

26 **Phosphodiesterase-5 inhibitor use; a probably under-reported cause of profuse**
27 **nasal bleeding**

28

29 **Abstract**

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31 **Background:** Phosphodiesterase (PDE)-5 inhibitors enhance penile erection and have
32 gained popularity not only for erectile dysfunction, but also in more recreational
33 settings. Nevertheless, adverse effects have been associated with their use, with nasal
34 bleeding among them. That is because PDE-5 inhibitor action is materialized through
35 the inhibition of the cyclic guanosine monophosphate (cGMP) enzyme. cGMP is
36 present at several sites of the human body in addition to the corpus cavernosum,
37 hence the adverse effects associated with its non-selective inhibition.

38 **Case-series:** Two male patients with severe epistaxis, who were taking PDE-5
39 inhibitors for erectile dysfunction, or recreational purposes, are discussed. Surgical
40 intervention was required in both patients to control the nasal hemorrhage.

41 **Why should an emergency physician be aware of this?** Nasal bleeding in patients
42 receiving PDE-5 inhibitors might represent an under-reported cause of epistaxis,
43 because of the unwillingness of most male patients to discuss issues pertaining their
44 use without hesitation. Yet such episodes are rather profuse. This is especially true
45 when the venous engorgement caused in the nasal mucosa by the smooth-muscle
46 relaxant effect of PDE-5 inhibitors is combined with a second event (i.e. specific
47 drugs, blood dyscrasia etc.). Emergency physicians should be also aware of the
48 possibility that in the next years the number of such cases might increase, due to the
49 increased use of these medications for erectile dysfunction, or recreational purposes.

50 It is likely that these patients could not be managed conservatively, but would rather
51 require referral to an ENT Department for a surgical intervention.

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53 **Keywords:** epistaxis, nasal bleeding, phosphodiesterase-5 inhibitors

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75 **Introduction**

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77 Phosphodiesterase (PDE)-5 inhibitors (i.e. Viagra®) enhance penile erection by
78 inducing smooth muscle relaxation in the corpus cavernosum. They have, hence,
79 gained popularity not only for erectile dysfunction, but also in more recreational
80 settings.

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82 However, the enzyme inhibited by the drugs of this category, cyclic guanosine
83 monophosphate (cGMP), is present at several sites of the human body in addition to
84 the corpus cavernosum. Therefore, adverse effects such as intracranial hemorrhage
85 variceal and hemorrhoidal bleeding, vocal fold hemorrhage and epistaxis have been
86 previously reported to follow its non-selective inhibition (1-6).

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88 The aim of the present case-series is to discuss the occurrence of nasal bleeding in
89 patients receiving PDE-5 inhibitors with emphasis in its management, since such
90 episodes might represent an under-reported cause of epistaxis, because of the
91 unwillingness of most male patients to openly discuss issues relating to PDE-5
92 inhibitor use.

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100 **Case series**

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102 *Case 1*

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104 A 51-year old man was admitted in our Department, due to tenacious epistaxis from
105 his left nostril of 10 days duration. On examination, there was severe septal deviation
106 to the left. No specific bleeding site was identified. His past medical history included
107 blood hypertension under amlodipine, and sildenafil overuse for recreational
108 purposes. Bleeding control required anterior and posterior packing, however an
109 attempt to remove the nasal packs resulted in bleeding recurrence.

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111 The patient underwent a septoplasty and cautery to the inferior turbinates under
112 general anesthesia. Anterior packing was placed postoperatively for two days. He was
113 also given 500 mg of tranexamic acid per os for three days after the operation, due to
114 mild bleeding leakage around the nasal packs. The patient was discharged four days
115 after the septoplasty, and a year after his operation he has not experienced any further
116 bleeding.

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119 *Case 2*

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121 A 67-year old man was again admitted in our Department, due to persistent epistaxis
122 from his left nostril of 10 days duration. Over the aforementioned time period the
123 patient underwent three nasal cauterizations under local anesthesia and endoscopic
124 guidance in another hospital. On examination, the patient had a 4-cm nasal pack

125 lodged between the middle turbinate and the nasal septum, but reported intermittent
126 posterior bleeding every four hours despite its presence and the previous
127 cauterizations. Upon pack removal, the patient started to experience profuse nasal
128 bleeding, which was only partially controlled by antero-posterior nasal packing. His
129 past medical history included irradiation for prostate cancer 8 years before, with
130 occasional use of tadalafil for erectile dysfunction. He had also been recently
131 diagnosed with leukemoid reaction of his white cell lineage (WBC~30.000), pending
132 bone marrow biopsy to determine the exact nature of the problem.

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134 The patient underwent endoscopic ligation of the left sphenopalatine artery under
135 general anesthesia, following the endoscopic discovery of a bleeding site between the
136 attachment of the left middle turbinate and the lateral nasal wall (Figures 1a & 1b, 2a
137 & 2b, 3). The patient was not packed postoperatively, and was discharged the next
138 day. Six months after his operation, he remains free of bleeding recurrence.

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150 **Discussion**

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152 Epistaxis is thought to affect 10–12% of the population, among which 10% require
153 medical attention (7). Epistaxis can be triggered by local (i.e. trauma, mucosal
154 inflammation, septal deviation, tumors), systemic (i.e. blood dyscrasias,
155 arteriosclerosis, hereditary hemorrhagic telangiectasia), and idiopathic causes.
156 Although most cases are self-limited, some do not resolve without intervention.

