A Randomized Controlled trial to compare Nitroglycerine with Dexmedetomidine for Controlled Hypotension during Endoscopic resection of Juvenile Nasopharyngeal Angiofibroma

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Abstract
Background: Juvenile nasopharyngeal angiofibroma(JNA) is a locally invasive benign vascular tumor. Controlled hypotension is used to facilitate endoscopic resection to reduce the blood loss and stabilize the hemodynamics. Various agents are tried till now to achieve the goal.
Objective: To compare the effectiveness of Nitroglycerine withDexmedetomidine in terms of hemodynamics and blood loss during Endoscopic resection of Juvenile Nasopharyngeal Angiofibroma
Methods: Ethics Committee has approved this Randomized Controlled trial which was conducted among 40 patients randomly divided into two groups by simple randomization using computer generated random numbers.Informed consent was taken from all the eligible participants. Group D(n=20) receivedDexmedetomidine 1µg/kg over 15 min followed by a

maintenance infusion at 0.5µg/kg/hourand GroupN (n=20)received (n=20), Nitroglycerine 0.5µg/kg/min and titrated in doses 0.5-5µg/kg/min for target blood pressure respectively. Standard guidelines were followed throughout the study protocol for data collection. Data was analyzed using mean and standard deviation in two groups.

Results: Both the groups were comparable for baseline parameters. There is statistically significant difference in mean pulse rate between two groups Group D: 66.09±2.83, Group N: 86.59±4.24 (p=0.0001). Blood loss was lower in Group D: 310.71±140.58 compared to Group N: 482.61±141.42, and is statistically significant (p=0.0004). SBP,DBPand MAP were lower in Group D throughout the surgery.

Conclusions: Dexmedetomidine is a better hypotensive agent with favorablehemodynamics and less blood loss when compared to Nitroglycerine. Hence we recommend use of Dexmedetomidine over nitroglycerine in patients during Endoscopic resection of Juvenile Nasopharyngeal Angiofibroma.

Keywords: Controlled Hypotension, Dexmedetomidine, Endoscopy, Juvenilenasopharyngealangiofibroma, Nitroglycerine, Massive Hemorrhage

INTRODUCTION

Juvenile nasopharyngeal angiofibroma (JNA) is a highly vascular, locally invasive benign tumor, exclusive of male adolescents, with an incidence of 1:150,000. JNA was first described byHippocrates 5th century BC. In 1940 Friedbergcalled it juvenile angiofibroma.[1]

JNA arises from posterolateral wall of nasal cavity,which has rich vascular supply from carotid system. Anatomicallocation of tumor is readily accessible for Transnasalendoscopic resection [2, 3]which is gold standard of care.The potential risk of massive bleeding [4] exist throughout surgery. IntraoperativeBleeding[5]interferes with surgical field visibility,posechallenge for both surgeon and anesthesiologist.

Controlled hypotension[6]provides a relatively bloodless field, improves visibility of anatomicallandmarks, minimizes blood lossandfacilitates safe, rapid and effective tumor resection. Induced hypotension involves reducing arterial blood pressures 30-40% below normal range. Various pharmacological agents are used to achieve controlled hypotension including vasodilators (Nitroprusside, Nitroglycerine,Hydralazine), inhaled anesthetics, propofol, beta blockers, adenosine and alpha 2 agonists.[6]

Nitroglycerine or Glyceryl nitrate was synthesized by Ascanio Sombrero in 1847, a directly acting vasodilator has been used to because of its rapid onset, rapid offset and easy titrability with a short half-life of 2 to 3 minutes. Dexmedetomidine is a highly selective alpha 2 adrenergic agonist with sedative,anxiolytic, sympatholytic and opioid sparingeffects. [3-6]

In thisstudy we compared nitroglycerine (NTG) versus Dexmedetomidinefor inducing controlled hypotension with primary objective- monitoring hemodynamic parametersand secondary objective:amount of blood loss during Endoscopic resection of nasopharyngeal angiofibroma.

PATIENTS AND METHODS:

A prospectiverandomizedsingle blinded study was conducted at Government ENT Hospital, Osmania Medical College, Hyderabad during 2016-2018,Institutional ethics committee has approved the study which included 40 patients in age group of 10-20 years posted for Transnasalendoscopic resection of Nasopharyngeal Angiofibroma.

At pre-anesthetic evaluation all patients were explained about surgery and written informed consent/assentwas obtained. All patients were thoroughly investigated for comorbid conditions and cleared for surgery.

