

Comparative evaluation of efficacy of sublingual atropine sulfate drops in reducing salivary flow during dental procedures: An in-vivo study

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Abstract

Background:

Excessive salivary flow during dental procedures compromises isolation, visibility, and adhesive performance. Although atropine sulfate is a known antisialagogue, evidence supporting its sublingual use for chairside salivary control in healthy adults remains limited.

Aim:

To evaluate the efficacy of sublingual atropine sulfate drops in reducing stimulated salivary flow during dental procedures and to assess associated cardiovascular responses.

Materials and Methods:

A prospective, randomized, placebo-controlled clinical trial was conducted on 40 healthy adults aged 18–47 years. Participants were randomly allocated into two groups (n = 20 each). Group I received two drops of 1% atropine sulfate sublingually, while Group II received an equivalent volume of normal saline. Stimulated salivary flow, heart rate, and systolic and diastolic blood pressure were recorded at baseline, 60 minutes, and 90 minutes.

Statistical Analysis:

Data were analyzed using repeated-measures ANOVA and independent samples t-tests ($p < 0.05$).

Results:

The atropine group showed a significant reduction in stimulated salivary flow at 60 and 90 minutes ($p < 0.001$), whereas no significant change was observed in the saline group. Intergroup analysis confirmed greater salivary flow reduction with atropine ($p < 0.001$). Transient changes in heart rate and diastolic blood pressure at 60 minutes returned toward baseline by 90 minutes.

Conclusion:

Sublingual atropine sulfate effectively reduces stimulated salivary flow with mild, transient cardiovascular changes, making it a well-tolerated adjunct for salivary control during dental procedures.

Keywords: Atropine sulfate, Salivary flow reduction, Sublingual administration, Antisialagogue, Dental procedures, Oral dryness, Clinical evaluation.

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INTRODUCTION

Saliva is essential for supporting and preserving overall oral health. It helps in oral homeostasis, aids in digestion, and provides antimicrobial protection. Saliva surrounds the hard and soft tissues of the oral cavity composed of organic and inorganic components. [1] However, in dentistry, it can be a major barrier, especially when performing procedures that require a sterile, dry, and isolated operative field. Restoring cervical carious lesions is difficult because of limited access, reduced visibility, moisture control issues, and the need to bond to multiple dental substrates.[2] Salivary contamination can compromise adhesive procedures, impression accuracy, and overall restoration longevity.

Achieving complete isolation is critical in restorative dentistry to ensure predictable treatment outcomes.[3] While mechanical isolation is the gold standard, newer methods can be clinically time-consuming and may induce irritation or anxiety in apprehensive patients, potentially complicating the procedure.

Atropine, a white crystalline alkaloid derived from the roots and leaves of *dianqiecao* (*Belladonnae Herba*) and *mantuoluo* (*Mandala*), functions as an M-choline receptor antagonist. Current evidence indicates that activation of muscarinic M3 receptors is chiefly responsible for salivary secretion (Sapkos SW, 1984).[4]

Parasympathetic input largely governs salivary gland activity, with acetylcholine binding to muscarinic receptors to stimulate secretion. Consequently, muscarinic receptor antagonists like atropine are well recognized for managing excessive glandular secretion (Joseph MC and Vale RJ, 1960; Mushin WW, et al.,1953).[5]

Sublingual atropine sulfate provides advantages such as simple use, quick mucosal absorption, low cost, and reversibility, all without requiring special training (Mushin WW, et al., 1953).⁵ The rationale for selecting the sublingual route of administration is its ability to bypass first-pass hepatic metabolism, allowing for rapid absorption through the highly vascularized sublingual mucosa, resulting in faster onset and greater bioavailability compared to oral tablets. Despite its potential, sublingual atropine for

reducing salivary flow in healthy adults is under-researched, with most studies focusing on systemic use in paediatric or surgical settings.

To address this gap in the literature (Samuel S et al. 2022), the present study evaluated the efficacy of sublingual atropine sulfate drops in reducing salivary flow in healthy adults aged 18–47 years.[7] It also assessed clinical feasibility, patient tolerance, and the potential of this method as a practical adjunct for salivary control in dental practice, including the optimal dosage and duration of its antisialogogue effect.

Materials and Methodology

Study Design and Ethical Approval

The study protocol was approved by the Institutional Ethics Committee and registered in the National Clinical Trials Registry of India (CTRI/2025/03/083225). The trial was conducted in accordance with the PRIRATE 2020 guidelines.[6] Written informed consent was obtained from all participants after explaining the study's purpose, benefits, and potential risks.

