Dexmedetomidine infusion as a supplement to isoflurane anaesthesia for vitreoretinal surgery

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Background. We explored the sympatholytic property of dexmedetomidine, especially its role in intraocular pressure (IOP) reduction, haemodynamic stability, and attenuation of extubation response.

Method. In this double-blind, randomized, controlled trial approved by the Hospital Ethics Committee, 60 patients undergoing elective vitreoretinal surgery were allocated to two groups, receiving either placebo or dexmedetomidine. A loading dose of dexmedetomidine 2.5 μg kg⁻¹ h⁻¹ (or placebo in same volume) was infused for 10 min immediately before induction of anaesthesia with propofol, followed by a maintenance dexmedetomidine or placebo infusion at 0.4 μg kg⁻¹ h⁻¹ till 30 min before the end of the operation. Anaesthesia was maintained with isoflurane, oxygen, and air mixture. IOP was measured before the loading dose and 1 min after tracheal intubation. The mean arterial pressure (MAP) and heart rate (HR) during loading, induction, maintenance, extubation, and recovery period were measured. The degree of strain on extubation was graded from 0 to 5.

Results. The use of vasopressor/labetalol/atropine and the reduction in IOP were comparable between the two groups. There was a significant variation in MAP and HR over time within group, but not between groups. The median degree of strain was significantly lower (P=0.049), and the time to reach Aldrete score of 10 shorter (P=0.031) in the dexmedetomidine group.

Conclusion. Dexmedetomidine can be used without undue haemodynamic fluctuation and can decrease the excitatory response during extubation. The reduction in IOP with dexmedetomidine was comparable with placebo.


Keywords: anaesthesia, ophthalmic; arterial pressure, drug effects; eye, intraocular pressure; sympathetic nervous system, dexmedetomidine

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Dexmedetomidine is a highly selective α₂-adrenergic agonist, that has a sedative effect¹² and has been shown to reduce anaesthetic requirement.³⁴ It also demonstrates a sympatholytic property,⁴⁻⁶ which may prove useful when used to blunt the sympathetic surge during intubation and extubation.

Providing an immobile and uncongested operative field without any major increase in intraocular pressure (IOP) is the anaesthetic goal for ophthalmic surgery. While two previous studies⁷⁻⁷ have demonstrated an IOP-reducing effect of dexmedetomidine, a reduction in mean arterial pressure (MAP) also accompanied the reduction in IOP. In this study, we explored whether we could maintain a haemodynamically stable anaesthesia with dexmedetomidine, and whether dexmedetomidine could still exert an IOP-reducing effect without a reduction in MAP. The sympatholytic effect of dexmedetomidine during extubation was also studied.

Methods

This prospective double-blind, randomized, controlled study was approved by the Kowloon Central/Kowloon East Cluster Ethics Committee. After written informed consent, 60 ASA I and II patients undergoing elective vitreoretinal surgery under general anaesthesia at the Queen Elizabeth Hospital and Hong Kong Eye Hospital were recruited from May 2004 to May 2005. All patients were aged between
18 and 75 years, and the duration of surgery was at least 60 min. Patients not recruited were those with hepatic impairment (liver enzyme/bilirubin/γ-glutamyl transpeptidase >1.1 × upper limit of normal), renal impairment (creatinine >2 mg dl⁻¹, 176 µmol litre⁻¹), hypertension with systolic blood pressure (BP) >160 mm Hg, obstructive sleep apnea, any degree of atroventricular conduction abnormality, or those on α₂ blocker in the preceding 30 days. Also excluded were pregnant and lactating women, those unable to give informed consent, patients with severe hearing impairment, patients with language barrier, those with potential difficult intubation, and patients with body mass index >30.

At the preoperative visits, standard assessment including the patient’s body weight, baseline MAP, and heart rate (HR) were recorded. Patients were fasted for 6 h before operation and premedicated with atropine 0.6 mg i.m.

During the pre-induction period, the patients were monitored with ECG, pulse oximeter, automatic non-invasive BP monitoring (NIBP) (Narkomed 4 monitoring system), every 5 min and auditory evoked potential (A-Line® monitor, version 4.1; Danmeter A/S, Odense, Denmark).

