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ORIGINAL ARTICLE

A comparative study of dexmedetomidine and propofol as sole sedative agents for patients with aneurysmal subarachnoid hemorrhage undergoing diagnostic cerebral angiography

Kamath Sriganesh · Madhusudan Reddy · Sritam Jena · Mohit Mittal · G. S. Umamaheswara Rao

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Abstract
Purpose Subarachnoid hemorrhage is an acute neurological emergency requiring urgent confirmation of the diagnosis for planning definitive management. Due to altered consciousness, most patients require sedation for conducting this procedure smoothly. Currently, it is unclear if any one particular sedative drug has a favorable profile in patients undergoing cerebral angiography. The aim of this study was to compare the traditionally used sedative drug propofol with a newer alternative, dexmedetomidine, in patients with subarachnoid hemorrhage undergoing cerebral angiography.
Methods Sixty adult patients with good grade subarachnoid hemorrhage undergoing diagnostic cerebral angiography were prospectively randomized to receive either propofol ($n = 30$) or dexmedetomidine ($n = 30$) following ethics committee approval and informed consent.
Results Compared to dexmadetomidine, propofol was associated with an earlier time for onset of sedation (2.3 ± 1.9 min vs. 15.4 ± 5.7 min; $P < 0.001$), but with an increased number of adverse respiratory events (11/30 vs 1/30; $P = 0.003$) and movement during the procedure (5/30 vs. 0/30; $P = 0.05$), necessitating additional supplementation of sedation (13/30 vs. 7/30; $P = 0.17$) and repetition of the imaging sequences. The total procedure time and time for recovery were similar for the propofol and dexmedetomidine groups, while the heart rate was lower in patients in the dexmedetomidine group.
Conclusion Dexmedetomidine appears to be superior to propofol as a sole sedative agent for sedation during cerebral angiography in patients with subarachnoid hemorrhage.

Keywords Cerebral angiography · Dexmedetomidine · Propofol · Aneurysmal subarachnoid hemorrhage

K. Sriganesh (✉) · M. Reddy · S. Jena · M. Mittal · G. S. Umamaheswara Rao
Department of Neuroanaesthesia, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India
e-mail: drsri23@rediffmail.com

Introduction

Subarachnoid hemorrhage (SAH) is a devastating complication of ruptured intracranial aneurysm. Among the various diagnostic tools available, cerebral angiography (CA) is considered to be the gold standard because of its high degree of accuracy, better visualization of the cerebrovascular anatomy and ability to assess cross-circulation and detect vasospasm. Patients with SAH, especially those with poor grade SAH, are often agitated, restless and disoriented and do not cooperate with the healthcare professionals carrying out this invasive procedure, thereby increasing the procedure-related risk. Pain, vomiting or movement adds further to this risk. Various drugs, such as propofol, fentanyl, midazolam, droperidol and diazepam, have been used either alone or in combination to provide sedation during CA in patients with intracranial aneurysms, with varying degrees of success and adverse effects [1–4]. Dexmedetomidine, a centrally acting alpha-2-agonist, is increasingly being used for sedation in patients undergoing radiological imaging, particularly in the pediatric patient population [5, 6]. Dexmedetomidine has a sympathetic suppressant effect which is advantageous in patients with aneurysmal SAH prior to the initiation of treatment of the aneurysm. In comparison, propofol causes a deeper level of sedation and higher degree of respiratory compromise unless the depth

of anesthesia is monitored [7]. The aim of our study was to compare dexmedetomidine with propofol, the most commonly used sedative agent when performing CA, in terms of its respiratory, hemodynamic and sedative effects during CA.

