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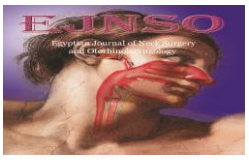

Evaluation of nasal hot water irrigation in the management of posterior epistaxis

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Abstract:

Background: The management of the posterior epistaxis is very challenging for any otorhinologist. Hot water irrigation (HWI) is a simple and non-invasive technique for the management of posterior epistaxis.

Objective: To evaluate the efficacy of HWI in the management of posterior epistaxis was including the advantages, complications, and factors affecting its success.

Patients and Methods: Forty-five patients with posterior epistaxis were included in this research. This is a prospective observational study.

Results: Using HWI, we achieved hemostasis in 39 patients (86.7%), two of them (4.4%) had complications in the form of minimal nasal adhesions. The mean hospital stay was 1.13 days (±0.344). The HWI failed in six patients (13.3%), we controlled epistaxis by anterior nasal packing (ANP) in four patients of them, and the remaining two patients by the posterior nasal pack.

Conclusions: HWI is a safe, efficient, and cost-effective treatment method for posterior epistaxis. This method has the additional benefits of less patient discomfort, less morbidity, less need for surgical intervention, and fewer days of hospitalization.

Keywords: Posterior epistaxis, hot water irrigation, hemostasis, control bleeding

Introduction

Temporal bone fractures associated Epistaxis is the most common otorhinolarynology emergency and one of the commonest presentations in an emergency department. It affects up to 10-60% of the population during their lifetime, with 10% requiring medical attention. The prevalence has two peaks are noted in children younger than 10 years old and adults over 40 years old. Approximately 7–14% of the adult population will have experienced epistaxis at some point in their life.[1]

Epistaxis is commonly classified into anterior and posterior epistaxis. This classification lies at the piriform aperture anatomically. 90% of episodes of epistaxis occur along the anterior part of the nasal septum which is supplied by Keisselbach's plexus in a site known as the Little's area. Approximately 10% of episodes of epistaxis are posterior bleeds. Posterior epistaxis is defined as cases where the bleeding point cannot be detected with anterior rhinoscopy.[2]

In contrast with anterior epistaxis, bleeding points can prove difficult to identify. The most common sites of posterior epistaxis are an area on the lateral nasal wall beginning near the

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sphenopalatine foramen and involving the mucosa of the posterior part of the middle meatus, inferior meatus, and the nasal floor. This area includes Woodruffs nasopharyngeal venous plexus and its accompanying arterial branches. [3]

Guice 1878 firstly used hot water irrigation (HWI) as a method in controlling of posterior epistaxis. In the second half of the twentieth century nasal packing and the development of endoscopic sinus surgery almost completely replaced the irrigation technique as a treatment for posterior epistaxis.

Ceylan, S.M., et al. 2020 [4], and **Özmen, S. and Ö.A. Özmen 2010** [5] showed the role of hot saline irrigation (HSI) in different types of nasal surgeries, for example showed that 50°C saline irrigation was more effective in post-adenoidectomy hemostasis in comparison to room-temperature (25°C) saline irrigation by providing a lesser hemostasis time and requiring the lesser need of re-curettage and electro-cauterization.

Nordström, A., et al.2013 [6], showed the hemostatic effect of HSI during functional endoscopic sinus surgery (FESS), they found that HSI had beneficial in improving the surgical field of view in FESS after 2 hours of operating time and a significant reduction in the rate of blood loss. The basis of HWI in controlling posterior epistaxis by inducing mucosal oedema with hot water which in turn leads to compression of blood vessels, vasodilation of the mucosal vessels, decreasing blood flow, and increasing the clotting cascade. The most important factor in this procedure is controlling the temperature of the water as the temperature below 480c is insufficient to cause mucosal oedema and above 520c causes local tissue necrosis.

The aim of the study was to evaluate the efficacy of HWI in the management of posterior epistaxis including its advantages, complications, and the factors affecting its success rate.

Patients and methods:

This prospective observational study was conducted in the otorhinolaryngology department in Assiut University Hospital from June 2020 to the end of June 2021, after obtaining approval from the Medical Ethics Committee 17100816, clinical trial NCT04151888, Faculty of Medicine, Assiut University.

Inclusion criteria: Forty-five consecutive patients were included in this study. The inclusion criteria patients older than 10 years, and if failed first aid measures.