Patients were randomized into two groups by simple randomization using computer generated random numbers Group D (N=20) received Dexmedetomidine 200µg in 100 ml of normal saline (2µg/ml), administered as IV infusion in pediatric volumetric burette set, dose 1µg/kg over 10 min followed by maintenance infusion0.5µg/kg/hour. Group N(N=20) received Nitroglycerine25mgin100ml normalsaline, infusion started $5\mu g^{-1}kg^{-1}min^{-1}$ adjusted in between $0.5\text{-}5\mu g^{-1}kg^{-1}min^{-1}$to achieve desired mean arterial pressureintraoperatively. Effects of both agents on hemodynamic parameters and blood loss during surgery were noted in a preset proforma.

Inclusion Criteria:

1. ASA Grade I or II patients
2. Age 10- 20 year

Exclusion Criteria:

1. ASA Grade III
2. History of Coagulopathy
3. Anticoagulants, history of Drug sensitivity

Standard General Anesthesia technique was used in both groups, Glycopyrrolate 0.04mg/kg, Ondansetron 0.08mg/Kg, Thiopentone 3-5mg/kg and vecuronium 0.08mg/kg, Intubated with appropriate sized cuffed ET tube and throat packed. IPPV, 33:66; O_2/N_2O, desflurane 4-6%, Ventilation adjusted to maintain EtCO2**:** 30-35 mm Hg. Two 16G venflon were secured on forearms, one for fluids, blood, drugs and other for infusion of hypotensive agents. A 15° Head up position used to facilitate venousdrainage.

Monitoring: ECG-V5lead with ST segment analysis to detect ischemia,NIBP, SPO2, EtCO2, Urineoutput.Before start of surgery, MAP was decreased to achieve a target MAP of 60-70 mmHg in both groups, baseline SBP, DBP,MAP,HR and S_PO_2 were recorded every 10min till end of surgery.Fasting fluid deficit was replaced during first 1 or 2 hour. Maintenance was given with 5 to 6 mL/kg-hour of Ringer'slactate. Blood loss was carefully observed and replaced with equal amount of colloid or three times the amount in crystalloid. Intraoperative blood loss was measured by blood volume in suction bottles and swabs, if blood loss exceeds 20% to 25% of patient's total blood volume it is replaced with blood. Total duration of surgery was 150mins in all patients. Intraoperatively severe hypotension(MAP<55mmHg) was corrected by stopping inhalation agent, Ringers lactate 200ml IV bolus, Mephenteramine 6mg IV bolus injection. Bradycardia (HR<50bpm) corrected by Atropine 0.6mg IV.Hypotensive agent was stopped 10 minutes before anticipated end of surgery, residual neuromuscular block antagonized with neostigmine 50µg/kg &Glycopyrrolate 10µg/kg. After recovery, patients were transferred to post anesthesia care unit (PACU) for monitoring.

Statistical analysis: Data was entered using MS Excel software.It was done using mean, standard deviation. Independent t test was used to test the difference in the mean. p values < 0.05 are considered statistically significant.

RESULTS

Table 1: Distribution of mean age & weight of study groups

Characteristics	GroupN (Mean±S.D.)	GroupD(Mean±S.D.)	P
Age (years)	15.33±2.64	15.94±2.26	0.4373
Weight (kg)	45.29±9.75	45.29±9.75	0.8192

All patients were males in the age group 10-20 years and weight in the range of 28-60Kg. No statistically significant difference was noted between both groups (p>0.05). (Table 1)

Table 2: Intraoperative Pulse Rate variations

Time (min)	Group N	Group D	't' value	'p' value

	Mean±S.D.	Mean±S.D.		
0	74.86±8.39	72.05±6.07	1.2135	0.2324
10	79.74±7.81	67.05±5.85	5.8159	0.0001
20	87.53±7.11	62.62±5.49	12.4015	0.0001
30	94.83±5.69	60.49±4.49	21.1878	0.0001
40	100.98±4.94	59.10±3.44	31.1132	0.0001
50	102.53±4.96	58.11±3.23	33.5618	0.0001
60	104.56±6.64	57.47±2.92	29.0325	0.0001
70	104.81±6.6	57.45±3.42	28.4928	0.0001
80	104.20±6.69	57.05±3.36	28.166	0.0001
90	102.72±6.23	57.34±3.45	28.4977	0.0001
100	102.40±5.8	57.48±3.6	29.1922	0.0001
110	102±5,66	57.39±3.54	29.8841	0.0001
120	101.99±5.98	57.35±3.34	29.146	0.0001
130	95.69±5.59	60.63±2.92	24.8613	0.0001
140	91.77±3.8	64.49±2.72	26.1065	0.0001
150	86.59±4.24	66.09±2.83	17.9844	0.0001

