

# Long-term result of out-patient neodymium-doped yttrium aluminium garnet laser photocoagulation surgery for patients with epistaxis

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## Abstract

**Objective:** To evaluate the long-term efficacy of out-patient neodymium-doped yttrium aluminium garnet laser photocoagulation surgery for patients with epistaxis.

**Methods:** A retrospective clinical study was conducted. A total of 217 consecutive patients who presented with acute or recurrent epistaxis received neodymium-doped yttrium aluminium garnet laser photocoagulation treatment in an out-patient setting.

**Results:** At three years, 94 per cent of acute epistaxis patients versus 88 per cent of recurrent epistaxis patients reported no bleeding. The outcome scores at 12 weeks and 3 years after treatment showed no significant differences between the 2 groups ( $p = 0.207$  and  $p = 0.186$ ). However, there was a significant difference in outcome scores at four weeks after treatment ( $p = 0.034$ ). The median (and mean  $\pm$  standard deviation) pain levels experienced during the laser operation (performed in an office setting) were 4.0 ( $3.75 \pm 2.09$ ) in the acute epistaxis group and 4.0 ( $3.83 \pm 2.01$ ) in the recurrent epistaxis group. Neither group had any complications.

**Conclusion:** Neodymium-doped yttrium aluminium garnet laser photocoagulation is desirable in the treatment of both acute and recurrent epistaxis, and has long-lasting efficacy.

**Key words:** Laser; Epistaxis; Photocoagulation

## Introduction

Epistaxis is extremely common and is usually managed with simple first aid measures in the community. It includes acute haemorrhage and refractory recurrent epistaxis. The majority of cases are self-limiting and do not require medical intervention. The reported incidence of an episode of epistaxis occurring during a lifetime is approximately 60 per cent, with less than 10 per cent of cases requiring medical attention.<sup>1</sup> There is a bimodal distribution of epistaxis incidence, with peaks in children and older adults. The peak incidence of epistaxis in adults is in 45–65-year-olds, in whom the incidence of severe posterior bleeding is greater.<sup>2</sup>

The aetiology of epistaxis is divided into local and systemic factors. Local factors include trauma, local inflammatory reactions, foreign bodies, post-surgical anatomical deformities, intranasal tumours, chemical inhalants, nasal-prong oxygen administration and continuous positive airway pressure therapy for obstructive sleep apnoea. Systemic causes of epistaxis include: vascular disorders, especially hereditary haemorrhagic telangiectasia; blood dyscrasias; haematological malignancies; and drugs affecting the normal clotting

mechanism.<sup>3</sup> Although local and general causes can occasionally be identified, the majority of cases (80–90 per cent) are idiopathic.<sup>4</sup>

Most epistaxis occurs on the anterior nasal septum at a region called Little's area, which is supplied by Kiesselbach's plexus. This network of vessels is a confluence of three terminal arteries and accounts for 90–95 per cent of epistaxis cases.<sup>5</sup>

There are many ways to achieve haemostasis in this region, such as by applying pressure to the nostrils, or by utilising: chemical or electrical cauterisation, topical haemostatic or vasoconstricting agents, cryotherapy, hot water irrigation, or anterior nasal packing.<sup>6</sup> The optimal treatment would accomplish haemostasis with minimal pain, no re-bleeding and with limited impact on patients' daily activities. Unfortunately, there is limited evidence in the literature on how to best manage and prevent recurrent epistaxis.

In our previous study, we compared the efficacy of neodymium-doped yttrium aluminium garnet (Nd:YAG) laser photocoagulation with that of liquid paraffin plus antiseptic cream in the management of recurrent epistaxis.<sup>7</sup> The outcome at 4 weeks after

treatment showed no significant difference between the 2 treatment groups; however, the outcome score at 12 weeks after treatment showed a significant difference between the 2 groups. Owing to some weaknesses in the former study, we decided to conduct a further study with a larger sample and a longer follow-up period, in order to evaluate the efficacy of out-patient Nd:YAG laser photocoagulation surgery performed for epistaxis.

## Materials and methods

### *Ethical considerations*

This study was approved by the Committee of Human Research Ethics at the Eye, Ear, Nose and Throat Hospital, Shanghai. Informed consent was obtained prior to participation in the study.