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158 PDE-5 inhibitors, on the other hand, have gained popularity due to their erectile
159 properties, which are materialized through the inhibition of the cGMP enzyme.
160 However, in addition to the presence of the inhibited enzyme at several sites of the
161 human body, in-vitro research suggests that sildenafil may inhibit collagen-induced
162 platelet aggregation (8). Furthermore, anti-hypertensive drugs metabolized in
163 cytochrome p450 could affect the pharmacokinetics of PDE-5 inhibitors, which share
164 the same metabolic pathway, rendering hemorrhage more likely (9).

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166 The nasal turbinates also demonstrate erectile properties (10), and nasal stuffiness
167 during sexual activity is an acknowledged phenomenon (11). Although nasal bleeding
168 in patients receiving PDE-5 inhibitors has been reported in the past (5, 6, 9, 12-14), it
169 might represent an under-reported cause of epistaxis, because of the unwillingness of
170 most male patients to discuss issues pertaining their use without hesitation.

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172 The patients in our series demonstrated PDE-5 inhibitor-induced severe epistaxis for
173 different reasons. The first presumably because of the combined amlodipine-sildenafil
174 intake, and the second due to the additionally impaired coagulation properties of his

175 platelets, resulting from his underlying disease (which was demonstrated two months
176 postoperatively with platelet function testing).

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178 Although packing has historically been the workhorse of nasal bleeding management,
179 it seems that such episodes in patients receiving PDE-5 inhibitors are rather profuse,
180 and surgical management is very often required. This is especially true when the
181 venous engorgement caused in the nasal mucosa by the smooth-muscle relaxant effect
182 of PDE-5 inhibitors is combined with a second event (i.e. specific drugs, blood
183 dyscrasia etc.). Nevertheless, the number of patients who experience this complication
184 is probably limited, taking into account that the use of the agent is quite widespread.
185 Yet, it is likely that these patients would require referral to an ENT Department for
186 surgical control of their hemorrhage. Surgical interventions in these patients not only
187 control the nasal hemorrhage, but may also be associated with improved cost-
188 effectiveness and patient comfort.

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190 **Why should an emergency physician be aware of this?**

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192 Nasal bleeding in patients receiving PDE-5 inhibitors might represent an under-
193 reported cause of epistaxis, because of the unwillingness of most male patients to
194 openly discuss issues relating to erectile dysfunction. Emergency physicians should
195 be aware of the possibility that in the next years the number of such cases might
196 increase due to the increased use of these medications. Episodes of nasal bleeding in
197 patients receiving PDE-5 inhibitors are rather profuse, and surgical management is
198 very often required. It is hence likely that these patients would require referral to an
199 ENT Department.

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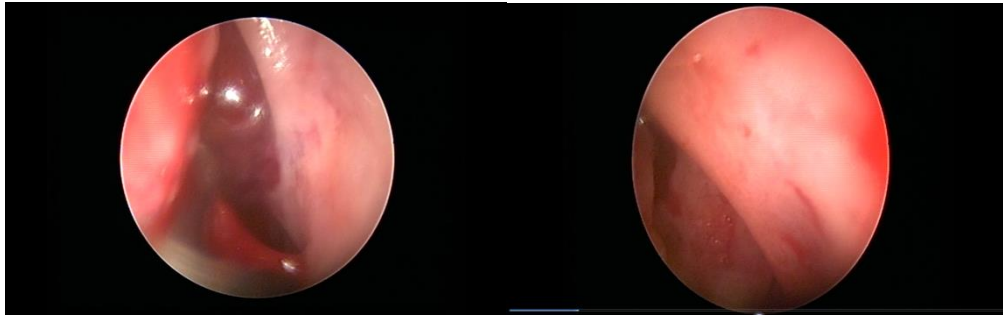
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Figures

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Figure 1a

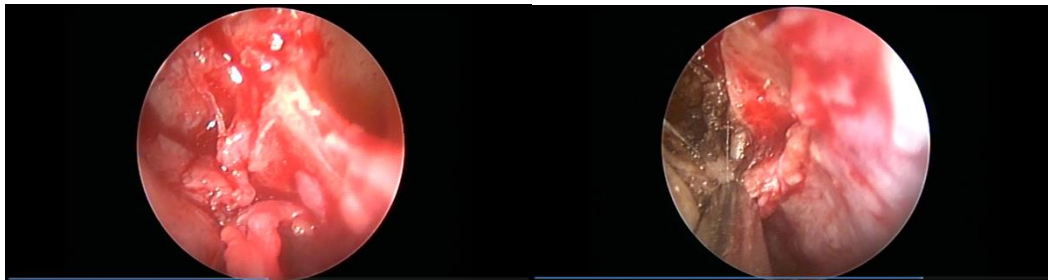
Figure 1b

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Patient N° 2. Bleeding in the left middle meatus (left image) and identification of bleeding site underneath the left middle turbinate (right image)

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Figure 2a

Figure 2b

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Patient N° 2. Main trunk of the left sphenopalatine artery (left image), and descending branch (right image)

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Figure 3

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Patient N° 2. Left sphenopalatine artery completely diathermized

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