (SD) and analyzed using t-test. Categorical data were presented as number of patients and percentage and analyzed using chi square test. Data were analyzed using IBM SPSS (Institute of Business Management Statistical Package For Social Sciences) Statistics 20.0 software and p value<0.05 was considered statistically significant.

III. Results

The study groups were similar in terms of age, gender, ASA status of patients, type and duration of surgeries and presence of co morbidities. (Table1).

There was less bleeding and better surgical field in group D as compared to group S (p value=0.0) (Table 2). In group D there was decreased requirement of muscle relaxants and isoflurane. (P value=0.0 and<0.001 respectively. (Table 2)

In the postoperative period desired sedation and pain scores were achieved in more number of patients in group D as compared to group S. (Table3). There was no significant incidence of complications in either group. (Table 4).One patient in group D had significant ST depression (1.5mm) which normalized after discontinuation of the study drug and was not included in the study. Patients in group D were more stable hemodynamically than group C at various points of time after induction. (Table 5, 6, 7)

IV. Figures and Tables

Table1. Demographic data

Variable	Group D		Group C		P value
	Mean	Standard deviation(+-)	Mean	Standard deviation(+-)	
Age(yrs)	52.2	13.2	54.2	15.1	0.70
Weight(kg)	74.2	13.4	72.4	11.4	0.69
Male	14	70%	15	75%	
Female	6	30%	5	25%	
Durationof surgery(min)	172.3	19.6	168.9	20.1	0.64

Table2. Drug Doses & Blood Loss

Variable	Group D		Group C		P value
	Mean	Standard Deviation(+-)	Mean	Standard deviation(+-)	
Dose of muscle relaxant(mg)	11.33	1.79	7.86	1.35	0
Isoflurane dial conc.(%)	0.26	0.16	0.53	0.08	<0.001
Blood loss (ml)	332	60.96	155.33	45.17	0

Table3. Postoperative Pain & Sedation Scores

Scores	Number of patients		P Value
	Group D	Group C	
VAS <3	18	2	0
VAS >3	0	20	0
RSS<3	19	1	0
RSS>3	0	20	0

VAS=Visual Analogue Scale(0=no pain…..10=severe pain) ;RSS=Ramsay Sedation Scale(0=agitated….6=unresponsive)

Table 4. Perioperative complications

Variables	Number of Patients	
	Group D	Group C
Respiratory depression	0	2
Bradycardia	3	0
Hypotension	0	0

Arrhythmias	1	0
Vomiting	0	2

Table5. Mean Arterial Blood Pressure

Various points of time	Group D		Group C		P value
	Mean(mm Hg)	Standard deviation(+-)	Mean (mm Hg)	Standard deviation(+-)	
Pre operative	99.8	11.00	99.80	8.50	1
Induction	96	10.90	103.90	8.90	0.038
Intubation	106	5.81	104.70	8.30	0.623
1 Min after Intubation	90	11.09	101	7.33	0.003
3 min	83	5.75	99.60	7.33	0
5min	80.53	7.26	99.70	7.61	0
10min	77.86	7.29	98.53	9.12	0
30min	76.86	4.80	97.86	10.34	0
50min	75	5.71	97.50	9.51	0
70min	77.66	6.99	97.30	9.70	0
90min	76.26	6.57	97.5	8.9	0
110min	77.53	7.50	96.50	9.02	0
130min	78	7.83	97.13	9.09	0
150min	79	10.24	96.80	8.11	0
170min	85.93	13.98	98.53	6.33	0.004
Extubation	96.40	9.86	100.96	7.98	0.175