### *Participants*

A retrospective study was undertaken. The study comprised patients with anterior epistaxis, determined by anterior rhinoscopy, who presented to the Otolaryngology Department at the Eye, Ear, Nose and Throat Hospital of Fudan University between February and September 2011.

All patients had a normal full blood count, including: white blood cell count and white blood cell types (white blood cell differential); red blood cell count; haematocrit levels; haemoglobin levels; red blood cell indices (mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration); platelet (thrombocyte) count; mean platelet volume; and normal coagulation test values (including D-dimer concentration, prothrombin time and international normalised ratio, and activated partial thromboplastin time).

The exclusion criteria were: pregnancy; active haemorrhage with risk of mortality; epistaxis after a nasal operation; nasal neoplasm; hereditary haemorrhagic telangiectasia; systemic diseases such as known bleeding disorders and untreated hypertension; silver nitrate cautery or other treatment within one month; and posterior epistaxis evaluated by endoscopy.

All eligible subjects were treated as out-patients and by the same physician.

### *Trial design*

All patients were allocated to one of two groups according to the duration of symptoms. Patients with symptoms lasting less than eight weeks were classified as acute epistaxis cases, whereas those with symptoms lasting more than one year were classified as recurrent epistaxis cases.

All patients underwent Nd:YAG laser photocoagulation once only, with no additional agents. Patients received routine care when seen in the clinic, consisting of history, physical examination, tests and nasal endoscopy. The patients were followed up 4 weeks, 12 weeks and 3 years after treatment.

### *Laser procedure*

The Nd:YAG laser treatments were performed in the operating theatre under local anaesthesia. First, the nose was moistened, and crusts and blood clots were removed with gentle saline rinses. The septal mucosa was then infiltrated with a solution containing local anaesthetic and a vasoconstricting agent (1 per cent tetracaine and 1:100 000 adrenaline) for better visualisation of the telangiectasia. Continuous wave Nd:YAG laser photocoagulation was performed at 3 W under magnification using an anterior rhinoscope and magnifying glasses, or with a nasal endoscope. The laser spot size was 1 mm. The laser was specifically applied onto obvious blood vessels. When bleeding was encountered during the operation, a topical vasoconstrictor was applied to temporise the bleeding (the presence of blood in the surgical field can compromise the technique). The laser power was then increased to 5 W. When no further telangiectasia or bleeding was visualised, the laser coagulation was discontinued. This procedure can be completed by one person utilising both the laser tip and the endoscope.

### *Data collection and follow up*

All patients completed questionnaires before and after treatment. The data collected and recorded included demographic parameters, bleeding intensity, nasal bleeding frequency, pain experienced during haemostasis and complications.

The patients ranked the intensity of bleeding as defined by Bergler *et al.*: 1 = stains on napkin, 2 = soaked napkin or 3 = a bowl needed.<sup>8</sup> The frequency of bleeding was defined as: 1 = less than one epistaxis episode per month, 2 = one episode per month, 3 = one episode per week or 4 = one episode every day or more.

Patients estimated the pain experienced during the laser procedure using a 10-point visual analogue scale, wherein 0 = no discomfort and 10 = unbearable. The outcome score assessed bleeding intensity and frequency after treatment, wherein 0 = no bleeding, 1 = reduced bleeding, 2 = the same amount of bleeding and 3 = worse bleeding.

### *Statistics*

Data were entered into the SPSS 18 statistical software program (IBM, Armonk, New York, USA) for analysis. Demographic data are presented as mean  $\pm$  standard deviation (SD) and mean rank. The paired-samples *t*-test was used for the analysis of means, the Mann–Whitney U test was used for mean rank and the chi-square test was used for associated factors. A 95 per cent confidence interval was used, and *p* values less than 0.05 were considered significant.