The commercially available monitor for auditory evoked potential (AEP) for this study generated an A-line autoregressive index (AAI), where an index <30 correlated with adequate depth during general anaesthesia. The index is derived from fast extracted middle latency AEP (MLAEP) wave with a 6–15-s response delay only. The MLAEP has been shown to correlate with anaesthetic drug effect and is a reflection of anaesthetic depth.⁸⁻¹⁰

All patients received a bolus of 500 ml normal saline before a 1.5 ml kg⁻¹ h⁻¹ infusion of normal saline. The patients were allocated randomly (by computer-generated random numbers) to receive an infusion of either dexmedetomidine or normal saline as placebo. The infusate was treated as if it was dexmedetomidine 2 µg ml⁻¹. A loading dose of the infusate was given at a rate of 2.5 µg kg⁻¹ h⁻¹ for 10 min followed by a maintenance infusion of 0.4 µg kg⁻¹ h⁻¹. As the incidence of bradycardia and hypotension is higher among the patients aged >65 years, we reduced the dosage in this group of patients as advised in the drug information insert. The loading and maintenance dosage was halved in these patients. Upon completion of the loading dose of dexmedetomidine or placebo, anaesthesia was induced with fentanyl 2 µg kg⁻¹ and propofol 1 mg kg⁻¹, with further doses of propofol (if needed) in 20 mg increment titrated to loss of eyelash reflex and AAI <30. Atracurium 0.5 mg kg⁻¹ was then given and intubation was done after the disappearance of the train-of-four twitch response. NIBP was monitored in continuous cycle (stat mode) during induction until the return of BP to the baseline. Hypotension with an MAP reduction of ≥30% from the baseline was treated with ephedrine 3 mg bolus (phenylephrine 50 µg bolus was used if repeated doses of ephedrine failed to increase the BP). Any bradycardia with an HR of <40 would have been treated with atropine 0.3 mg.

The maximum (max) and minimum (min) MAP and HR were recorded for each patient during the loading and induction periods. The MAP, HR, end-tidal isoflurane (εiso) concentration, AAI, and body temperature were recorded every 5 min during the maintenance phase, and the mean values during this period were obtained for data analysis. The maintenance phase was defined as the period starting 30 min after induction till 15 min before the last suture of the operation. The εiso was titrated to give an AAI of 15–25. Fentanyl 0.5 µg kg⁻¹ was given at incision, and a further bolus of 0.5 µg kg⁻¹ was given when the MAP rose to 20% above the baseline or the HR rose to 20% above the baseline in the presence of an AAI <25. Muscle relaxation was maintained with an atracurium infusion. Body temperature was monitored and a forced air warming device was used when the temperature was <36°C.

The dexmedetomidine/placebo infusion was stopped 30 min before the expected completion of operation. Isoflurane was turned off with the last suture. Neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg and the trachea extubated when the patients obeyed commands. The degree of strain on extubation was graded from 0 to 5 in a six-point Likert scale (0=extremely smooth, 1=very smooth, 2=somewhat smooth, 3= somewhat strained, 4=very strained, 5=extremely strained) by an observer unaware of the study drug used.

The maximum MAP and HR were recorded for each patient during extubation. A rise in the MAP to 30% above the baseline was treated with a 5-mg bolus of labetolol. The Aldrete score, MAP, and HR were recorded every 5 min during the recovery room stay of the patients. The mean values of recovery room MAP and HR were calculated for data analysis.

The baseline IOP on the non-operative eye was measured in the supine position after a drop of topical local anaesthetic (Benoxinate HCl) with a hand-held applanation tonometer, which has been shown to correlate well with the standard Goldmann tonometer¹¹ (Tonopen XL, Medronic, SOLAN), by an ophthalmologist (who was blinded to the dexmedetomidine/placebo groups) before the loading dose was given, and again 1 min after intubation. The Tonopen was re-calibrated again before the post-intubation readings were taken. At each of the two phases, three IOP readings were taken and averaged. The direct laryngoscopy (DL) grading and the number of attempts for the intubation were recorded.

The results were analysed with SPSS 12.0 software for Windows. Paired t-test was used for post-intubation vs baseline IOP change. Independent t-test was used for inter-group comparison of continuous data that were normally distributed. Data for t-test were first tested for normality by Kolmogorov–Smirnov test, and equality of variance
by Levene’s test. Non-normally distributed data (average 
values at maintenance, time from turning off of isoflurane 
to the ability to obey command, and time for Aldrete score 
returning to 10) were log transformed before analysis. 
ANOVA and repeated measure ANOVA were used to analyse 
MAP and HR. Mann–Whitney U-test was used for ordinal 
variables and continuous variables not following the 
normal distribution despite transformation. Binary vari-
ables were tested by \( \chi^2 \) test or Fisher’s exact test where 
appropriate. \( P<0.05 \) was considered to be statistically 
significant.

