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Preoperative hypertension increases intraoperative bleeding in patients undergoing Mohs micrographic surgery

To the Editor: Complications after Mohs micrographic surgery (MMS) often involve difficulties with hemostasis.[1,2] An association between systolic blood pressure (BP) and bleeding complications has been reported by others.[3-5] We investigated the role of BP in bleeding outcomes in patients who are undergoing MMS.

BP measurements were recorded in 209 patients (120 men and 89 women who were a median of 73 years of age [interquartile range {IQR} 63-79 years]) who were undergoing MMS for head and neck cancer using a Welch Allyn sphygmomanometer without the surgeon being aware of the result until the procedure was complete.

BP was measured before, during, and after the procedure in 92 patients. In the subsequent 117 patients, only preoperative BP measurements were recorded. The surgeon subjectively graded intraoperative bleeding as mild (no abnormal bleeding), moderate (bleeding increased but controllable), or severe (bleeding very difficult to control) before the BP result was seen. A postoperative review was conducted after 7 days or sooner if required. Hypertension was defined as systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg. Twenty-one patients (10%) were taking an anticoagulant; 47 (22%) patients were taking a platelet inhibitor. Two patients were taking both aspirin and an anticoagulant.

Serial measurements showed that BP was highest preoperatively and fell slightly during the procedure. In all 209 patients, preoperative BP ranged from 104/54 mm Hg to 191/112 mm Hg (mean 145/81 mm Hg). Intraoperative bleeding (Fig 1) was graded as mild in

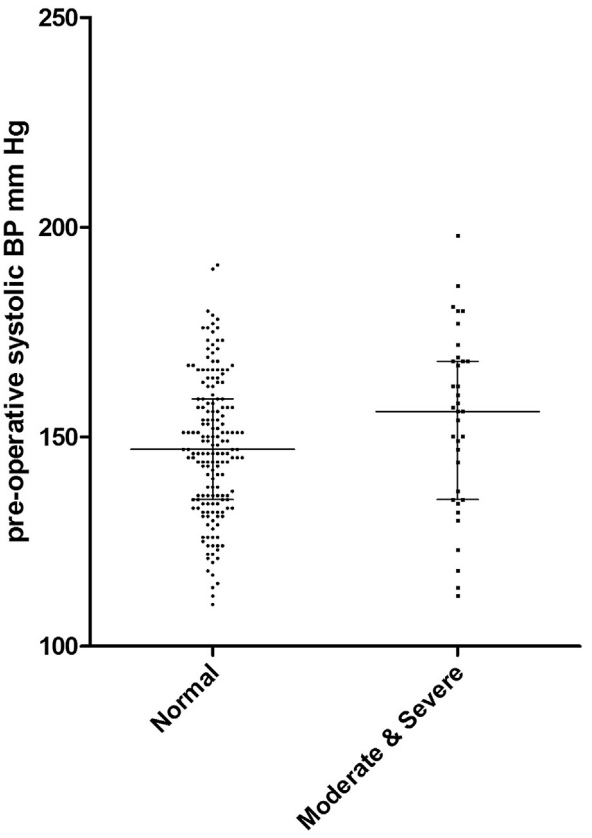

Fig 1. Preoperative systolic blood pressure (BP) and intraoperative bleeding grade. Individual data points shown with median plus or minus interquartile range. The Mann-Whitney U test shows that the 172 patients with normal bleeding (solid diamonds) had a significantly ($P < .05$) lower systolic BP (147 [135-159] mm Hg) than the 35 patients with moderate and severe intraoperative bleeding (solid squares; 156 [135-168] mm Hg).