## Results

A total of 217 patients with idiopathic epistaxis (118 men and 99 women) were studied; 68 had acute

TABLE I  
PATIENT CHARACTERISTICS FOR EACH GROUP\*

Variable	Acute epistaxis <sup>†</sup>	Recurrent epistaxis <sup>‡</sup>	<i>p</i>
Age (mean ± SD; years)	57.59 ± 16.52	46.26 ± 17.82	<0.001
Sex			
– Male	34 (50)	84 (56)	
– Female	34 (50)	65 (44)	
Bleeding intensity history (score)			
– 1	19 (28)	64 (43)	<0.001
– 2	18 (26)	44 (30)	
– 3	31 (46)	41 (27)	
Bleeding frequency history (score)			
– 1	0 (0)	25 (17)	0.134
– 2	3 (4)	33 (22)	
– 3	34 (50)	65 (44)	
– 4	31 (46)	26 (17)	
Symptom duration (mean ± SD; weeks)	3.9 ± 3.4	315.94 ± 447.88	<0.001
Associated factors			
– Hypertension	34 (50)	31 (21)	<0.001
– Antiplatelet (aspirin)	5 (7)	3 (2)	0.053
– Inflammation (allergic rhinitis)	7 (10)	23 (15)	0.309
– Trauma	0 (0)	2 (1)	
– Others	8 (12)	14 (9)	0.592
Bleeding source			
– Nasal septum	56 (82)	128 (86)	
– Inferior turbinate	8 (12)	12 (8)	
– Middle turbinate	1 (1)	1 (1)	
– Basis nasi	0 (0)	2 (1)	
– Nasal lateralis	1 (1)	4 (3)	

Data represent numbers (and percentages) of patients unless indicated otherwise. \*Total  $n = 217$ ; <sup>†</sup> $n = 68$ ; <sup>‡</sup> $n = 149$ . SD = standard deviation

epistaxis and the remaining 149 had recurrent epistaxis. Of these, 10 children (aged 15 years or younger) were excluded. In contrast to adults, epistaxis in children is usually caused by picking, rubbing or hitting their nose, and infection.<sup>9,10</sup> A further 4 patients with traumatic epistaxis, 9 with bleeding from the nasal cavity and paranasal sinus tumours, 2 with post-operative epistaxis, and 15 with hereditary haemorrhagic telangiectasia were excluded because the methods to stop such bleeding differ from those for idiopathic epistaxis. Thirty-one patients were lost to follow up, including two patients who died. Thirty-two patients were excluded for non-conformity with the study criteria.

Table I shows the baseline characteristics of each group, which demonstrates some interesting differences. The mean age of the acute epistaxis group was higher than that of the recurrent epistaxis group ( $p < 0.001$ ). The bleeding intensity of past epistaxis was significantly greater in the acute epistaxis group than in the recurrent epistaxis group ( $p < 0.001$ ) (Table I). There was an obvious difference between the two groups in terms of symptom duration: patients in the acute epistaxis group experienced symptoms over a significantly shorter timeframe because of the grouping criteria ( $p < 0.001$ ). In addition, there were more patients with hypertension in the acute epistaxis group than in the recurrent epistaxis group.

The procedure-related pain, the operative time and the bleeding situation during the procedure are shown in Table II. The procedure was generally short in duration and well tolerated by patients. The operative

time was less in the acute epistaxis group than in the recurrent epistaxis group ( $p < 0.05$ ). All patients were able to go home on the day of surgery and resume their daily activities. There was no retained material in the nasal cavity of most patients, with the exception of six patients in the recurrent epistaxis group and two patients in the acute epistaxis group who required a small piece of gelatine sponge in their nasal cavity to prevent bleeding. In general, the patients did not feel any discomfort after treatment, and the treatment did not have a significant impact on their life.

Tables III and IV show significant differences in bleeding intensity and frequency before and after treatment (up to three years) in the two groups.

At three years, 94 per cent of patients in the acute epistaxis group and 88 per cent of patients in the recurrent epistaxis group reported no bleeding (Table V). There were no statistically significant differences between the 2 groups in terms of the outcome score of the 217 patients at 12 weeks and 3 years after treatment ( $p = 0.207$  and  $p = 0.186$ ). However, there was a significant difference between the two groups for the outcome score at four weeks after treatment ( $p = 0.034$ ): more patients in the recurrent epistaxis group experienced bleeding than the acute group at four weeks.

There were no complications, such as blood transfusion, hospitalisation, visible nasal scars, nasal adhesions or nasal septum perforation, in either study group.