Sample size was calculated to be 29 for each group to 
achieve power=0.8, \( \alpha=0.05 \) to detect a 30% reduction in 
IOP. For a 20% difference in MAP, the sample size was 
calculated to be 12 in each group.

**Results**

Sixty patients were recruited and completed the study. 
There were 30 patients in the dexmedetomidine group and 
30 in the placebo group. Patient characteristics and base-
line measurements of the two groups were comparable 
except for the baseline MAP (Table 1). The number of 
patients having hypertension, ischemic heart disease, dia-
betes, anxiety disorder, and glaucoma were similar in both 
groups. The number of patients on antihypertensive treat-
ment was also comparable. There was no significant differ-
ence in the types of antihypertensive taken by the two 
groups of patient. In view of this, the BP was converted to 
a percentage of their own baseline before comparison.

The baseline IOP values were comparable in the dexme-
detomidine and placebo groups (Table 2). In both groups, 
there was a significant reduction in IOP values from the 
baseline after induction and intubation, but it was not sig-
nificantly different between the two groups. The number 
of attempts required for intubation and the DL grading 
were comparable between the two groups (Mann–Whitney 
U-test; \( P=0.70 \) and \( P=1.00 \), respectively).

The dexmedetomidine group required less propofol and 
isoflurane to maintain the same anaesthetic concentra-
tion as recorded by the AEP (Table 3), but required similar 
amount of vasopressors and labetalol to maintain the 
haemodynamic stability. There was a significant within 
group variation in MAP and HR over different anaesthetic 
periods: \( F(6, 53) =153.51, P<0.001 \) and \( F(6, 53)=83.75, 
\( P<0.001 \), respectively. However, the study drug did not 
interact with the anaesthetic periods to give the differences 
in MAP and HR over time: \( F(6, 53)=1.45, P=0.21 \) and 
\( F(6, 53)=0.79, P=0.59 \), respectively. The between groups 
effect on both the MAP and HR was not significantly 
different, with \( F(1, 58)=1.71, P=0.20 \) and \( F(1, 58)= 
1.77, P=0.19 \), respectively.

The MAP was tested in each anaesthetic period and was 
comparable in the two groups except during the recovery 
phase (Fig. 1). The heart rate for the dexmedetomidine 
group was significantly lower than the placebo group 
when tested in individual anaesthetic periods apart from the 
minimum HR during loading, and the maximum HR at 
extubation (Fig. 2). However, no patient required atropine 
for bradycardia.

### Table 1 Patient characteristics and baseline. *Statistically significant difference; †\( P\)-value from independent \( t \)-test; NS, not significant; IQR, interquartile range; AAI, A-line autoregressive index

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dexmedetomidine (n=30)</th>
<th>Placebo (n=30)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>51.5 (43.5–61.25)</td>
<td>53 (41.25–58)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M to F ratio)</td>
<td>17:13</td>
<td>18:12</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, kg, mean (SD)</td>
<td>62.9 (12.25)</td>
<td>60.4 (11.32)</td>
<td>NS</td>
</tr>
<tr>
<td>ASA (I:II)</td>
<td>15:15</td>
<td>14:16</td>
<td>NS</td>
</tr>
<tr>
<td>Non-smoker to smoker ratio</td>
<td>28:2</td>
<td>24:6</td>
<td>NS</td>
</tr>
<tr>
<td>Non-drinker to drinker ratio</td>
<td>30:0</td>
<td>28:2</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline MAP, mm Hg, mean (SD)</td>
<td>96.2 (13.00)</td>
<td>102.8 (11.42)</td>
<td>0.042†</td>
</tr>
<tr>
<td>Baseline HR, beats min (^{-1}), mean (SD)</td>
<td>74.0 (11.70)</td>
<td>79.1 (13.35)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline AAI, %, median (IQR)</td>
<td>99.5 (98–100)</td>
<td>99 (98–99.25)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline AAI median (IQR)</td>
<td>89 (80.75–99)</td>
<td>91 (84–99)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of maintenance, min, mean (SD)</td>
<td>82 (34.6)</td>
<td>74 (42.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2 Intraocular pressure (IOP) data. *Statistically significant difference