Exclusion criteria: This procedure could not be done on patients with anterior epistaxis, patients who presented with hemorrhagic shock, and secondary epistaxis including Posttraumatic epistaxis, postoperative epistaxis after turbinectomy, septoplasty, or FESS, bleeding from nasal or nasopharyngeal neoplasia, and bleeding from diseased nasal mucosa such as atrophic rhinitis.

Patients were subjected to the following:

Data collection:

1. Personal History (name, age, sex, occupation, and smoking history)
2. Onset, severity, frequency, precipitating factors, laterality of nosebleed, and the previous management of epistaxis; packing, cautery, arterial ligation, etc.
3. Other nasal and ENT symptoms
4. General symptoms and Systemic diseases (hypertension, chronic liver disease, leukemia, renal disease, and history of bleeding

from other sites or orifices in the body.

5. History of medications e.g. anticoagulant and antiplatelet drugs.
6. History of nasal surgery.
7. Menstrual history {in females}.
8. Family history of any bleeding diathesis.

Methods:

Control of epistaxis in our study was done according to the following management plan:

A. First-aid measures:

1. Instruction to the patient to gently blow the nose to remove blood clots.
2. A cannula was inserted for venous access.
3. Fluid resuscitation: initiated if volume depletion is suspected. In cases of hemorrhagic shock, the bleeding stopped immediately using a balloon catheter or urgent surgery.

The use of nasal vasoconstrictors before commencing HWI was avoided.

B. Full examination:

- According to general examination: initial physical evaluation included ensuring patency of the airway, appropriate breathing, and circulation (ABCs), obtaining vital signs, and checking mental status. Check for signs of shock, and signs of coagulopathy.
- Nasal examination: it is performed in a well-lighted room with the patient seated and using protective equipment for both patient and physicians. The patient expectorated blood/clots as tolerated to better visualize the nasal cavity, and maintain the sniffing position. A nasal speculum was used initially for optimal visualization, and suction was used to remove blood and clots. Relevant anatomic locations such as Kiesselbach's plexus, septum, and turbinates were inspected. 0° endoscopy (Karl Storz RG, Germany) was utilized if the source of bleeding was not clear on anterior rhinoscopy. In cases with a visible source of bleeding, cauterization by any means should be attempted before HWI.

C. Hot water irrigation:

- This procedure was started with the application of topical anesthesia to the relevant nasal cavity was applied using cotton nasal packing impregnated with 10 % lidocaine.
- A Foley's rubber balloon catheter (ULTRA, Egypt), size French 10 in young patients and size 14 French in adult patients, was inserted into the affected nasal cavity. The balloon was inflated within the nasopharynx using saline, and then gently pulled back until the choana was blocked off and supported by an umbilical clamp in front of the columella, to avoid aspiration.
- Then a suction catheter plain (ULTRA MED, Egypt), French 10 in young patients and French 14 in adults, with proximal irrigation opening was applied above Foley's catheter in the affected nasal cavity, and it was supported in place by the help of nurses. The proximal irrigation opening enabled the free flow of irrigation water in the region of the sphenopalatine foramen. The affected nasal cavity was then continuously irrigated using a Mutifunctional Bulb Irrigation syringe 50 Cc.(ULTRA, Egypt) for 3 minutes with 500 ml of water heated to 50°C (it was measured by a digital thermometer).
- The patient was then seated upright with his face pointed downward over a kidney-shaped pool, to allow the outflow of water

from the affected nasal cavity into the pool.

- After controlling epistaxis, the plain suction catheter was removed and the foley's catheter was left in place for 5 minutes.
- Reevaluation was done after 5 minutes, if epistaxis was controlled, we removed the foley catheter gently, and patients were discharged home after 2 hours of observation.
- In case of recurrent epistaxis occurred we didn't remove the foley catheter and reapplied the plain suction catheter for the second trial of irrigation. After two failed hot water irrigation attempts, conventional nasal packing.

Statistical analysis:

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York).

Quantitative data were expressed as mean ± standard deviation (SD) and compared with the Student t-test.

Nominal data were given as a number (n) and percentage (%). Chi2 test was implemented on such data. The level of confidence was kept at 95% and hence, the P-value was considered significant if < 0.05.

Results

Forty-five patients were included in this study. Their ages ranged from ten to 84 years with the mean age of enrolled patients was 41.08 SD ± 21.12 years, and a male predominance of 71.1% (32 patients). Twenty-seven (60%) patients were smokers

The mean time of the whole procedure was 19.11 ± 8.61 (minute) with a range between 10 and 35 minutes. Pain according to the visual analog scale (VAS) was subjectively reported by the patients as hurting a little bit, hurting a little more, and hurts even more in 31 (68.9%), 13 (28.9%) and, one (2.2%) patients, respectively. According to VAS (which measures pain from no hurts with a score of zero up to hurts worst with a score of ten) means pain intensity was 2.7.