## Discussion

Although epistaxis is perceived by many to be a relatively minor problem and the general course of

TABLE II  
OPERATIVE TIME, INTRA-OPERATIVE PAIN AND BLEEDING SITUATION

Variable	Acute epistaxis*	Recurrent epistaxis <sup>†</sup>	<i>p</i>
Operative time (min)			
– Median	5.0	7.0	0.023
– Mean ± SD	7.31 ± 5.39	8.96 ± 6.07	
Intra-operative pain (VAS score)			
– Median	4.0	4.0	0.84
– Mean ± SD	3.75 ± 2.09	3.83 ± 2.01	
Intra-operative bleeding ( <i>n</i> (%))	15 (22)	43 (29)	0.294
No bleeding ( <i>n</i> (%))	53 (78)	106 (71)	

\**n* = 68; <sup>†</sup>*n* = 149. Min = minutes; SD = standard deviation; VAS = visual analogue scale

TABLE III  
PRE- AND POST-TREATMENT (THREE YEARS) BLEEDING INTENSITY

Group	Intensity score				Mean rank	<i>p</i>
	0	1	2	3		
Acute epistaxis*						
– Pre-treatment intensity	0 (0)	19 (28)	18 (26)	31 (46)	100.82	<0.001
– Post-treatment intensity	65 (96)	1 (1)	0 (0)	2 (3)	36.18	
Recurrent epistaxis <sup>†</sup>						
– Pre-treatment intensity	0 (0)	64 (43)	44 (30)	41 (27)	219.77	<0.001
– Post-treatment intensity	131 (88)	17 (11)	1 (1)	0 (0)	79.23	

Data represent numbers (and percentages) of patients. \**n* = 68; <sup>†</sup>*n* = 149. 0 = no bleeding; 1 = stains on napkin; 2 = soaked napkin; 3 = bowl needed

TABLE IV  
PRE- AND POST-TREATMENT (THREE YEARS) BLEEDING FREQUENCY

Group	Frequency score					Mean rank	<i>p</i>
	0	1	2	3	4		
Acute epistaxis*							
– Pre-treatment frequency	0 (0)	0 (0)	3 (4)	34 (50)	31 (46)	102.48	<0.001
– Post-treatment frequency	65 (96)	2 (3)	1 (1)	0 (0)	0 (0)	34.52	
Recurrent epistaxis <sup>†</sup>							
– Pre-treatment frequency	0 (0)	25 (17)	33 (22)	65 (44)	26 (17)	221.91	<0.001
– Post-treatment frequency	131 (88)	15 (10)	3 (2)	0 (0)	0 (0)	77.09	

Data represent numbers (and percentages) of patients. \**n* = 68; <sup>†</sup>*n* = 149. 0 = no bleeding; 1 = less than one episode per month; 2 = one episode per month; 3 = one episode per week; 4 = one episode every day or more

TABLE V  
OUTCOME SCORES AT 4 AND 12 WEEKS, AND 3 YEARS AFTER TREATMENT

Time post-treatment	Outcome score				Mean rank	<i>p</i>
	0	1	2	3		
4 weeks						
– Acute epistaxis	64 (94)	4 (6)	0 (0)	0 (0)	101.24	0.034
– Recurrent epistaxis	125 (84)	19 (13)	3 (2)	2 (1)	112.54	
12 weeks						
– Acute epistaxis	64 (94)	3 (40)	0 (0)	1 (1)	104.92	0.207
– Recurrent epistaxis	132 (89)	13 (9)	4 (3)	0 (0)	110.86	
3 years						
– Acute epistaxis	64 (94)	2 (3)	0 (0)	2 (3)	104.63	0.186
– Recurrent epistaxis	131 (88)	17 (11)	1 (1)	0 (0)	110.99	

Data represent numbers (and percentages) of patients. 0 = no bleeding; 1 = reduced bleeding; 2 = the same amount of bleeding; 3 = worse bleeding

the condition is benign, its management continues to pose a problem to general practitioners and otolaryngologists alike.<sup>11</sup> Recurrent epistaxis can be distressing and alarming, and it causes inconvenience to patients. Furthermore, it results in a significant number of referrals to ENT out-patient clinics. The quality of life of recurrent epistaxis patients is poor;<sup>12</sup> work and daily life will be affected. Hence, this study was designed to investigate the long-term result of out-patient Nd:YAG laser photocoagulation surgery for patients with epistaxis.