Materials and methods

Methods

After institutional ethics committee approval and a completed written informed consent form from the next of the kin, 60 adult patients with SAH based on computed tomography (CT) scan findings were included in this prospective study. The patients were allocated randomly to either the dexmedetomidine ($n = 30$) or propofol ($n = 30$) arm based on a computer-generated random number table. The sample size of 30 in each group was calculated based on the time taken for onset of sedation from an earlier study and the results of our pilot study [6]. The results of these earlier studies revealed that 28 patients in each group were required to detect a 20 % difference in the onset of sedation with an α error level of 0.05 (two-sided) and a power of 0.8. Hence, we allocated 30 patients to each group to compensate for any possible early withdrawals from our study. Patients in a poor neurological state [World Federation of Neurological Surgeons (WFNS) grades IV–V], age <18 years, traumatic SAH, history of drug or alcohol abuse, allergy to the study drugs, respiratory problems and heart block were excluded from the study. Patients with a heart rate (HR) of <50 beat per minute and a mean arterial pressure (MAP) of <60 mmHg were also excluded. All patients were monitored with electrocardiogram (ECG), non-invasive blood pressure monitor, pulse-oximetry and capnography during the procedure. The Ramsay Sedation Scale (RSS) was used to assess the level of sedation during the procedure [7, 8]. Supplemental oxygen at 4 l/min was administered to all patients through a facemask. The procedure was started after the RSS reached 4. The actual diagnostic procedure involved femoral arterial catheterization and bilateral carotid and vertebral artery angiography. All patients received local anesthetic infiltration in the groin before the femoral arterial puncture. Heparin was continuously infused at 1,000 U/h during the procedure through the microcatheter to prevent thrombus formation.

Sedation protocol

In the study group, dexmedetomidine (Dexem®; Themis Medicare Limited, Haridwar, India) was administered at 1 μg/kg over a 10-min period followed by a continuous infusion at a rate of 0.5 μg/kg/h until the end of the procedure, using a dedicated peripheral venous access. The control group received propofol (Profol®; Claris Lifesciences Limited, Ahmedabad, India) 1.5 mg/kg bolus followed by 1.5 mg/kg/h infusion. In cases of failure of the initial sedation protocol to provide optimal RSS level or movement of the patient at any time during the procedure, in the dexmedetomidine group, a 0.25 μg/kg bolus was administered and the infusion rate increased by 0.25 μg/kg/h, and in the propofol group, the 0.5 mg/kg bolus was repeated and the infusion rate increased by 1 mg/kg/h. If the above measures failed to allow the procedure to be completed, in both groups fentanyl 1 μg/kg was given or the technique was converted to general anesthesia. The effect of dexmedetomidine and propofol on HR, MAP, oxygen saturation (SpO_2), end-tidal carbon dioxide concentration ($ETCO_2$), respiratory rate (RR) and RSS was recorded every 5 min starting from baseline until the RSS returned to the baseline value after the procedure. Bradycardia and hypotension were defined as a decrease from baseline value by 20 %. Bradycardia was managed with atropine 0.6 mg intravenous (IV) and hypotension with intravenous fluids, bolus of vasopressor or temporary reduction of the infusion rate of the sedative drug—in that order. Respiratory events, such as apnea, oxygen desaturation and airway obstruction, were monitored. Apnea was defined as cessation of respiration for >20 s; desaturation was defined as an SpO_2 value of <92 % and airway obstruction was defined as noisy breathing with paradoxical chest expansion. Intervention, in the form of neck repositioning, jaw thrust, airway insertion or endotracheal intubation, was carried out if the SpO_2 decreased to <92 %.

The primary outcome variable in this study was the incidence of adverse respiratory events with dexmedetomidine and propofol when each was used as a sole sedative agent. The secondary outcome variables were the onset and recovery times, movement during the procedure and additional sedative supplement to complete the procedure.

Data analysis

Changes in hemodynamic and respiratory variables and sedation scores were compared within and between the groups using a repeated-measures analysis of variance with a post hoc Bonferroni test where applicable. All continuous variables were expressed as mean ± standard deviation. Categorical variables were analyzed using Fisher's exact test. The RSS between the two groups were analyzed by a Kruskal–Wallis test. A p value of <0.05 was considered to be significant. The SPSS® version 17.0 (SPSS Inc., Chicago, IL) statistical package for Windows was used for analysis.