Heart rate in both study groups were observed at specified intervals. The difference in heart rate was highly significant($p<0.0001$) statistically, with lower pulse rates recorded in Dexmedetomidine group from 10 minutes of starting test drug infusions to stopping infusion (57.05±3.36 and 67.05±5.85 respectively) when compared with nitroglycerine group(79.74±7.81and 104.81±6.6). (Table 2)

Table 3:Systolic blood pressure variations

Time (min)	Group N	Group D	t value	P value
	Mean±S.D.	Mean±S.D.		
0	112.47±10.02	110.37±11.11	0.6277	0.5339
10	105.62±9.65	109.79±9.72	1.3615	0.1814
20	98.91±8.95	104.30±9.33	1.8644	0.07
30	94.11±7.86	99.02±8.33	1.8241	0.07
40	90.74±7.24	95.85±8.28	2.0017	0.0525
50	87.37±6.15	91.96±7.17	2.0145	0.0511
60	85.24±5.02	89.01±6.08	1.9961	0.0531
70	85.03±4.52	87.71±5.48	1.6127	0.1151
80	85.05±4.42	86.33±5.17	0.8336	**0.0497**
90	85.73±4.39	85.89±4.65	0.1122	0.9113
100	85.34±3.99	85.33±4.53	0.007	0.9945
110	85.26±4.18	85.23±4.69	0.0222	0.9824
120	84.95±5.98	84.87±3.34	0.0569	0.9549
130	90.71±3.94	88.10±4.22	2.0217	0.0503
140	91.77±3.8	91.99±4.42	0.1688	0.8669
150	103.89±5.88	93.56±4.14	6.4241	**0.0001**

The systolic blood pressure was almost similar ($p>0.05$) in two groups except at 80 min and 150 min where it was significantly lower in dexmedetomidinegroup compared to nitroglycerine group ($p<0.05$). (Table 3)

Table 4: Diastolic blood pressure variations

Time (min)	Group N	Group D	t value	'p' value
	Mean±S.D.	Mean±S.D.		
0	74.91±6.14	71.88±7.01	1.4493	0.1555
10	69.14±5.53	72.25±7.26	1.524	0.1358
20	64.22±4.9	67.98±6.75	2.016	0.0509
30	60.04±4.52	63.27±6	1.9229	0.062
40	57.85±3.41	59.12±3.12	1.2288	0.2267
50	54±3.38	55.25±3.34	1.1764	0.2467
60	52.75±3.23	53.74±2.6	1.0678	0.2924
70	52.51±3.15	52.85±2.38	0.3851	0.7023
80	52.82±2.82	53.25±3.26	0.4461	0.658
90	52.98±2.79	52.92±2.95	0.76	0.452
100	52.58±2.83	52.57±2.87	0.00111	0.9912
110	52.48±2.83	52.42±2.89	0.0663	0.9475
120	52.79±2.43	52.54±2.41	0.3267	0.7457
130	57.72±3.01	56.49±2.54	1.3967	0.1706
140	62.56±3.36	60.96±2.12	1.8011	0.0769
150	70.75±4.8	63.02±1.95	6.6724	0.0001

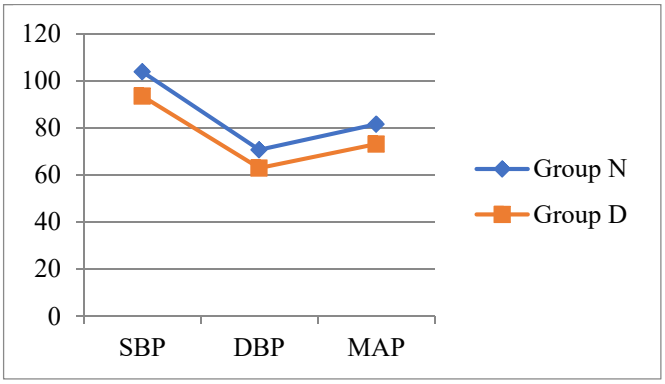
There was no significant differences related to diastolic blood pressure in two groups ($p>0.05$). (Table 4).

