Original Article

Comparison of hemodynamic response to adrenaline infiltration in children undergoing cleft palate repair during general anesthesia with sevoflurane and isoflurane

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Abstract

Background and Aims: Systemic absorption of adrenaline often used for infiltration during cleft palate surgery leads to adverse hemodynamic responses. These hemodynamic responses may be attenuated by the volatile anesthetics. This study aims to compare the hemodynamic responses to adrenaline infiltration during isoflurane (ISO) and sevoflurane (SEVO) anesthesia.
Material and Methods: Sixty children aged between 9 months and 48 months, weighing between 8 kg and 20 kg, undergoing primary repair of cleft palate were randomly allocated into two groups: Group ISO — anesthesia maintained with ISO (2 minimum alveolar concentrations [MAC]) and nitrous oxide 50% and group SEVO — maintained on SEVO (2 MAC) and nitrous oxide 50%. Surgical site was infiltrated with 1 ml/kg of 1:200,000 solution of adrenaline with 0.5% lignocaine. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were noted at the end of infiltration and every 1 min for 5 min following infiltration. The percentage change of hemodynamic responses from baseline, following infiltration were compared between the two groups.
Results: There was no significant change in HR from baseline, and the response was comparable between the agents at all times. The blood pressure (BP) increased from baseline in both the groups but the increase was greater in SEVO than ISO group at 2 and 3 min after infiltration. The maximum change in HR from baseline (group ISO median 10.9% [interquartile range (IQR) 4.5-23.0] vs. group SEVO 26.5% [11.9-44.6]) was comparable in both the groups ($P = 0.169$). The maximum change in SBP was significantly greater in group SEVO than group ISO (42.8% [IQR 20.0-60.9] vs. 26.0 [11.3-44.5], $P = 0.04$). The incidence of significant change (>20%) of SBP, DBP, and MAP from baseline was significantly greater in group SEVO after infiltration and 1 min and 2 min after infiltration. There were no arrhythmias in any of the groups.
Conclusion: Isoflurane results in greater attenuation of rise in BP during adrenaline infiltration compared to SEVO at similar MAC.

Key words: Adrenaline, blood pressure, cleft palate, infiltration, isoflurane, sevoflurane

Introduction

Surgical field infiltration with adrenaline is a common practice to improve the quality of surgical field during cleft lip and palate repair in children. Systemic absorption of adrenaline often leads to adverse hemodynamic responses such as hypertension and arrhythmias.[1] Anesthetic agents can modulate these hemodynamic responses. It is known that hemodynamic responses to low-dose of adrenaline used to test accidental intravascular placement of epidural catheter is attenuated by anesthetics.[2] Infiltration of surgical incision site

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Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/0970-9185.175650

How to cite this article: Gunnam PR, Durga P, Gurajala I, Kaluvala PR, Veerabathula P, Ramachandran G. Comparison of hemodynamic response to adrenaline infiltration in children undergoing cleft palate repair during general anesthesia with sevoflurane and isoflurane. J Anaesthesiol Clin Pharmacol 2016;32:12-7.

for cleft palate surgery is likely to result in significant systemic absorption of adrenaline due to the high vascularity of the tissues.[3] The effects of isoflurane (ISO) and sevoflurane (SEVO) in modulating the hemodynamic response to surgical site infiltration of adrenaline in children undergoing cleft palate surgery have not been compared. The aim of this study was to compare the hemodynamic changes to adrenaline infiltration during general anesthesia with iso-minimum alveolar concentrations (MAC) of ISO and SEVO.