Results

The study included 60 adult patients (age range 21–72 years), with 30 randomly allotted to receiving dexmedetomidine (study group) and 30 randomly alloted to receiving propofol (control group). All patients successfully underwent CA with either dexmedetomidine or propofol sedation, with the exception of one patient in the propofol group who required conversion to general anesthesia to complete the study.

Demographic data

There was no statistically significant differences in the demographic characteristics of the two groups (Table 1). The WFNS and Fischer grades were comparable between the two groups.

Cardiorespiratory changes

Baseline HR was similar between the groups, and there was a decrease in HR in both the groups following administration of the sedative drug ($p < 0.05$), with this decrease significantly higher in the dexmedetomidine group than in the propofol group ($p = 0.007$). HR changes were, however, within 20 % of the baseline values and did not warrant any intervention.

The changes in MAP in both groups were similar to the changes in HR. After an initial decline (more rapidly in propofol group), MAP remained constant throughout the procedure. A statistically significant decrease of MAP from the baseline occurred in both groups ($p < 0.05$), but there was no significant difference between the two groups during the study period ($p = 0.86$).

In the dexmedetomidine group, there was a statistically significant but clinically inconsequential decrease in RR following administration of the drug ($p < 0.05$). There was no significant change in RR in the propofol group during the study period. The difference between the groups was also not significant ($p = 0.07$). The $ETCO_2$ did not change significantly from the baseline in both groups, but there was a consistent difference between the groups throughout the study, with the propofol group having lower values

Table 1 Demographic data of the patients undergoing cerebral angiography

Parameter	Dexmedetomidine ($n = 30$) Mean ± SD	Propofol ($n = 30$) Mean ± SD	p value
Age (years)	49.0 ± 10.7	49.0 ± 11.4	0.99
Weight (kg)	56 ± 10	59 ± 11	0.21
Sex (male:female)	15:15	12:18	0.60
Total sedation duration (min)	48 ± 12	45 ± 13	0.31
Duration after SAH (days)	5.0 ± 3.6	3.8 ± 2.4	0.12
SAH grade (WFNS)			
I	17	10	0.18
II	12	19	
III	1	1	
Fischer grade			
I	2	3	0.87
II	3	4	
III	17	16	
IV	8	7	
Location of aneurysm			
Negative study	10	8	0.26
ACA/ACoA	16	9	
MCA	2	2	
ICA	3	8	
Posterior circulation	0	3	
Co-morbidity			
Hypertension	6	7	0.64
Diabetes	1	3	
Hyponatremia	2	1	
Deranged liver function tests	1	2	
Anemia	0	1	

Data are presented as the mean ± standard deviation (SD)

SAH Subarachnoid hemorrhage, *WFNS* World Federation of Neurological Surgeons, *ACA* Anterior cerebral artery, *ACoA* Anterior communicating artery, *MCA* Middle cerebral artery, *ICA* Internal carotid artery