Table6. Heart rate

Various points of time	Group D		Group C		P value
	Mean(/min)	Standard deviation(+-)	Mean (/min)	Standard deviation(+-)	
Pre operative	101.26	4.23	96.4	7.3	0.034
Induction	95.66	2.28	99.73	4.2	0.003
Intubation	104.5	3.6	107.06	4.07	0.079
1 Min after Intubation	88.2	5.2	98.7	5.1	0
3 min	78.9	6.6	89.46	4.53	0
5min	74.5	5.9	82.26	4.57	0
10min	75.6	2.28	80	5.01	0.004
30min	67	3.74	83.3	4.08	0
50min	64.2	2.37	84.13	3.15	0
70min	64.2	3.5	90.33	4.99	0
90min	57.46	4.627	89.86	4.2	0
110min	55.13	2.64	95.13	3.8	0
130min	62.26	4.92	87.2	3.14	0
150min	60.5	4.15	89.13	7.8	0
170min	65.9	2.93	98.86	2.44	0
Extubation	89.6	8.78	114.66	3.61	0

V. Conclusion

Radical neck dissection includes wide dissection around major blood vessels and nerves in the neck, making it imperative to provide adequate analgesia and hypotensive anesthesia .This not only minimizes blood loss but also provides clear surgical field thus minimizing the chances of injury to vital structures thus reducing surgeon anxiety and has better surgical outcome. Many drugs have been used to provide hypotensive anesthesia in these patients viz, NTG, propofol, clonidine etc[7].Malignancy patients have associated respiratory and cardiovascular compromises either due to disease, metastasis or due to prior administration of radiotherapy or chemotherapy. Moreover the metabolism and elimination of the drugs is impaired due to poor tissue perfusion and involvement of liver or kidney [8].Hence the drug used should have wider therapeutic range and margin of safety. Moreover there is airway compromise due to edema and hematoma in the post operative period thus the drug should cause minimal respiratory depression and maintain stable hemodynamics so as to minimize bleeding.

Dexmedetomidine, a selective alpha 2 receptor agonist is suited for the purpose since it provides sedation and analgesia without respiratory depression; hemodynamic stability helps in regulating blood pressure in the desired range of hypotensive anesthesia. Originally meant to be used for sedating critically ill patients, it is being widely used intraoperatively. Durmus et al have studied its use in providing hypotensive anesthesia in ottorhinolaryngological surgeries[9].Dexmedetomidine provides analgesia via its action on locus coeruleus and spinal cord[10].Studies by Talke et al have demonstrated its sympatholytic effects which may contribute to reduction in heart rate and blood pressure [11].We also observed that it provided better hemodynamic stability and thereby less bleeding in our patients.

It has been routinely administered as initial loading dose of 0.5 -1 mcg/kg/hr followed by maintenance infusion of 0.2 -0.6 mcg/kg/hr. But loading doses have been associated with initial hypertension and sometimes severe bradycardia warranting discontinuation of infusion, sometimes atropine has to be used.Hence we avoided the loading dose and maintenance infusion was also given at lower recommended doses (0.2mcg/kg/hr) .Similar doses have been used by Hall et al and compared with higher doses, they found no significant difference in pharmacological actions; and decreased incidence of bradyarrythmias as an advantage[6].We used lower doses also because malignancy patients are already compromised as discussed previously. In this study we observed there was markedly decreased bleeding and better operative conditions thus increasing surgeon satisfaction in group D as compared to group S .Our findings are in accordance with the studies by Malhotra et al [12].Besides induced hypotension, this may be due to sedative and analgesic effects of dexmedetomidine. This beneficial effect was used as an advantage in the postoperative period also. Group D patients were more comfortable in the postoperative period and had better grafts. Besides control of bleeding it is necessary to avoid hypertension in the postoperative period because rise in blood pressure may lead to flap edema and inadequate perfusion of the graft [13].These measures increase the chances of survival of the graft. Thus we continued the study drug in the postoperative period and used it as an advantage. Since these patients have to be kept on elective mechanical ventilation in the postoperative period, continuation of study drug helped to attain sedation, analgesia and stable hemodynamics in this period[14].

We thus conclude that low dose (0.2mcg/kg/hr) dexmedetomidine provides better surgical field and adequate postoperative analgesia & sedation without causing complications in patients undergoing radical neck dissection.

The limitations of this study are that the sample size could have been larger for more accurate analysis of the data. We could have studied the depth of anesthesia as well, using entropy or bispectral index monitoring; for better authentication of the results.

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