Regards the efficacy of irrigation, it was found that 39 (86.7%) patients had successful irrigation with controlled epistaxis. 31 (68.9%) of these patients had only one session while irrigation was repeated twice in eight (17.8%). Trauma during irrigation (in the form of minimal injury of the nasal vestibule or laceration of the nasal mucosa during insertion of any type of both catheters) was reported in four (8.9%) patients. While two (4.4%) had complications following the procedure in the form of minimal adhesions (discovered by 0oendoscopic examination in the follow up of the patients within the first week at the site of the irrigation end of the plain suction catheter and nasal septum, released, and local lubricant was applied, then in the follow up after two weeks, it was disappeared).

The HWI was failed in six (13.3%) patients. The epistaxis was controlled by anterior nasal packing using Merocel in four patients of them, and the remaining two patients by a posterior nasal pack using the Foley's catheter (Table 1).

Among successful cases N=39, hospital stay was 24 patients (53.3%) of the patients didn't require hospital admission. Four (8.9%) patients suffered from the recurrence of epistaxis. Two of them had the recurrence after a day and the remaining two patients had the recurrence after a longer duration (more than 2 days). We used other options for the management of the recurrent epistaxis in the form of the anterior nasal packing (merocel pack) for two patients, posterior nasal packing for one patient, and surgical intervention for the last patient (Table 2).

Table 1: Outcome of irrigation among studied patients

	N= 45
Duration of irrigation (minute) Range	19.11 (± 8.61) 10-35 minutes
Frequency of irrigation	
Once	31 (68.9%)
Twice	8 (17.8%)
Pain	
Hurts little bit	31 (68.9%)
Hurts little more	13 (28.9%)
Hurts even more	1 (2.2%)
Mean of pain intensity	2.7
Trauma during irrigation	4 (8.9%)
Complications (adhesions)	2 (4.4%)
Efficacy of irrigation	
Successful	39 (86.7%)
Failed	6 (13.3%)

Data expressed as frequency (percentage), mean (SD), range

Table 2: Hospital stay and recurrent epistaxis among the succeeded cases

	N= 39
Hospital stay	
No inward	24 (53.3%)
admission	10 (22.2%)
One day	3 (6.7%)
Two days	2 (4.4%)
More than 2 days	1.13 (±0.344)
Mean	
Recurrence	
None	35 (77.8%)
Once	4 (8.9%)

Data expressed as frequency (%)

Based on the outcome of the irrigation procedure was found that both groups (successful and failed) had insignificant differences as regard baseline characteristics and comorbidities (p> 0.05) Significant differences were noticed as regard drug therapy (p 0.04). It was found that the majority of those with successful irrigation procedures didn't receive any medications (Table 3).

Based on the outcome of the irrigation procedure was found that both groups (successful and failed) had significant differences in regards platelets count (p< 0.001). Other data showed no significant differences (p> 0.05) (Table 4).

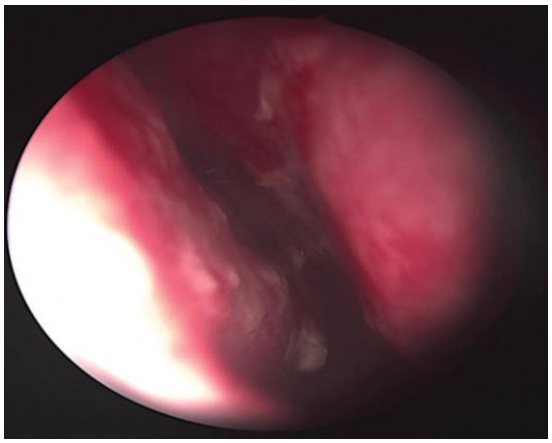

Figure 1: 0 endoscopic nasal examination after two hours of HWI.