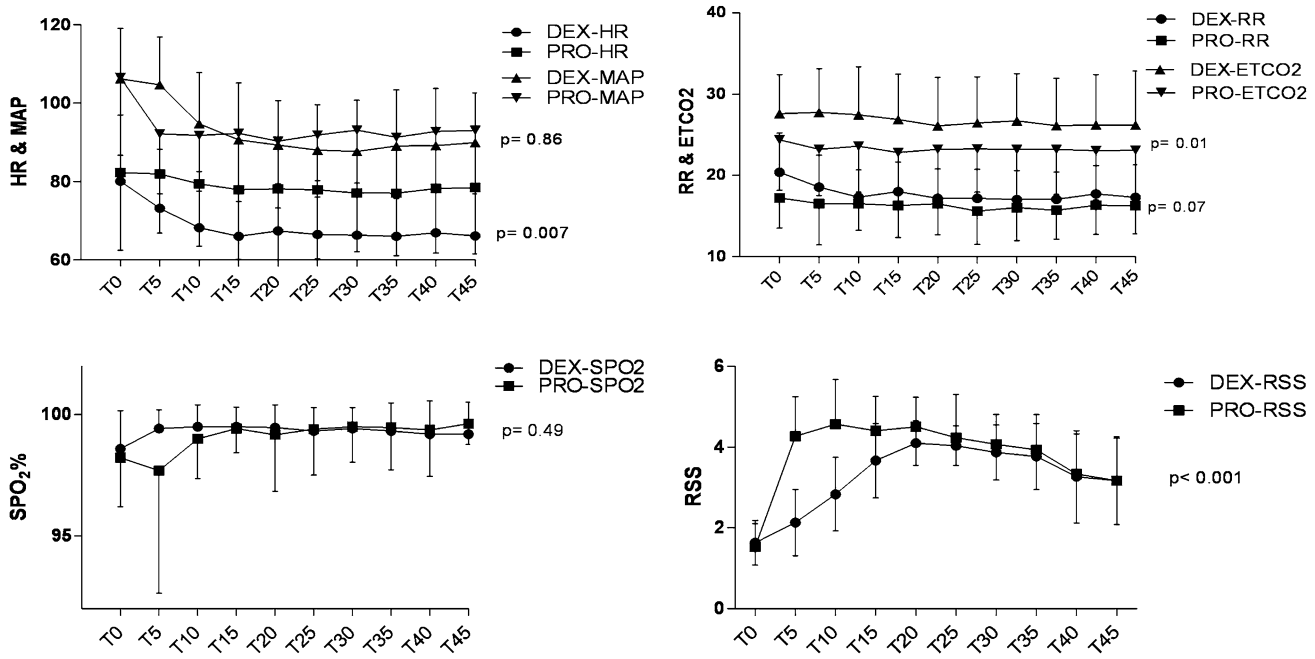

Fig. 1 Changes in various physiological parameters in patients randomized to dexmedetomidine (*DEX*) and propofol (*PRO*) groups from baseline (*T0*) until 45 min post-administration (*T45*). *Left upper quadrant* Heart rate (*HR*) and mean arterial blood pressure (*MAP*), *right upper quadrant* respiratory rate (RR) and end-tidal carbon dioxide level ($ETCO_2$), *left lower quadrant* oxygen saturation (SPO_2, *right lower quadrant* Ramsay sedation score (*RSS*)

($p = 0.01$). There was a significant decrease in SpO_2 in the propofol group following bolus administration which was not seen in the dexmedetomidine group ($p = 0.03$). This difference was not seen at other time intervals. The changes in hemodynamic and respiratory parameters with time in both groups are shown in Fig. 1.

Sedation scores

The RSS between the groups were significantly different up to 20 min from the start of sedation; thereafter it was similar between the groups until the end of the study. The mean onset time for sedation (RSS 4) was 15.4 ± 5.7 min in the dexmedetomidine group and 2.3 ± 1.9 min in the propofol group. Time for RSS to return to baseline was 8.7 ± 5.8 and 8.4 ± 4.8 min in the dexmedetomidine and propofol group, respectively. The mean RSS during the procedure with dexmedetomidine was significantly lower than that with propofol (3.2 ± 0.83 vs. 3.8 ± 0.92; $p < 0.001$). The changes in RSS over time are shown in Fig. 1.

Efficacy of the sedative technique

Seven patients moved during the procedure (at skin puncture or carotid/femoral compression) in the dexmedetomidine group. Except for one patient requiring additional fentanyl bolus, the rest of those who moved (six) successfully completed the study solely with additional supplementation of dexmedetomidine. All patients achieved sedative depth appropriate for conducting the CA. In the propofol group, 13 patients moved during the procedure requiring additional propofol. Five patients also required fentanyl to prevent movement.