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dexmedetomidine (n=30)</th>
<th>Placebo (n=30)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline IOP, mm Hg, mean (SD)</td>
<td>19.25 (3.71)</td>
<td>18.08 (3.63)</td>
<td>0.223</td>
</tr>
<tr>
<td>IOP (_{1min}) after intubation, mm Hg, mean (SD)</td>
<td>14.54 (4.37)</td>
<td>13.97 (4.69)</td>
<td>0.635</td>
</tr>
<tr>
<td>Per cent reduction in IOP, %, mean (SD)</td>
<td>22.85 (19.06)</td>
<td>22.54 (23.20)</td>
<td>0.814</td>
</tr>
<tr>
<td>Absolute reduction in IOP, mm Hg, mean (SD)</td>
<td>4.72 (4.42)</td>
<td>4.10 (3.93)</td>
<td>0.567</td>
</tr>
<tr>
<td>Baseline IOP–IOP(_{1min})</td>
<td>( P&lt;0.001^* ) (paired ( t )-test)</td>
<td>( P&lt;0.001^* ) (paired ( t )-test)</td>
<td></td>
</tr>
</tbody>
</table>
Factors that may prolong awakening such as age, body temperature, duration, and depth of anaesthesia (intraoperative AAI level) were all comparable between the two groups. The duration from cessation of isoflurane to the patient’s ability to obey command was not statistically different between the two groups (mean value: dexmedetomidine, 298 s; placebo, 385 s, \( P = 0.072 \)). The time from cessation of infusion to the last suture did not correlate with the time to obey command in the dexmedetomidine group. The number of patients with maximum extubation MAP rising 20% above the baseline in the dexmedetomidine and placebo groups were 10 and 17, respectively (\( \chi^2 \)-test, \( P = 0.069 \)). The degree of strain was less in patients in the dexmedetomidine group (median score 1, IQR 0–2; median score for placebo 2, IQR 1–2.75; Mann–Whitney \( U \)-test, \( P = 0.049 \); Fig. 3).

The mean time for the Aldrete score to reach 10 was 14.4 min for the dexmedetomidine group and 20.9 min for the placebo group (\( t \)-test, \( P = 0.031 \)).

**Discussion**

In this study, arterial pressure was maintained at similar levels for both groups. While its use was shown to decrease extubation strain, dexmedetomidine could not additionally reduce IOP nor attenuate the extubation hypertensive effect significantly.

Standard dexmedetomidine loading at a rate of 1 \( \mu \)g kg\(^{-1}\) given over a 10 min period could give rise to hypertensive and hypotensive episodes.\(^7\) To achieve better haemodynamic stability, we had adopted the loading of 2.5 \( \mu \)g kg\(^{-1}\) h\(^{-1}\) given for 10 min as described by Venn and colleagues\(^14\) who also achieved stable haemodynamics in their study. Besides modifying our loading dose, we had kept our patients well hydrated with i.v. fluid supplement. These measures were taken to avoid the hypertensive phenomenon of dexmedetomidine where the BP could decrease to <50% of the initial level.\(^15\) Even though the minimum MAP during induction was low in our groups, these were transient and the amount of vasopressors required was similar in both groups. Having achieved haemodynamics similar to the placebo group, we could not, however, produce the desirable blunting of BP increase during intubation and extubation with our protocol. In the previous studies\(^3\)–\(^5\) where BP was blunted during intubation, the dose of dexmedetomidine used was 0.6 \( \mu \)g kg\(^{-1}\) or higher. In this study, the loading dose corresponded to 0.42 \( \mu \)g kg\(^{-1}\) which may account for our inability to attenuate the increase in BP during intubation.

**Table 3** Anaesthetic and analgesic requirement. \(^*\)Statistically significant difference; \(^\dagger\)\( P \)-value from independent \( t \)-test; \(^\ddagger\)\( P \)-value from Mann–Whitney test

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (( n = 30 ))</th>
<th>Placebo (( n = 30 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol, mg kg(^{-1}), mean (95% CI)</td>
<td>1.50 (1.41–1.60)</td>
<td>1.93 (1.77–2.09)</td>
<td>&lt;0.001(^*)</td>
</tr>
<tr>
<td>End-tidal isoflurane concentration, %, mean (95% CI)</td>
<td>0.53 (0.45–0.61)</td>
<td>0.69 (0.61–0.78)</td>
<td>0.007(^*)</td>
</tr>
<tr>
<td>Additional fentanyl during maintenance, no. of doses, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