Table 3: Characteristics of patients based on the outcome of irrigation

	Irrigation		***P* value**
	Successful (n= 39)	Failed (n= 6)	
Age (years)	40.15 (± 20.68)	47.17 (± 24.96)	0.45
Age class			0.37
< 20 years	8 (20.5%)	2 (33.3%)	
21-40 years	14 (35.9%)	0	
41-60 years	12 (30.8%)	2 (33.3%)	
> 61 years	5 (12.8%)	2 (33.3%)	
Sex			0.22
Male	29 (74.4%)	3 (50%)	
Female	10 (25.6%)	3 (50%)	
Smoking	24 (61.5%)	3 (50%)	0.59
Addiction	0	1 (2.6%)	0.11
Comorbidities			**0.06**
None	22 (56.4%)	1 (16.7%)	
Cardiac disease	9 (23.1%)	0	
Hypertension	4 (10.3%)	0	
Liver diseases	2 (5.1%)	0	
Thrombocytopenia	1 (2.6%)	1 (16.7%)	
CKD	0	1 (16.7%)	
Malignant diseases	1 (2.6%)	3 (50%)	
Drug therapy			**0.04**
None	23 (59%)	1 (16.7%)	
Anti-platelets	8 (20.5 %)	1 (16.7%)	
Anticoagulants	7 (17.9%)	0	
Chemotherapy	1 (2.6%)	3 (50%)	
Cryoprecipitate	0	1 (16.7%)	

Data expressed as frequency (percentage), and mean (SD). P-value was significant if < 0.05. CKD: chronic kidney disease.

Table 4: Severity and clinical, and laboratory data based on the outcome of irrigation

	Irrigation		***P*-value**
	Successful (n= 39)	Failed (n= 6)	
Affected side			0.34
Right side	18 (46.2%)	4 (66.7%)	
Left side	17 (43.6 %)	1 (16.7%)	
Bilateral	4 (10.3 %)	1 (16.7%)	
Severity of epistaxis			0.82
Moderate	8 (20.5%)	1 (16.7%)	
Severe	31 (79.5%)	5 (83.3%)	
Blood pressure			0.50
Normal pressure	14 (35.9%)	3 (50%)	
High HTN	10 (25.6%)	2 (33.3%)	
Mild HTN	12 (30.8%)	1 (16.7%)	
Moderate HTN	3 (7.7%)	0	
Pulse (beat/minute)	66 (±7.3)	62.5 (±4.1)	0.26
Hemoglobin (mg/dl)	10.31 (± 1.82)	10.85 (± 2.30)	0.51
PC (%)	78.23 (± 20.32)	75.42 (± 11.32)	0.74
Platelets (10^3/ul)	248.71 (± 108.17)	73 (± 84.81)	**< 0.001**

Data expressed as frequency (percentage), mean (SD), range. P value was significant if < 0.05. HTN: hypertension; PC: prothrombin concentration

Discussion :

According to the cause and source of bleeding, epistaxis can be an easily treatable clinical issue or may deteriorate into a painful, prolonged, and even life-threatening condition. Although posterior epistaxis is less common than anterior epistaxis, it mostly needs the emergency department for controlling it. Most of these patients are controlled by posterior nasal packing while others are controlled by using Foley's catheter. These patients had to be admitted and a lot of complications had to be controlled. Besides pain, there can be some serious complications like sinusitis, nasal septal pressure necrosis, abscesses formation, neurogenic syncope, toxic shock syndrome, etc. Gudziol, V. et al. 2005 found that the success rate of posterior nasal packing varies from 55%-70% [7, 8], and Klotz, D.A., et al. 2002 found that the success rate of surgical interventions vary from 70-90%.[9]

In our study, we used one of the non-invasive methods for controlling posterior epistaxis which is HWI. we found that the mean (±SD) age of the studied patients was 41.08 (± 21.12) years with a range between 10 and 84 years, these results agree with some studies, **Tobari et al. 2018**[10], and Wei, W., et al. 2018[11] .We also found that males were affected more than females 32 (71.1%):13 (28.9%) respectively. This agrees with Parajuli**, 2015** [12], as they found that males: females were (61%): (39%). They explained the reason for this might be the more involvement of males in outdoor activities and the more street violence among teenager-males.

Côrte et al. 2018 [13] explained this phenomenon as it has been attributed to the protective effect of estrogen in women, either by promoting a healthy nasal mucosa or by preventing vascular disease in general. 27 (60%) were smoking and among these patients, 3 (50%) of failed patients were smoking. Some studies linked smoking with a higher incidence of epistaxis as **Huange et al. 2002** [14]. Others failed to assure this link as **Sim et al.2002**[15].While a third group established a link between epistaxis and smoking-cessation medicine in Harrison-**Wooolrych et al. 2012** [16].