Material and Methods

Approval of Institutional Ethics Committee and informed consent from the legal guardians of the participating children was obtained. Sixty American Society of Anesthesiologists Physical Status 1 children undergoing cleft palate surgery aged between 9 and 48 months, belonging to either sex, weighing between 8 and 20 kg were enrolled. Children with re-operations, congenital syndromes, cardiac disease, arrhythmias, respiratory disorders including upper respiratory infections within 3 weeks of surgery, renal or hepatic dysfunction, and muscular dystrophy were excluded at initial assessment for eligibility. The eligible children were randomly allocated into two groups using computer-generated random numbers, group ISO — maintained on ISO at 2 MAC with nitrous oxide 50% and group SEVO — maintained on SEVO 2 MAC with nitrous oxide 50%. All patients were premedicated with oral midazolam 0.5 mg/kg. After 15 min of premedication, when the children were sedated and separable from parents, they were brought into the operating room (OR) and induced with inhaled SEVO 7% with O_2. Monitoring in the OR included electrocardiogram, pulse oximetry, noninvasive blood pressure (BP), temperature, and capnography. Venous access was obtained after induction and intravenous fentanyl 1 μg/kg was administered. Intubation was done when MAC was about 3 and the following criteria were met — the child was immobile, and the limbs were floppy. Intubation was performed with appropriated sized RAE tube and connected to closed circuit with a tidal volume of 8 ml/kg and respiratory rate adjusted to obtain normocapnia ($EtCO_2$ of 35-40 mmHg). Anesthesia was maintained with O_2 (50%), N_2O (50%) and SEVO or ISO at 2 MAC as per randomization. The initial gas flow rates were set around 2-3 l to obtain the desired end tidal anesthetic agent (ETAA) concentration and then reduced to 1 l. After the initial inclusion, patients who required more than one attempt, more lifting force or pressure on the neck at intubation were excluded. Events such as bronchospasm, change or adjustment of the endotracheal tube, movement of patient requiring intervention with change in inhalational agent or administration of vasoactive drug were excluded after initial inclusion. $EtCO_2$ and ETAA were stabilized for 5 min. The baseline heart rate (HR) and BP were noted. The surgical site was infiltrated with 1 ml/kg of 1:200,000 solution of adrenaline with 0.5% lignocaine. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were noted at the end of infiltration and every 1 min for 5 min following infiltration. The highest HR, SBP, and any arrhythmias were noted. No surgical stimulus or movement of the patient was performed during this period. Patients who required alteration of anesthetic agent concentration during the study period were excluded from the study. The bleeding from the incision site was graded as mild, moderate and severe by the operating surgeon. The anesthetic management and the surgical management after the study period were as per the institutional protocol.

Statistical analysis

Sample size

The sample size was determined using PASS based on the results from the pilot study on 20 children (6 excluded). A group sample size of 19 each (allocation ratio 1:1) was required to achieve 80% power to detect a difference of −24.0 in SBP with standard deviations of 24.0 and 27.0 and with a significance level (alpha) of 0.05 using a two-sided two-sample *t*-test (equal variance not assumed). Hence, 60 children were recruited.

The statistical analysis was performed using SPSS Statistics for Windows, Version 17.0, Chicago, SPSS Inc. The normality of the data was tested using two-sample Kolmogorov–Smirnov Z. The normally distributed continuous data were described as mean and 95% confidence interval for mean (95% CI), as median with interquartile range (IQR) when the distribution was not normal, and categorical data are expressed as number with percentage. The continuous variables were compared between the groups using independent sample *t*-test for data distributed normally and nonparametric Mann–Whitney U-test when skewed, and categorical data were compared using Chi-square test and fishers exact test when the expected cell value of >50% of the cells was <5. The changes in the hemodynamics from baseline within groups were analyzed using ANOVA for repeated variables and *post-hoc* Dunnett test was performed with baseline as control. A two-sided $P < 0.05$ was considered as statistically significant for all tests.

Results

Sixty patients were recruited for the study. Fifteen patients were excluded after initial inclusion and data of 24 patients from group ISO and 21 patients from group SEVO were

analyzed [Figure 1]. There was no significant difference in the demographic data and baseline hemodynamics between the groups [Table 1]. Figure 2a-d shows the hemodynamic responses to adrenaline infiltration. There was no significant change in HR from baseline, and the response was comparable between the two groups. The SBP, DBP, and MAP increased from baseline in both the groups but the blood pressure in SEVO group was significantly greater than ISO group [Figure 2]. The percentage change from baseline was comparable between the groups [Table 2]. The change was significantly greater in SEVO group than ISO at 2 and 3 min after infiltration. The maximum change in HR from baseline (group ISO median 10.9% [IQR 4.5-23.0] vs. group SEVO 26.5% [11.9-44.6]) was comparable in both the groups ($P = 0.169$). The maximum change in SBP was significantly greater in group SEVO than group ISO (42.8% [IQR 20.0-60.9] vs. 26.0% [11.3-44.5], $P = 0.04$). The number of patients with more than 20% change in HR from the baseline was comparable between the groups. The incidence of significant change (>20% of baseline) of SBP, DBP and MAP was significantly greater in group SEVO after infiltration and 1 min and 2 min at the end of infiltration [Figure 3a-d]. There were no arrhythmias in both the groups. The bleeding from the surgical field was similar in both the groups.