**Fig 1** Interquartile range (IQR) and median MAP of dexmedetomidine and placebo groups during different phases of anaesthesia. \(^*\)Statistically significant difference between dexmedetomidine and placebo group.
Two studies\textsuperscript{17, 18} using single-dose dexmedetomidine 0.5 μg kg\textsuperscript{-1} 5 min before the end of surgery had attenuated the increase in BP during extubation and decreased the agitation and cough scores. The time to emergence and extubation was however significantly longer with dexmedetomidine use in one of these two studies.\textsuperscript{18} Talke and colleagues\textsuperscript{6} continued the use of dexmedetomidine infusion from before induction to the postoperative period and showed a decrease in HR and noradrenaline level during emergence in their study populations. While dexmedetomidine is known to produce a conscious sedative effect with minimal respiratory depression,\textsuperscript{11, 9} in one of the studies on dexmedetomidine use in ICU,\textsuperscript{14} it was shown that the mean time required from cessation of infusion to extubation was 28 min (range 20–50 min). In our study, besides having dexmedetomidine, which has a terminal elimination half-time of 2 h, our patients also received isoflurane and fentanyl. To avoid delayed awakening and to minimize any undue sedative effect and aspiration risk, we stopped the dexmedetomidine infusion 30 min before the anticipated end of the operation. In addition, central apnoea had been reported when dexmedetomidine was continued through extubation.\textsuperscript{20} The priority of attenuating the BP would therefore need to be balanced against the risk of delayed awakening and even the risk of apnoea after extubation.

Although we were not able to show a smaller rise in BP after extubation for the dexmedetomidine group, the degree of strain on extubation was attenuated. The emergence response on extubation was usually just crudely classified as ‘good, medium, poor’\textsuperscript{21} or the number of coughs in other studies.\textsuperscript{17, 22} The number of coughs post-extubation or the bucking of endotracheal tube is difficult to count. The BP and HR were more frequently reported without mentioning the agitation manifested by the patients. However, these two aspects do not necessarily correlate as shown in our study and the study of Fagan and colleagues.\textsuperscript{23} Therefore, we devised a 0–5 scale to reflect the overall extubation strain. There were only two observers involved in this study, and both of them were present in the majority of cases. In this way, the inter-observer and intra-observer variability over time were minimized.

While mild to moderate coughing and straining after eye operations should not cause major damage to the eyes, potential risk of intraocular content prolapse, lens displacement, or suture disruption still exists. Therefore, dexmedetomidine use may be helpful especially in ophthalmic surgery with large wounds such as penetrating keratoplasty.
and traditional extracapsular cataract extraction, and cataract operations done with sutureless technique.

IOP control is important during ophthalmic surgery, especially in patients with penetrating eye injury. During surgery, the major categories of factors affecting IOP include the aqueous humour fluid dynamics, choroidal blood volume, vitreous volume, and extraocular muscle tone. Choroidal blood flow is autoregulated through a range of perfusion pressure. However, when the MAP reduces to <90 mm Hg, a marked reduction in IOP occurs.

We found no difference in the IOP reduction between the dexmedetomidine and placebo groups when they were maintained in similar anaesthetic level. In previous studies, where dexmedetomidine was shown to reduce IOP, there was also a significant reduction in BP. We believe that the reduction in IOP shown in the previous studies was most likely a manifestation of BP effect on IOP instead of dexmedetomidine effect on a2-adrenoceptor, and dexmedetomidine may not have any IOP reducing effect besides its indirect haemodynamic effect.

The requirement for IOP control in intraocular surgery may not be as high in vitreoretinal surgery as in surgery such as corneal transplant surgery and our surgeons found the operative condition equally satisfactory in both groups of patients. There was a recent case report of lens extrusion in an open eye surgery where atropine was used to treat an episode of intraoperative bradycardia. The heart rate and the BP increased substantially after the use of atropine and there was a spontaneous extrusion of the lens with vitreous prolapse. Taking into account dexmedetomidine’s propensity to produce bradycardia, we had premedicated our patients with atropine and this had successfully prevented any significant reduction in HR and the risk of sudden BP and IOP change associated with its treatment.

With i.v. fluid supplement and a reduction in the loading dose, the use of dexmedetomidine can produce stable haemodynamics. With similar arterial pressure changes, the reduction in IOP with dexmedetomidine use was comparable with a standard general anaesthetic technique. Even though the extubation BP could not be attenuated when the dexmedetomidine infusion was stopped 30 min before the end of the operation, the extubation strain was reduced and there was no delay in awakening or in recovery.

Acknowledgements

We would like to thank the vitreoretinal team of Hong Kong Eye Hospital and Queen Elizabeth Hospital for their help in taking the IOP measurements and making the necessary arrangement to accommodate this study. We would also like to thank Abbott Laboratories Ltd for providing the dexmedetomidine used in this study free of charge, with no constraint attached.

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