Table 5: Intraoperative Mean Arterial Pressures between study groups

Time (min)	Group N	Group D	t value	P value
	Mean±S.D.	Mean±S.D.		
0	87.48±7.04	84.73±8.12	1.1444	0.2596
10	81.51±6.4	84.92±7.72	1.5208	0.1366
20	75.88±5.89	79.89±7.23	1.923	0.062
30	71.41±5.32	75.08±6.5	1.954	0.0581
40	68.33±4.87	71.05±3.75	1.979	0.0551
50	65.11±4.27	67.18±4	1.5822	0.1219
60	63.64±3.09	65.61±4.27	1.737	0.0905
70	63.36±3.34	64.48±3.01	1.114	0.2723
80	63.67±3.3	64.42±3.3	0.4461	0.4767
90	63.92±3.16	63.87±3.3	0.7187	0.9612
100	63.52±3.16	63.52±3.28	0	1
110	63.48±3.05	63.47±3.18	0.0101	0.992
120	63.58±2.97	63.38±2.99	0.2122	0.8331
130	68.89±2.91	67.14±2.82	1.9313	0.0609
140	73.62±3.34	71.35±2.66	2.3776	**0.0226**
150	81.7±5.01	73.2±2.55	6.762	**0.0001**

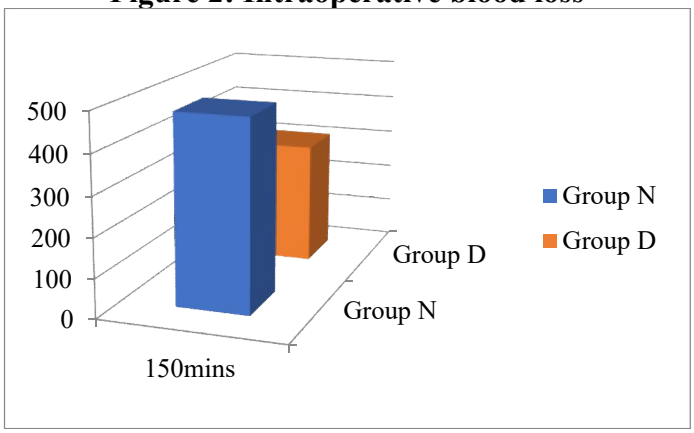
The mean arterial pressure was significantly lower in dexmedetomidine group at 140 and 150 min compared to nitroglycerine group ($p<0.05$). (Table 5)

Figure 1: Blood pressure variations after stopping test drug infusion in both study groups



The systolic blood pressure, diastolic blood pressure and mean arterial pressure was significantly lower dexmedetomidine group compared to nitroglycerine group after stopping test drug infusion ($p<0.05$). (Figure 1)

Figure 2: Intraoperative blood loss



Intraoperative blood loss was significantly lower dexmedetomidine group compared to nitroglycerine group($p<0.05$). (Figure 2)

DISCUSSION:

In 1918, Canon and his colleagues introduced concept of permissive hypotension[7] as a resuscitation strategy used in acute phase of traumatic hemorrhagic shock and its variation known as controlled or induced hypotension (IH) were used intraoperatively in various specialtiesto facilitate surgery by creating a clearer surgical view, reduce intraoperative blood loss . The etiology of JNA is unknown,anesthesiamanagement[4] of these tumors is a challenge owing to vascularity, adjacent anatomical structures and intraoperative bleeding,trans nasalendoscopic[8]resection is gold standard of care, with controlled hypotension tumor removal is easier, quicker and satisfactory.

Enderby GEH et al[9] used ganglionic blocking drugs for controlled hypotension in maxillofacial surgery.SchalbergSJ et al [10]reported using sodium nitroprusside for hypotensive anesthesia and blood loss in orofacial corrective surgery.A mean arterial pressure 30% below a patient's usual MAP, with a minimum of 50 mmHg in ASA Class I patients and 80 mmHg in elderly, is clinically acceptable. [11]Hypotension should be considered satisfactory when bleeding appears to be minimal with adequate organ perfusion (urine out > 0.5ml/kg/min). In theory, as long as mean arterial pressure exceeds sum of colloid osmotic pressure and venous pressure, circulation should be adequate for tissue needs, theoretically a pressure of 32 mmHg should be sufficient, in practice it is below the safe limit due to specific blood flow requirements of different organs. Controlled hypotension rarely results in vital organ damage as autoregulation maintains their perfusion over a wide range of blood pressures. The use of Dexmedetomidine for providing hypotensive anesthesia during