Numerous treatment modalities have been investigated; however, no single method has been accepted as universally ideal. In our previous study, we compared the efficacy of Nd:YAG laser photocoagulation with that of liquid paraffin plus antiseptic cream in the management of recurrent epistaxis.<sup>7</sup> The outcome score at 12 weeks after treatment was significantly better in the Nd:YAG laser group than in the medicine group. However, the follow-up duration of that study was short. Hence, this study was conducted, which has a larger sample and a longer follow-up period.

This study adds to previous literature that seeks to identify a treatment which is well tolerated, results in minimal or no bleeding during treatment, prevents recurrences long-term, and is associated with a short recovery time (allowing patients to return to work quickly and resume normal daily activities).

Several previous studies have shown Nd:YAG laser surgery to be effective for treatment of hereditary haemorrhagic telangiectasia.<sup>13–15</sup> However, to our knowledge, there are currently few studies reporting the efficacy of Nd:YAG laser treatment for epistaxis.

With an Nd:YAG laser wavelength of 1064 nm, less absorption occurs in the pigmented tissue compared with the argon (488–514 nm) or potassium titanyl phosphate (532 nm) lasers. This theoretically results in greater depth of penetration and a subsequently greater zone of inflammation.<sup>15,16</sup> A more extensive zone of inflammation, in turn, increases the damage to the submucosal plexus of veins, which is the origin of epistaxis.

In our study, the most common source of bleeding was the nasal septum; 84 per cent of patients exhibited bleeding from this site, which is similar to the rates reported in the literature.

This study demonstrated that photocoagulation using an Nd:YAG laser had beneficial effects in approximately 97 per cent of patients with acute epistaxis and in 99 per cent of those with recurrent epistaxis. Furthermore, there were no complications of Nd:YAG laser treatment in our series, regardless of whether the epistaxis was acute or recurrent. The median (and mean  $\pm$  SD) pain levels experienced during the laser operation (performed in an office setting) were 4.0 (3.75  $\pm$  2.09) in the acute epistaxis group and 4.0 (3.83  $\pm$  2.01) in the recurrent epistaxis group, which are levels that can be well tolerated. The duration of the Nd:YAG laser photocoagulation

surgery ranged from 2 to 30 minutes, with median (and mean  $\pm$  SD) values of 5.0 (7.31  $\pm$  5.39) minutes in the acute epistaxis group and 7.0 (8.96  $\pm$  6.07) minutes in the recurrent epistaxis group. The bleeding stopped during the procedure in about three out of four patients. Overall, photocoagulation using an Nd:YAG laser appears to be a well-tolerated intervention for epistaxis patients.

The aetiology of epistaxis is diverse, and includes local and systemic factors. In our study, we found that the average age of acute epistaxis patients was higher than that of recurrent epistaxis patients, and the intensity of bleeding was more serious in the acute epistaxis patients than in the recurrent epistaxis patients. Moreover, there were more patients with hypertension in the acute epistaxis group than in the recurrent epistaxis group. These differences were all statistically significantly different. Overall, the findings indicate that acute epistaxis patients are generally older, the intensity of bleeding is more severe in this group, and hypertension may be one of the main causes of the epistaxis. The majority of recurrent epistaxis cases were idiopathic, which may result in different outcomes.

The outcome scores at 12 weeks and at 3 years after treatment indicated no significant difference between the 2 groups ( $p = 0.207$  and  $p = 0.186$ ). However, the outcome scores at four weeks after treatment revealed a significant difference between the two groups ( $p = 0.034$ ). Although Nd:YAG laser photocoagulation demonstrated effectiveness in more than 97 per cent of cases in both the acute epistaxis and recurrent epistaxis groups, which lasted long-term, the benefits may take effect faster in the acute epistaxis group.