The group sample sizes of 24 and 21 achieved 77% power to detect a difference of 18%, with a mean maximum percentage change in SBP of 26.0% in group ISO and 44.0% in group SEVO and standard deviations of 19.0 and 25.0 respectively using a two-sided two-sample *t*-test (equal variance not assumed).

Discussion

Surgical field infiltration with adrenaline is commonly performed to improve the quality of surgical field during cleft lip and palate repair in children. Systemic absorption of adrenaline infiltration often leads to adverse hemodynamic responses.[4,5] Some authors have shown minimal adverse effects with adrenaline infiltration[6] while others reported that increased blood levels of adrenaline results in major changes in arterial BP and HR even following sub-maximal doses of adrenaline in association with anesthetics.[7] There are several reports of hypertension,[8] arrhythmia[9] and cardiac arrest resulting from surgical field infiltration of adrenaline.[10] Matsumae reported ventricular tachycardia, severe hypertension, and pulmonary edema following infiltration of adrenalnine.[10] Hypertension was noted in 21.6% children, and there were no instances of clinically unstable tachycardia or arrhythmia with a dose of 12.5 μg/kg of adrenaline used as infiltration in children undergoing palate surgeries.[6] However, their definition of significant change was

Table 1: Comparison of demographic data between the groups

Parameter	Group ISO (n = 24)	Group SEVO (n = 21)	P
Age (months)[a] mean (95% CI)	31.38 (17.9-44.8)	24.7 (14.9-34.5)	0.42
Weight (kg)[a] mean (95% CI)	11.08 (9.2-12.9)	10.05 (8.7-11.4)	0.36
Sex n (%)[b]			
Male	10 (47.6)	10 (41.7)	0.77
Female	11 (52.4)	14 (58.3)	

[a]Compared using Independent Sample t-test, [b]Compared using Chi-square test. CI = Confidence interval, ISO = Isoflurane, SEVO = Sevoflurane

Table 2: Comparison of hemodynamic changes (percentage of change from baseline) between the groups

Parameter	Median (IQR)		P
	Group ISO (n = 24)	Group SEVO (n = 21)	
HR (bpm)			
End of infiltration	5.3 (0.0-12.3)	7.9 (1.2-15.3)	0.554
1 min	5.0 (0.6-15.5)	10.9 (4.1-21.8)	0.145
2 min	6.8 (0.1-15.6)	10.3 (1.6-19.9)	0.339
3 min	5.2 (0.1-11.2)	7.2 (3.6-17.3)	0.767
4 min	3.7 (−0.5-11.3)	5.4 (4.8-17.6)	0.699
5 min	2.29 (−1-11.9)	4.5 (4.8-17.6)	0.716
SBP (mmHg)			
End of infiltration	8.4 (−2.5-19.2)	13.1 (2.8-34.5)	0.130
1 min	7.9 (3.6-31.3)	28.9 (9.3-47.4)*	0.025
2 min	10.1 (4.2-38.4)	28.5 (16.9-41.5)*	0.038
3 min	8.6 (1.4-27.3)	15.3 (1.7-32.5)	0.467
4 min	7.2 (−0.9-15.9)	9.6 (–1.1-25.5)	0.439
5 min	1.4 (−5.2-7.7)	2.0 (–3.0-22.1)	0.375
DBP (mmHg)			
End of infiltration	14.6 (2.6-21.6)	26.9 (12.9-49.4)*	0.03
1 min	20.0 (8.3-37.1)	38.8 (18.3-59.4)	0.24
2 min	14.2 (6.2-28.2)	37.2 (20.3-58.6)*	0.01
3 min	3.3 (−7.0-23.3)	16.0 (2.4-46.4)*	0.34
4 min	0.0 (−8.0-8.5)	5.0 (–8-21.9)*	0.03
5 min	−4.6 (−10-6.6)	−3.8 (−12.5-12.2)	0.06
MAP (mmHg)			
End of infiltration	10.2 (2.0-23.1)	17.66 (11.4-30.4)*	0.034
1 min	18.9 (5.4-38.1)	34.6 (24.8-44.7)*	0.014
2 min	18.6 (6.6-38.2)	35.4 (20.6-43.7)*	0.029
3 min	9.3 (−3-31.2)	22.3 (6.6-29.7)	0.145
4 min	7.2 (−4-13.3)	5.6 (0.0-20.7)	0.439
5 min	−2.6 (−6.8-7.4)	1.2 (−6.3-12.6)	0.351