Sample size calculation

With 80% statistical power and a 5% alpha error (two-tailed), a minimum sample size requirement of 18 participants per group was obtained, considering an effect size of 0.85 derived from the previous study.[7] A total of 36 patients between the age of 18 to 47 years were selected. Assuming a 10% dropout rate, the final sample size was increased to 20 participants per group.

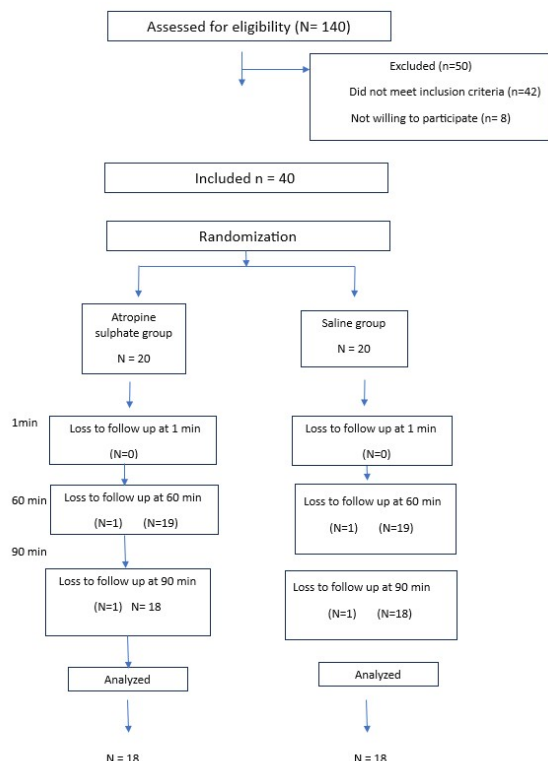
Setting/environment of the study

This study was designed as a prospective, parallel-group, randomized, placebo-controlled trial. A total of 40 patients referred to the outpatient clinics of the Department of Conservative Dentistry and Endodontics between 1st April 2025 and 31st May 2025 were evaluated for eligibility. No changes were made to the study protocol after trial initiation. Only healthy adult volunteers meeting the predefined eligibility criteria were included.

Inclusion Criteria

The study included adults aged 18 years or older who were classified as ASA I (a normal healthy patient) or ASA II (a patient with mild systemic disease without substantive functional limitations). ASA I participants included those who were non-smoking, with no or minimal alcohol use, while ASA II included individuals with well-controlled conditions such as mild hypertension or controlled diabetes. All participants were required to be normotensive and, in the case of female participants, non-pregnant and non-lactating.[8]

Figure 2:



Exclusion Criteria

Participants were excluded if they had a known allergy to atropine, a history of kidney, liver, cardiac disease, or conditions where anticholinergics are contraindicated.[8]

Randomization

Randomization was performed using the lottery method to avoid selection bias and to ensure equal distribution across the groups. Participants were randomly assigned to one of two groups (n = 20 each) based on the final solution. Both the patients and the statistician were blinded to the group allocation.

- Group I - atropine sulfate group
- Group II - saline group

Preoperative assessment

Each patient's blood pressure and heart rate were checked before the beginning of the procedure. Only the patients with salivary flow within the normal limit were taken into consideration. Assessment of Normal Salivary Flow to ensure standardization, only patients with a normal baseline stimulated salivary flow rate ($>1\text{ mL/min}$) were included. Normal flow was measured using the "spit method": participants chewed a standardized piece of paraffin wax to stimulate secretion and expectorated into a calibrated test tube over 5 minutes. The total volume was divided by five to determine the flow rate in mL/min , ensuring all participants met the threshold for healthy salivary gland activity prior to randomization.

CLINICAL PROCEDURE

Two designated observers were utilized to standardize data collection: one for physiological monitoring and one for salivary measurement. The average flow rates of stimulated saliva in healthy individuals is $1.5 (\pm 0.7) \text{ mL/min}$. [9] Therefore, participants without any systemic diseases and with a normal stimulated salivary flow rate ($\geq 1 \text{ mL/min}$) were enrolled in the study. Baseline vital parameters, including blood pressure, heart rate were recorded for all participants. Commercially available 1% atropine sulfate ophthalmic drops (Jawa Pharmaceuticals, India) (fig1a), and based on prior pharmacokinetic studies in which $50 \mu\text{L}$ of 1% solution corresponded to 0.5 mg atropine (Schwartz MD et al. 2022), we administered two drops ($\approx 1.0\text{--}1.2 \text{ mg}$) sublingually (Mubaslat O et al 2022). [8,10] While drug titration is possible, a fixed dosage was selected to evaluate the clinical feasibility of a standardized "chairside" protocol.