- **Epistaxis is a common emergency presentation, but there is no defined and standardised treatment protocol**
- **Neodymium-doped yttrium aluminium garnet (Nd:YAG) laser photocoagulation is a simple, easy, safe and rapid therapy, which can be performed in an office setting**
- **This study, with a larger sample and longer follow up, confirmed our previous study findings**
- **Use of Nd:YAG laser in epistaxis management can reduce hospital admissions and cost, and improve patient experience**

The septal mucosa was infiltrated with a solution containing 1 per cent tetracaine and 1:100 000 adrenaline in order to achieve local anaesthetic and better visualisation of the telangiectasias. Despite its vasoconstriction properties, this solution did not influence the efficacy of the treatment. This is because the medicine

was not injected into the mucosa, but was infiltrated into the septal mucosa for only a few minutes.

## Conclusion

This study employed a larger sample and longer follow-up period than our previous study.<sup>7</sup> The findings demonstrated that Nd:YAG laser photocoagulation in the out-patient setting is a safe, convenient and simple procedure that is associated with minimal bleeding and well-tolerated levels of pain. This procedure allows patients to resume work and other daily activities in a short period of time (the same day). The value of this treatment should be generalised.

## References

- 1 Gifford TO, Orlandi RR. Epistaxis. *Otolaryngol Clin North Am* 2008;**41**:525–36
- 2 Watkinson JC. Epistaxis. In: Mackay IS, Bull TR, eds. *Scott-Brown's Otolaryngology*, 6th edn, vol 4(18). London: Butterworths, 1997;5–7
- 3 Krajina A, Chrobok V. Radiological diagnosis and management of epistaxis. *Cardiovasc Intervent Radiol* 2014;**37**:26–36
- 4 Pope LE, Hobbs CG. Epistaxis: an update on current management. *Postgrad Med J* 2005;**81**:309–14
- 5 Chiu T, Dunn JS. An anatomical study of the arteries of the anterior nasal septum. *Otolaryngol Head Neck Surg* 2006;**134**:33–6
- 6 Viehweg TL, Roberson JB, Hudson JW. Epistaxis: diagnosis and treatment. *J Oral Maxillofac Surg* 2006;**64**:511–18
- 7 Zhang J, Qiu R. A prospective randomized controlled trial of Nd:YAG laser photocoagulation versus liquid paraffin plus antiseptic cream in the treatment of recurrent epistaxis. *Clin Otolaryngol* 2012;**37**:271–5
- 8 Bergler W, Sadick H, Gotte K, Riedel F, Hörmann K. Topical estrogens combined with argon plasma coagulation in the management of epistaxis in hereditary hemorrhagic telangiectasia. *Ann Otol Rhinol Laryngol* 2002;**111**(3 Pt 1):222–8
- 9 McGarry G. Nosebleeds in children. *Clin Evid* 2006;**15**:496–9
- 10 Burton MJ, Doree C. Interventions for recurrent idiopathic epistaxis (nosebleeds) in children. *Cochrane Database Syst Rev* 2004;(1):CD004461
- 11 Murthy P, Nilssen EL, Rao S, McClymont LG. A randomised clinical trial of antiseptic nasal carrier cream and silver nitrate cautery in the treatment of recurrent anterior epistaxis. *Clin Otolaryngol Allied Sci* 1999;**24**:228–31
- 12 Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *Laryngoscope* 2010;**120**:838–43
- 13 Karapantzos I, Tsimpliris N, Goulis DG, Van Hoecke H, Van Cauwenberge P, Danielides V. Management of epistaxis in hereditary hemorrhagic telangiectasia by Nd:YAG laser and quality of life assessment using the HR-QoL questionnaire. *Eur Arch Otorhinolaryngol* 2005;**262**:830–3
- 14 Velegrakis GA, Prokopakis EP, Papadakis CE, Helidonis ES. Nd:YAG laser treatment of recurrent epistaxis in hereditary hemorrhagic telangiectasia. *J Otolaryngol* 1997;**26**:384–6
- 15 Mahoney EJ, Shapshay SM. Nd-YAG laser photocoagulation for epistaxis associated with hereditary hemorrhagic telangiectasia. *Laryngoscope* 2005;**115**:373–5
- 16 Shah RK, Dhingra JK, Shapshay SM. Hereditary hemorrhagic telangiectasia: a review of 76 cases. *Laryngoscope* 2002;**112**:767–73

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