The exact mechanism that smoking can affect epistaxis incidence is not known, but the fact that the incidence of smoking in our patients was more than 50 % is really scary to anyone who does care about the health of people in this country. The risk is doubled when we get a look at the age of these patients. Other comorbidities also affect the posterior epistaxis and the efficacy of the procedure as we found 20% were cardiac, 8.9% were hypertensive and 8.9% had malignant diseases other than nasal causes, and 3 (50%) of failed patients had malignancy.

Klossek et al. 2005[17] suggested that prolonged hypertension might contribute to a high risk of epistaxis, probably due to vasculopathic effects, including degenerative fibrous changes in the tunica media, luminal narrowing, alteration of normal endothelial function, and divert hemostasis. [18-19]

According to the drug therapy affecting coagulation profile, we found that nine (20%) patients received anti-platelets agents while seven (15.6%) patients were on anticoagulant therapy these results close with **Côrte et al. 2018** [13] that found (33%) of patients were on antiplatelet and (17%) on anticoagulants.

However, **Schlegel-Wagner 2006** [20] noticed that 47 of the patients (56%) were receiving medication with antiplatelet agents or anticoagulants. We also found 4 (8.9%) of patients were on chemotherapy, this may be according to

inhibition of platelet aggregation and platelet factor-3 even in 8thday of chemotherapy which cause various hemorrhagic manifestation as mucositis and epistaxis. These changes precede the onset of life-threatening complication of thrombocytopenia. [21]

The severity of epistaxis may be an important factor affecting the failure rate of the procedure as we found 36 (80%) had severe epistaxis and the procedure failed in 5 (83.3%). The mean duration (±SD) of the whole procedure was 19.11 (± 8.61), this is close to results seen in **Stangurup 1999** [22], that found mean-time of obtaining hemostasis was five minutes (range, between 1-35 minutes), but this against other studies, in **Srinagar, 2012** [23], that found 22 (73.3%) out of the successfully treated patients, bleeding was controlled during the procedure in 13 (59%) patients, and during the first five minutes in seven (31.8%) patients. While in the rest of the two (9%) patients bleeding was controlled in the first 10 minutes of the procedure, the time difference between the results may be due to time taken in regulating the temperature of water coordination between patients and doctors.

The irrigation was repeated in 17.8 %. 68.9 % had hurt a little bit according to VAS. This supports that the procedure is less painful than other options in controlling posterior epistaxis. The HWI was successful in 86.7 % of patients with posterior epistaxis, this agrees with **Schlegel-Wagner 2006** [20], in which the bleeding was successfully and permanently stopped in 84 of 103 patients (82%). 4.4% of them had complications in the form of minimal adhesions which resolved within 2 weeks, these results agree with **Srinagar, 2012** [23], that found six patients (20%) only had adhesions and zero patients had crusts. The recurrence of epistaxis occurred in 8.9 % and other options were used to control the recurrence in the form of anterior nasal packs in two, posterior nasal packs in one patient, and surgical intervention in the last one. 53.3 % of successful cases did not need hospital admission and 22.2 % had admitted for one day only. This agrees with **Srinagar, 2012** [23], that found the mean of hospital stay was 0.9 days.

In **Schlegel-Wagner 2006** [20], All successfully treated patients were observed for 2 hours and discharged afterward.

The procedure failed in 13.3% of patients. We used anterior nasal packs in the form of merocel in two patients, and the remaining two had the posterior nasal packs in the form of Foley catheters.

The limitation of the study: this method needed good monitoring of the temperature of the water, as temperatures below 48 degrees failed to make mucosal edema and the subsequent control of bleeding, while temperatures above 52 degrees caused local tissue necrosis. Another limitation of our study was that all of our patients were in stable condition. In case of hemorrhagic shock, the bleeding must be immediately stopped using a balloon catheter as an emergency measure or through urgent surgery, so our study wasn't used. It also was not effective in cases of post-operative bleeding after endo-nasal surgery of the turbinates or paranasal sinuses, as there is insufficient intact mucosa to induce local edema.

Conclusion:

To be concluded hot water irrigation is considered a safe, efficient, and cost-effective treatment method for posterior epistaxis. This method has the additional benefits of less pain, less need for surgical intervention, and less duration of hospitalization. Hot water irrigation

should be considered the first line of treatment for posterior epistaxis, and medical trainees should be repeatedly instructed in its use in outpatient and emergency settings.

Conflict of interest: There is no conflict of interest.