*Data were compared between the groups using nonparametric Mann–Whitney U-test. *P < 0.05 was considered as significant difference. HR = Heart rate, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, MAP = mean arterial blood pressure IQR = Interquartile range, ISO = Isoflurane, SEVO = Sevoflurane*

SBP, >120 or DBP, >70 and tachycardia (>190 beats/min) as defined by the American Heart Association guidelines. A change of >20% from the baseline was defined as significant change in our study. The addition of lignocaine to adrenaline[1] and use of lower adrenaline concentrations have shown to limit the hemodynamic responses.[5] Muthukumar *et al*. have

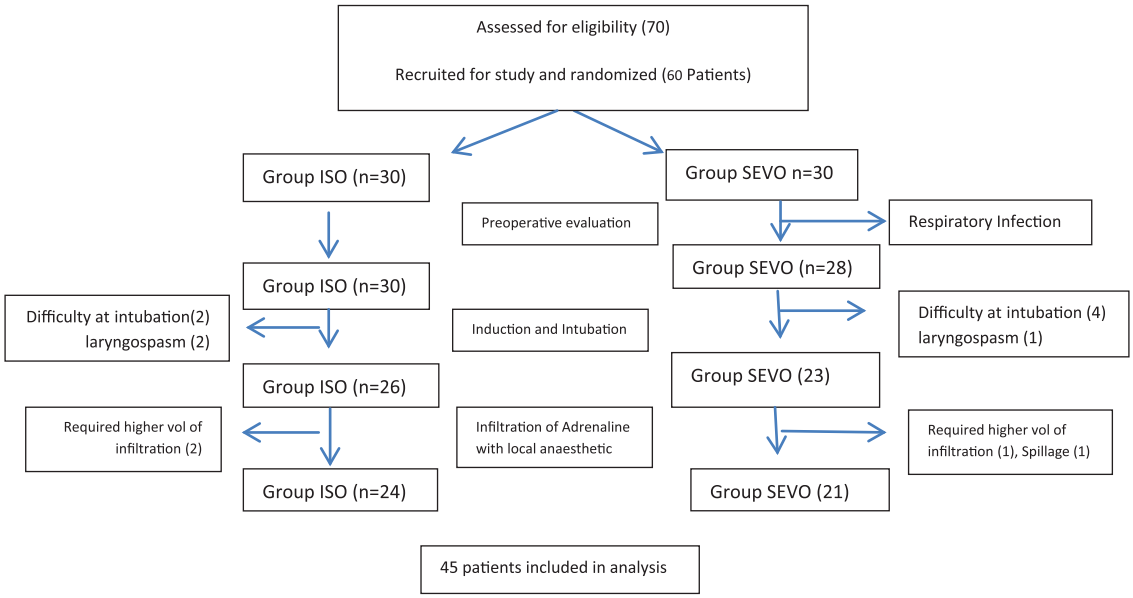

Figure 1: Consort diagram

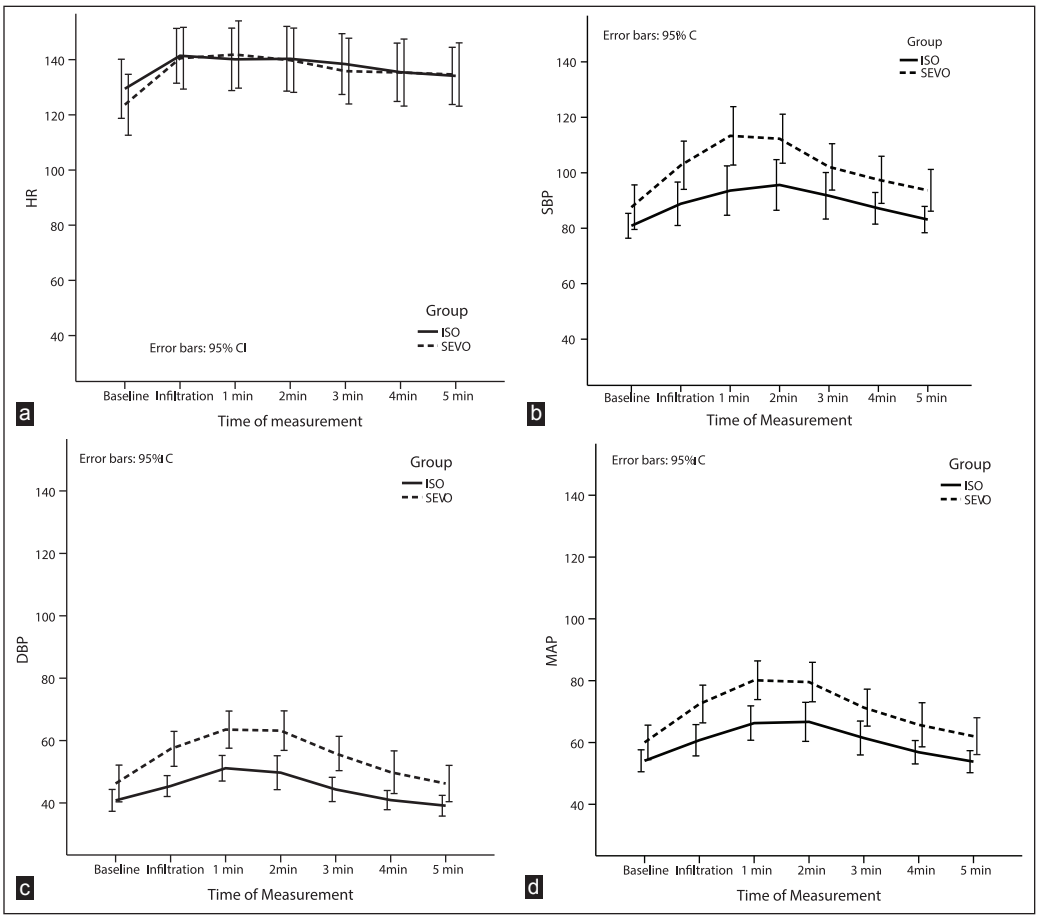

Figure 2: Comparison of hemodynamic changes during adrenaline infiltration during isoflurane and sevoflurane anesthesia, (a) changes in heart rate, (b) changes in systolic blood pressure, (c) changes in diastolic blood pressure, (d) changes in mean arterial pressure