A total of 40 participants were randomly allocated into two groups.

Group I – Sublingual Atropine Sulfate

Participants were asked to expectorate into a calibrated test tube to collect the baseline sample (Fig. 1d). Afterward, the participant received the dose of sublingual atropine sulfate drops (Fig. 1c). They were instructed to maintain the medication under the tongue without swallowing or spitting for 1 minute to ensure adequate mucosal absorption. Assessment of drug onset was ensured by asking patients to report the time of first perception of oral dryness following administration. Following this period, Subsequent salivary samples were collected at 60 minutes and 90 minutes using the same protocol during the dental treatment procedure (Fig. 1e–1f). Heart rate and blood pressure were recorded at each corresponding time interval to monitor physiological responses to the drug.

Group II – Sublingual Saline (Control Group)

Participants in the control group received an equivalent volume of normal saline (Fig 1b) sublingually. Instructions regarding retention time and saliva collection were identical to those followed in the atropine group. Salivary samples and vital parameters were recorded at 0, 60, and 90 minutes following administration. (Fig. 1g,h,i)

After completion of the sampling schedule, all participants were reassessed for salivary flow. In the atropine group, stimulated salivary flow returned to baseline approximately 4 hours after administration based on observations within the study indicating a temporary and reversible pharmacological effect.

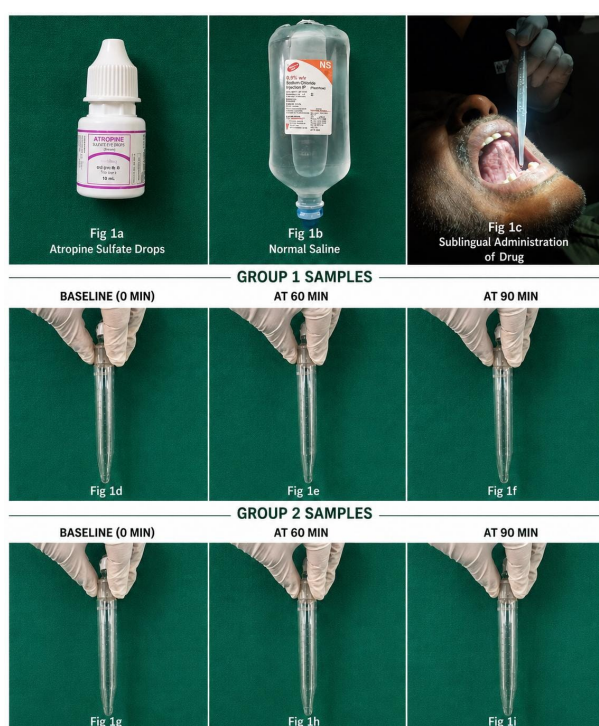


Figure 1 – samples of salivary flow at baseline, 60 minutes and 90 minutes.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean $\pm$ standard deviation (SD). The normality of data distribution was assessed using the Shapiro–Wilk test. Within-group differences across the three time intervals (0, 60, and 90 minutes) were evaluated using repeated-measures ANOVA, followed by Bonferroni post hoc tests for pairwise comparisons. Between-group differences at each time point were analyzed using the independent samples t-test. A p -value ≤ 0.05 was considered statistically significant.

Results

A total of 140 individuals were screened; 50 were excluded (42 not meeting criteria, 8 unwilling). Forty participants were randomized equally into Atropine ($n=20$) and Saline ($n=20$) groups. Four participants (two from each group) were lost to follow-up. Thus, 18 per group completed the study for final analysis. Patient distribution is shown in the CONSORT diagram [Figure 2].