Reference:

1. Tikka, T., The Aetiology and Management of Epistaxis. Otolaryngology Online Journal, 2016. 6(2).:p.487-493.
2. El-Guindy, A., Endoscopic Transseptal Sphenopalatine Artery Ligation for Intractable Posterior Epistaxis. Annals of Otology, Rhinology & Laryngology, 1998. 107(12): p. 1033-1037.
3. Hara, H.J., Severe epistaxis. Arch Otolaryngol, 1962. 75: p. 258-69.
4. Ceylan, S.M., et al., Hot nasal packing with hot saline irrigation for hemostasis after adenoidectomy: A prospective randomized controlled study. International Journal of Pediatric Otorhinolaryngology, 2020. 130: p. 109792.
5. Özmen, S. and Ö.A. Özmen, Hot saline irrigation for control of intraoperative bleeding in adenoidectomy: A randomized controlled trial. Otolaryngology–Head and Neck Surgery, 2010. 142(6): p. 893-897.
6. Nordström, A., et al., Hot saline irrigation in comparison to nasal packing after sinus surgery. Laryngoscope Investigative Otolaryngology, 2014.4(11):p.877-884.
7. Gudziol, V., T. Mewes, and W.J. Mann, Rapid Rhino: A new pneumatic nasal tamponade for posterior epistaxis. Otolaryngology–Head and Neck Surgery, 2005. 132(1): p. 152-155.
8. Shaw, C.B., M.K. Wax, and S.J. Wetmore, Epistaxis: a comparison of treatment. Otolaryngol Head Neck Surg, 1993. 109(1): p. 60-5.
9. Klotz, D.A., et al., Surgical management of posterior epistaxis: a changing paradigm. Laryngoscope, 2002. 112(9): p. 1577-82.
10. Torabi, M., A. Esfahani, and M. Baneshi, A new method of epistaxis management using nasal gel: a single centre randomized clinical trial. Asian J Pharm Clin Res, 2018. 11(3): p. 104-8.
11. Wei, W., et al., A blind area of origins of epistaxis: technical or cognitive? European Archives of Oto-Rhino-Laryngology, 2018. 275(6): p. 1501-1505.
12. Parajuli, R., Evaluation of etiology and treatment methods for epistaxis: a review at a tertiary care hospital in central Nepal. International journal of otolaryngology, 2015. 2015 (4): p.1-5.
13. Côrte, F.C., et al., Risk factors for the occurrence of epistaxis: Prospective study. Auris Nasus Larynx, 2018. 45(3): p. 471-475.
14. Huang, C.-L. and C.-H. Shu, Epistaxis: a review of hospitalized patients. CHINESE MEDICAL JOURNAL-TAIPEI-, 2002. 65(2): p. 74-78.
15. Sim, W., et al., Risk factors for epistaxis during nasotracheal intubation. Anaesthesia and intensive care, 2002. 30(4): p. 449-452.
16. Harrison-Woolrych, M., et al., Epistaxis and other haemorrhagic events associated with the smoking cessation medicine varenicline: a case series from two national pharmacovigilance centres. European journal of clinical

pharmacology, 2012. 68(7): p. 1065-1072.
17. Klossek, J.-M., et al., Epistaxis and its management: an observational pilot study carried out in 23 hospital centres in France. Rhinology, 2006. 44(2): p. 151-155.
18. Knopfholz, J., et al., Association between epistaxis and hypertension: a one year follow-up after an index episode of nose bleeding in hypertensive patients. International journal of cardiology, 2009. 134(3): p. e107-e109.
19. Neto, J.F.L., et al., Is epistaxis evidence of end- organ damage in patients with hypertension? The Laryngoscope, 1999. 109(7): p. 1111-1115.
20. Schlegel-Wagner, C., U. Siekmann, and T. Linder, Non-invasive treatment of intractable posterior epistaxis with hot-water irrigation. Rhinology, 2006. 44(1): p. 90-93.
21. Kumar, A., P. Chaturvedi, and Y.N. Gupta, Combination chemotherapy for breast carcinoma using a combination of cyclophosphamide, methotrexate and 5- fluorouracil (CMF) causes a platelet aggregation defect. International journal of cancer, 1996. 66(2): p. 159-161.
22. Stangerup, S.E., et al., New modification of hot-water irrigation in the treatment of posterior epistaxis. Archives of Otolaryngology-Head & Neck Surgery, 1999. 125(6): p. 686-690.
23. Sheikh, I., et al., Hot Water Irrigation Versus Conventional Nasal Packing in Epistaxis. EXECUTIVE EDITOR, 2015. 6(4): p. 280.