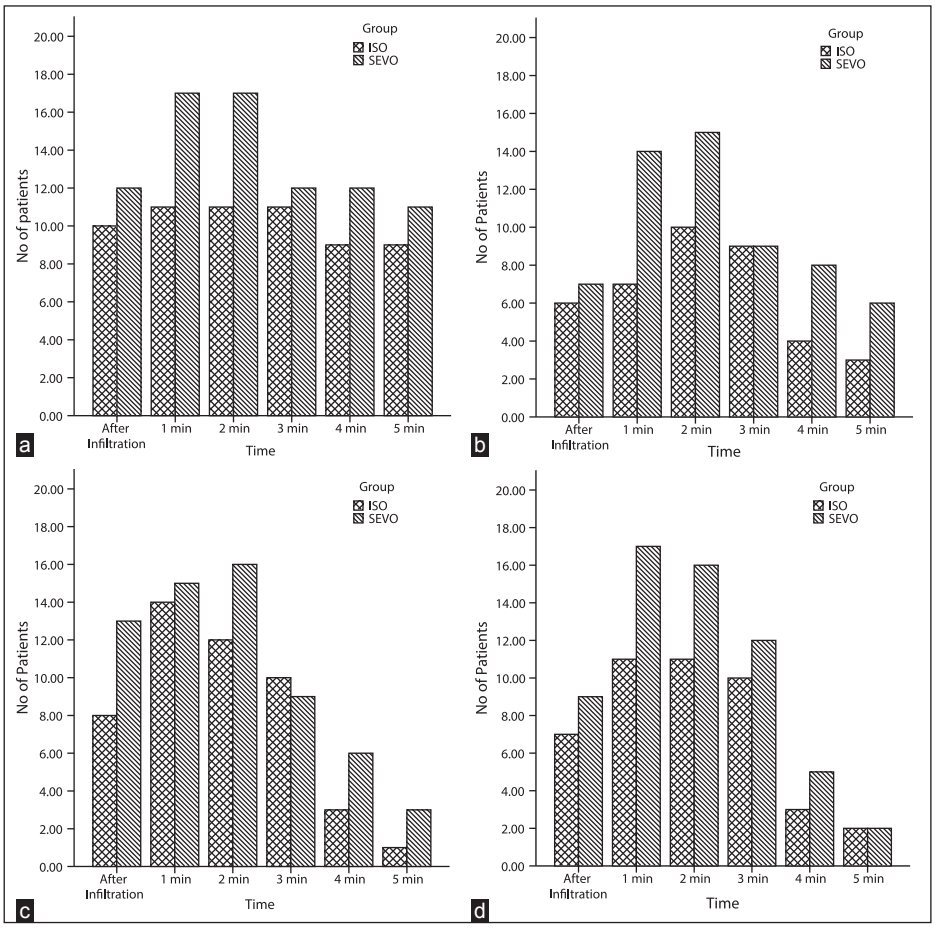

Figure 3: (a) Comparison of incidence of increase in heart rate by 20% of baseline, (b) comparison of incidence of increase in systolic blood pressure by 20% of baseline, (c) comparison of incidence of increase in diastolic blood pressure by 20% of baseline, (d) comparison of incidence of increase in mean blood pressure by 20% of baseline

shown that 1:400,000 adrenaline and 1:200,000 adrenaline with lignocaine 0.5-0.7% provided stable hemodynamics. Significant hemodynamic changes were seen only in children administered 1:200,000 adrenaline without lignocaine.[1]

General anesthesia with volatile anesthetic agents is commonly practiced in children.[11] The anesthetic agents influence the cardiovascular function. Some authors reported more hemodynamic stability with SEVO[12] while others reported no significant difference in hemodynamics during maintenance of anesthesia with ISO or SEVO.[13] The hemodynamics during maintenance of anesthesia with ISO or SEVO was comparable in this study. The arrhythmogenicity of ISO and SEVO was also found to be comparable.[14] It has been observed that there has been only moderate change in cardio-circulatory parameters during general anesthesia despite significant elevations of epinephrine serum levels after local infiltration for surgical correction of clefts.[3] The hemodynamic responses to intravascular injection of low-dose adrenaline, commonly used as test doses of the epidural, are altered by volatile anesthetic agents during general anesthesia.[2,15] The peak HR response and the sensitivity to detect intravascular injection following 15 μg of adrenaline were significantly lower during general anesthesia. However, the influence of ISO and SEVO on the hemodynamic responses to adrenaline infiltration of the surgical field have not been compared. In this study, we compared the hemodynamic responses to surgical field infiltration of adrenaline during general anesthesia with ISO and SEVO. The HR responses to infiltration were comparable with both anesthetic agents. The increase in BP was lesser with ISO than SEVO. ISO produces greater relaxation of vascular smooth muscle and decrease in cytosolic calcium than SEVO.[16,17] This could have resulted in the attenuation of BP following adrenaline infiltration during ISO anesthesia observed in our study. The peak presser responses in both the groups occurred after about 2 min of infiltration of adrenaline and were transient. The peak response was greater during SEVO anesthesia than ISO anesthesia. The hemodynamic responses exhibited a trend to return to baseline by 5 min. The time required to return to baseline was not noted as the study concluded 5 min after the infiltration. There were no instances of arrhythmia in any of the patients in this study. There is a high incidence of associated congenital heart disease in children undergoing cleft lip and palate surgery.[18,19]

The hemodynamic responses to adrenaline infiltration can be potentially hazardous in these children as it can alter the shunt fraction. The results of this study may guide the choice of anesthetic agents during adrenaline infiltration.

Conclusion

Isoflurane results in greater attenuation of the rise in BP during adrenaline infiltration compared to SEVO at similar MAC values.

Acknowledgment

The authors would like to acknowledge Mrs. Nagamani, Anesthesia Technician, for her assistance in the conduct of the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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