The Atropine group showed a highly significant reduction in salivary flow from a baseline of 1.29 ± 0.12 mL to 0.45 ± 0.12 mL at 60 minutes and 0.23 ± 0.09 mL at 90 minutes ($p < 0.001$) [Table 1]. Bonferroni post hoc tests confirmed significant differences across all intervals (0 vs 60, 0 vs 90, and 60 vs 90 minutes) ($p < 0.001$). Heart rate in the atropine group showed a transient, statistically significant reduction at 60 minutes (69.73 ± 0.65 bpm) compared to baseline (77.73 ± 1.95 bpm) ($p < 0.001$), returning toward baseline by 90 minutes. Diastolic blood pressure (DBP) rose significantly at 60 minutes (87.64 ± 1.91 mmHg) compared to baseline (78.27 ± 2.05 mmHg) ($p < 0.001$). [Table 1].

Between-group comparison showed that atropine produced a significantly greater reduction in salivary flow at both 60 and 90 minutes than saline ($p < 0.001$) [Table 2][Graph 1]. Inter-group analysis showed significantly higher DBP and SBP in the atropine group at 60 minutes ($p < 0.001$ and $p = 0.032$), with no differences at baseline or 90 minutes [Table 2].

Repeated-measures ANOVA confirmed a highly significant reduction in salivary flow across all intervals within the atropine group ($p < 0.001$), while no significant changes occurred in the saline group. All participants tolerated the drug well, and no adverse effects were reported.

Discussion

Long-term restoration success relies on maintaining a sound interface between the tooth and the restorative material.[11] The fact remains that in order to have successful adhesion between resin and the tooth substrate, it is necessary that the adhesive substrate should not be contaminated. Contaminants such as saliva, blood, hemostatic agents, gingival fluid, and handpiece oil can adversely affect the longevity of the restoration owing to microleakage, which in turn leads to sensitivity, tooth discoloration, secondary caries, and eventual loss of the restoration. Additionally, achieving adequate isolation becomes difficult when cavity margins extend beneath the gingival tissues.[12] Clinically, while the effects of saliva can often be controlled using a rubber dam, sublingual atropine remains a

valid pharmacological adjunct in cases where mechanical isolation is difficult, such as in patients with severe gag reflexes, anxiety, subgingival margins where rubber dam placement is impossible, or latex allergy.

Atropine was administered through multiple routes across the studies. Reported delivery methods include sublingual, intravenous, subcutaneous, oral (tablet or solution), and direct injections into the parotid gland or the base of the tongue.[13] Kubota C et al. reported that chewing-stimulated salivary flow significantly declined between 50 and 120 minutes following oral atropine administration. [14]

The findings offer strong evidence in Favor of its application as a quick, efficient, and minimally invasive moisture control adjunct; this is particularly important for patients who are young or uncooperative.

Key finding was the atropine group's marked reduction in salivary flow, dropping from 1.29 mL at baseline to 0.23 mL at 90 minutes, with significant decreases at all intervals ($p < 0.001$). In contrast, the placebo group showed no meaningful change across time points.

Atropine, an anticholinergic agent, decreases gastric, salivary, bronchial, and sweat secretions by competitively blocking muscarinic Type 3 receptors.[15] Atropine competitively blocks M3 muscarinic receptors on salivary acinar cells, limiting parasympathetic activity and producing a temporary reduction in salivary output. The sublingual route bypasses first-pass metabolism and allows rapid systemic absorption through the highly vascular mucosa, providing faster onset and greater bioavailability than oral or intramuscular delivery (Rajpal S, et al., 2010).[16]

These findings are consistent with other recent research, such as that conducted by Mubaslat et al. (2022) and Wang et al. (2024), which showed that sublingual atropine effectively decreased salivation in both neurologically impaired patients and healthy individuals.[8]

Atropine affects cardiovascular parameters in addition to its anticholinergic effects on salivation. At 60 minutes after administration, the atropine group showed a statistically significant, transient reduction in heart rate from 77.73 ± 1.95 to 69.73 ± 0.65 bpm ($p < 0.001$), with values returning toward baseline by 90 minutes (76.82 ± 2.32 bpm). This brief bradycardia, which may be attributed to localized sublingual absorption and dosage limits, contrasts with the tachycardia typically expected with systemic atropine administration.⁷

Atropine's non-tissue-specific blockade of muscarinic receptors exerts generalized

parasympathetic inhibition. Beyond the salivary and cardiovascular effects observed here, systemic anticholinergic activity can reduce smooth muscle motility in the gastrointestinal and urinary tracts, potentially leading to delayed gastric emptying or urinary retention (Mubaslat et al., 2022; Yellepeddi et al., 2024). [8,13] Although not clinically reported in our ASA I and II cohort, these systemic implications necessitate thorough medical screening to mitigate risks in susceptible patients.