Safety

Two patients in the dexmedetomidine group had significant but transient hypotension (MAP decreased from 126 to 67 mmHg in one patient and from 93 to 59 mmHg in the other patient). The blood pressure of both patients improved following rapid administration of fluids and temporary reduction in the infusion rate of the drug. No patient required inotropic or vasopressor therapy, and there were no manifestations of bradycardia, hypoventilation or oxygen desaturation. One patient had airway obstruction, which was relieved by adjusting the head position. This patient was obese and a known alcoholic and required two additional boluses of dexmedetomidine to be sedated to an RSS of 4.

In the propofol group, ten of the 30 patients (33 %) developed airway obstruction requiring either jaw thrust, chin lift or airway insertion. In one patient who developed apnea and airway obstruction, the SpO_2 decreased to 76 %, with no improvement from the measures mentioned

Table 2 Sedation characteristics and safety profile of dexmedetomidine and propofol

Parameters	Dexmedetomidine ($n = 30$)	Propofol ($n = 30$)	Significance (p)
Onset of action (min)	15.4 ± 5.7	2.3 ± 1.9	<0.001*
Recovery time (min)	8.7 ± 5.8	8.4 ± 4.8	0.79
Airway events	1/30	11/30	0.003*
Movement at skin puncture	7/30	11/30	0.398
Movement at carotid compression	0/30	5/30	0.05*
Requirement of sedation supplements	7/30	13/30	0.17

* Significant at $p \leq 0.05$

Data are presented as the mean ± SD, or as the number (of patients), where appropriate

above. His trachea was intubated and the procedure continued under general anesthesia. None of the patients in the propofol group had bradycardia or hypotension. The drug characteristics and adverse events during the procedure are shown in Table 2. In none of the patients in both groups did the WFNS grade deteriorate or rebleeding occur during the procedure.

Discussion

Dexmedetomidine has been successfully used in various diagnostic procedures and for sedation in the intensive care unit [5, 6, 9]. The results of the present study illustrate the successful use of dexmedetomidine as a sole sedative agent in patients with SAH undergoing CA. There is very little documented experience on the use of dexmedetomidine in SAH patients [9]. Few studies have examined the safety and efficacy of various sedative and anesthetic techniques for CA [1–4]. Rossi et al. [1] compared two techniques of propofol sedation during CA. In one group, patients ($n = 38$) received propofol 1–2 mg/kg followed by 25–50 mg repeated boluses; fentanyl, droperidol and diazepam were also administered. In the second group, propofol was used for general endotracheal anesthesia. The authors found that although both the methods were reliable and safe, the second approach provided better physiologic stability [1]. However, in their study, Clayton et al. [2] observed better hemodynamic stability with local anesthesia and IV sedation than with general anesthesia. Allan et al. [3] compared fentanyl–midazolam and fentanyl–propofol for sedation in patients undergoing neuroradiological investigations. Although patients in both the groups had satisfactory sedation and recovery, these authors observed unacceptable PaO_2 values in some patients in both groups. Also, patients in the fentanyl–propofol group had a higher incidence of recall [3]. Bewlay and Laurence [4] compared three anesthetic techniques in 88 neuroradiological patients and reported satisfactory sedation and recovery in all three groups, namely, propofol–alfentanil infusion, propofol infusion + fentanyl boluses and boluses of fentanyl + midazolam. In the present study, our aim was to examine if dexmedetomidine can be effectively and safely used as a sole sedative agent for CA. Using a single agent will obviate the effect of multiple drugs on cardiovascular physiology and the central nervous system while achieving adequate sedation for smooth conduct of this invasive procedure.

Dexmedetomidine is increasingly being used in neurosurgical patients because of its non-interference or even favorable response on intracranial dynamics in patients with SAH and head injury [9, 10]. This property of dexmedetomidine can be useful in acute neurological emergency, such as aneurysmal SAH, where the twin objective of adequate sedation and early recovery for neurological assessment can be successfully achieved.