septoplasty and tympanoplastywas studied by Durmus M et al[12]and Ayoglu H et al.[13]Hypotensive anesthesia should be induced in relation to patient's preoperative blood pressure rather than specific target pressure and limited to level necessary to provide a bloodless field,within safety limits of cerebral and coronary blood flow.
Efficacy of Dexmedetomidine in providing better surgical field and less blood loss during controlled hypotension was reported by Durmus M et al [12]intympanoplasty, septoplasty and maxillofacial surgeries. Asingle dose of Dexmedetomidine0.5µg/kg/min IV,10mins before induction produced a significant fall in MAP and Heart rate as reported byBasarH etal. [14]Controlled hypotension with Dexmedetomidine in middle ear and maxillofacial surgeries provided an ideal surgical field with predictable hemodynamic effectsresults of this study concluded the same.UlgerMH et al[15] comparednitroglycerine with Dexmedetomidineas hypotensive agents (MAP 65-75mmHg) inmiddle ear surgery, and concludedthat hypotension and hemodynamic stabilitywas better with Dexmedetomidine,results in present studyare in accordance with this study. Dexmedetomidine shows better hemodynamic stability, clear surgical field,lower(VAS) pain scores and few side effects as reported by Guven DG et al. [16]CincikasD et al [17] used nitroglycerine infusion (0.79±0.34 µg/kg/min) during endoscopic nasal surgery to maintain MAP of 50-60 mmHg, observed reduced surgical bleeding and improved endoscopic vision.In this prospective randomized study, Dexmedetomidine and Nitroglycerine were equally effective as hypotensive agents(MAP of 60-70mmHg).It was observed that Dexmedetomidine ensured ideal surgical conditions during endoscopic resection and average blood loss was less when compared with nitroglycerin.In Group N, Fentanyl was used @ 2ug/Kg and NTG infusion(0.5-5ug/Kg/min) started after intubation and before surgical incision and rate of infusion titrated to maintain mean pressure range of 60-70mmHg. Induction of controlled hypotension with NTG depends on intravascular fluid volume. Excessive decreases in diastolic blood pressuredecreases coronary blood flow and mayevoke baroreceptor-mediated reflex increases in sympathetic nervous system activity result in tachycardia and increased myocardial contractility. Nitroglycerin produces a dose-related prolongation of bleeding time thatparallels hypotension, it may also be due to direct effect of nitroglycerin on vascular tone resulting in vasodilation.Karl-Erik Karlberg associates[18] assessed effect of IV NTGand concludedNTG inhibits plateletaggregationin higher doses due to glyceryl dinitrate formation.
In this study throughout surgery,difference in mean heart rates in,GroupD: (60.61±4.49) and Group-N(95.58±9.41), and which is statistically significant from 10mins of starting the test drug infusions ($p<0.0001$).The mean SBP(GroupD-92.73±8.58,GroupN-91.86±8.77),DBP(GroupD-58.40±7.03,GroupN-58.33±7.48), MAP(GroupD-69.85±7.47, GroupN-69.54±7.91) between two groups shows no statistically significant difference.
Infusion of hypotensive agent was stopped 10mins before end of surgery.Intraoperatively mean blood loss in GroupN-482 ± 141.42 andGroupD-310.71±140.58 respectively. Results in this study suggests that both Nitroglycerine and Dexmedetomidine are equally good for inducing controlled hypotension in endoscopic resection of NPA. Intraoperative blood loss in Group D was significantly less when compared withGroup N. The increased blood loss with nitroglycerin can be due to increased heart rate, prolongation of bleeding time by NTG due to inhibition of platelet aggregation partially offsettingbeneficial effects of hypotension.

Conclusion:
Dexmedetomidinewas safeand equally effective in producing controlled hypotension when compared with Nitroglycerine, Dexmedetomidinehas the advantage of cardiovascular stability and less blood loss.The inherent propertiesofanxiolysis,sedation, analgesia,opioid

and anesthetic sparing effects, easy administration, predictability with anesthetic agents and lack of toxic side effects while maintaining adequate perfusion of vital organs makesDexmedetomidine a safe and near ideal agent for hypotensive anesthesia .

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