While the influence of atropine on heart rate and blood pressure observed in this study was transient, these fluctuations specifically the brief bradycardia and rise in DBP highlight the importance of medical screening. Systemic anticholinergic effects can impact the body in general, and practitioners should exercise caution in patients with undiagnosed cardiac sensitivities, as well as monitor for potential risks such as blurred vision, xerostomia, or urinary retention.

Both groups showed stable systolic pressure at all time points, with the atropine group showing a small increase at 60 minutes ($p = 0.032$). Diastolic pressure in the atropine group rose significantly at 60 minutes ($p < 0.001$) but returned to baseline by 90 minutes, likely due to atropine's transient peripheral anticholinergic effects. No adverse effects or signs of intolerance were observed, confirming the protocol's safety in healthy adults classified as ASA I and II.

Limitations of the Study

1. The study included only healthy adults, which limits its applicability to pediatric, geriatric, or medically compromised patients.
2. Only a single dose of atropine sulfate was evaluated, and no comparison was made with other anticholinergic agents, limiting the ability to determine relative efficacy.
3. Pharmacokinetic parameters such as onset time, peak effect, and duration of action were not measured, restricting a deeper understanding of the drug's systemic behavior.

Conclusion

Within the limitations of this study, sublingual atropine sulfate produced a significant and sustained reduction in salivary flow, with peak efficacy observed between 60 and 90 minutes. Although mild, transient cardiovascular fluctuations were recorded, they remained within physiological limits and were well-tolerated by all participants. Given its safety profile, cost-effectiveness, and ease of administration, sublingual atropine sulfate

serves as a valuable pharmacological adjunct for chairside salivary control, particularly in cases where conventional mechanical isolation is challenging or unfeasible.

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Table 1: Intra-group comparison of mean salivary flow rates and vital parameters between Atropine and Normal Saline groups at baseline, 60 minutes, and 90 minutes.

Variable	Group	0 minutes		60 minutes		90 minutes		p-value
		Mean	SD	Mean	SD	Mean	SD	
Salivary flow	Atropine	1.29	0.12	0.45	0.12	0.23	0.09	<0.001*
	Normal saline	1.42	0.24	1.53	0.23	1.53	0.16	0.184
Heart rate	Atropine	77.73	1.95	69.73	0.65	76.82	2.32	<0.001*
	Normal saline	77.55	2.42	76.91	2.84	76.64	3.36	0.318
SBP	Atropine	121.18	1.40	121.91	2.17	121.64	1.86	0.277
	Normal saline	119.00	3.90	118.91	3.73	119.00	3.90	0.832

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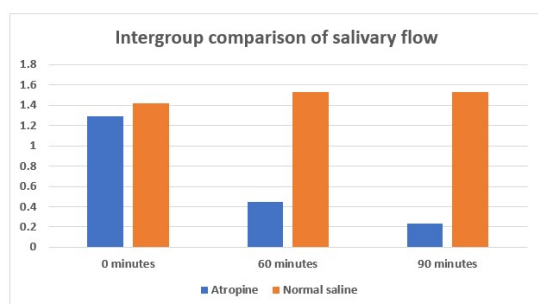
DBP	Atropine	78 .2 7	2. 0 5	87 .6 4	1. 9 1	79 .8 2	1. 7 2	<0. 00 1*
	Normal saline	78 .4 5	1. 9 7	78 .8 2	1. 7 8	78 .8 2	1. 7 8	0.2 67

Repeated measures ANOVA test; * indicates a significant difference at $p \leq 0.05$

Table 2: Pairwise post hoc (Bonferroni) comparison of salivary flow and vital parameters across different time intervals.

Variable	Group	0 mins vs 60 mins	0 mins vs 90 mins	60 mins vs 90 mins
Salivary flow	Atropine	<0.001*	<0.001*	<0.001*
	Normal saline	0.156	0.440	1.000
Heart rate	Atropine	<0.001*	0.099*	<0.001*
	Normal saline	0.267	0.556	1.000
SBP	Atropine	0.664	1.000	0.245
	Normal saline	1.000	1.000	1.000
DBP	Atropine	<0.001*	0.001*	<0.001*
	Normal saline	0.802	0.802	0.802

Bonferroni post hoc tests; * indicates a significant difference at $p \leq 0.05$



Graph 1 – Intergroup comparison of salivary flow at baseline, 60 minutes, and 90 minutes