The significant decrease in HR in the dexmedetomidine group in this study can be explained by the reduced sympathetic tone and catecholamine levels that occur following dexmedetomidine administration. The first of the two patients who developed significant hypotension in this study had received three intra-arterial injections of 1 mg nimodipine to relieve catheter-induced vasospasm; the second patient was a known hypertensive on an angiotensin-converting enzyme inhibitor. Similar changes in HR and MAP with dexmedetomidine have been reported in earlier studies [6, 11, 13].

There was no significant difference between the two groups in terms of RR during the study period, but the $ETCO_2$ values were significantly lower in the propofol group than in the dexmedetomidine group. With the exception of the immediate period after bolus drug administration (lower in the propofol group compared to the dexmedetomidine group), there was no significant difference in SpO_2 throughout the procedure. Episodes of airway obstruction and apnea in patients in the propofol group corresponded to this lower saturation value. Our findings are consistent with those of previous studies and reiterate that dexmedetomidine is not associated with respiratory depression [6, 14].

Compared to the dexmedetomidine group, there were more frequent interruptions in the propofol group during the procedure due to the need to provide supplemental drugs and maintain a patent airway. However, the total duration from the beginning of sedation in both the groups was similar due to the longer (prolonged) onset time in the

dexmedetomidine group. In our study, a lower propofol dose (1.5 mg/kg/h) was used, resulting in more frequent patient movement that required additional supplementation. However, using a higher dose would have resulted in a further increase in adverse respiratory events. Although the depth of sedation achieved by all patients was sufficient for the procedure to be completed, fentanyl was required by more patients in the propofol group to prevent movement. The analgesic effect of dexmedetomidine might have resulted in lesser movement and reduced the need of supplemental fentanyl in that group.

One of our more interesting findings was the similar recovery time in both groups. In a study by Zeyneloglu et al. [12], dexmedetomidine resulted in a prolonged recovery time and delayed discharge from the post-anesthesia care unit in patients undergoing lithotripsy. Similar observations were reported in a study by Alhashemi [13] who compared dexmedetomidine with midazolam in patients undergoing cataract surgery. These results are in contrast to our findings which indicated only a marginal increase in recovery time with dexmedetomidine compared to propofol, with the difference being both clinically and statistically insignificant. Thus, immediate neurological assessment was possible in both groups of our study at the end of the procedure. The delay in recovery in the patient cohort of Zeyneloglu et al.'s study [12] may have been due to an effect of co-administration of midazolam and fentanyl, and that in the patient cohort of Alhashemi's study [13] could be due to the continuation of the infusion until the completion of surgery. In our study, we used a relatively lower dose of dexmedetomidine, which might explain the comparatively faster recovery time. In a recent study comparing propofol and dexmedetomidine for CA in children, Peng et al. [15] also observed an increased number of adverse respiratory events in those receiving propofol, thereby also supporting our findings that dexmedetomidine is superior to propofol with respect to respiratory stability.

There are certain limitations to our study. All our patients had good SAH grades. Whether the results would have been similar in patients with poor grade SAH cannot be inferred from our data. The difference in hemodynamic variables, especially HR, would have been different if the patients were premedicated with atropine. The adequacy of sedation and onset and recovery could have been more precisely measured by using depth of anesthesia monitors, such as the Bispectral index or spectral entropy. However, these have not been validated in the setting of neurological insults such as SAH. Also, since this study was not intended to study the dose–response relationship between dexmedetomidine and propofol, use of RSS to achieve a predefined endpoint in both the groups can be justified. Another important limitation of the study was that the anesthesiologist was not blinded to the intervention (administration of propofol and dexmedetomidine) as he was involved in the primary care of the patient; however, an unbiased person collected the data. This bias is likely to be minimal as the hypothesis was not known to the anesthesiologist administering the drugs.

Conclusion

Based on the reported findings, dexmedetomidine as a sole sedative agent may provide safe and effective sedation in aneurysmal SAH patients undergoing CA without significant hemodynamic or respiratory changes, thereby making it a better choice compared to propofol. Further studies are needed to establish its safety in poor grade SAH patients.

Conflict of interest None.

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