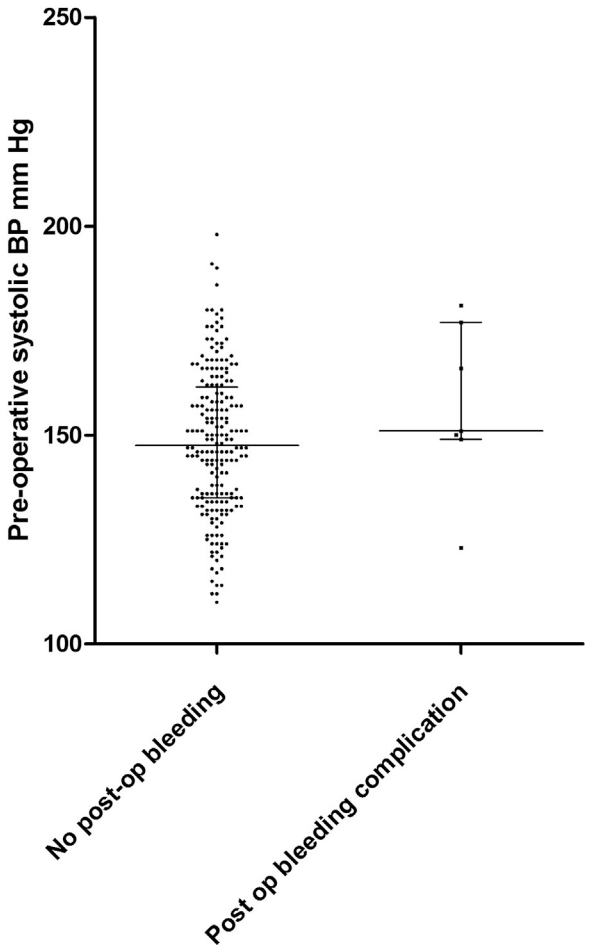

Fig 2. Preoperative systolic blood pressure (BP) and postoperative bleeding complications. Individual data points with median plus or minus interquartile range. The Mann-Whitney U test shows that the systolic BP of the 200 patients (solid circles) with no postoperative bleeding complications (148 [135-162] mm Hg) was not significantly different from the 7 patients with postoperative bleeding complications (solid squares; 151 [149-177] mm Hg).

172 (82%), moderate in 33 (16%), and severe in 2 (1%) patients; intraoperative bleeding was not documented in 2 (1%) patients.

Postoperative bleeding complications occurred in 7 (3%) of 209 patients; 5 had been graded as moderate to severe intraoperative bleeding and 2 as normal bleeding. In 5 patients, postoperative bleeding settled after firm pressure and a dressing change, 1 patient required further diathermy, and 1 patient had to be admitted with persistent bleeding (Fig 2).

A comparison of groups was made using the Mann-Whitney U test. The systolic BP of the 33 moderate plus 2 severe intraoperative bleeding graded patients (median 156 mm Hg [IQR 135-168 mm Hg]) was significantly higher ($P < .05$) than the BP of the 172 patients graded as having mild bleeding (median 147 mm Hg [IQR 135-159 mm Hg]; Fig 1). There was no difference in diastolic BP.

Comparison of systolic BP of the 200 patients with no postoperative bleeding complications (median 148 mm Hg [IQR 135-162 mm Hg]) with the 7 who experienced postoperative bleeding complications (median 151 mm Hg [IQR 149-177 mm Hg]; Fig 2) showed no significant difference ($P < .05$).

Six of 7 patients with postoperative bleeding problems were taking either clopidogrel (n = 4) or warfarin (n = 2).

Using a subjective measure, we have shown that preoperative systolic BP is significantly higher in patients who are more likely to experience increased bleeding during surgery. It is interesting to speculate if there are other consequences of increased BP, such as more bruising or postoperative pain, and whether preoperative anxiolytics, music, et cetera might reduce this effect. We did not show that this leads to a significantly greater number of postoperative bleeding complications. The risk of intraoperative bleeding detected does not pose a significant risk to patients beyond a slight increase in operative time and should not prevent or delay surgery. The effect is minor compared with the postoperative bleeding risks associated with anticoagulant and antiplatelet therapies.

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Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study

To the Editor: Case reports[1] and the high tumor mutational burden[2] of basal cell carcinomas (BCCs) compared with other tumor types suggest that programmed death-ligand 1 (PD-L1) inhibitors may be active against advanced BCCs. Many advanced BCCs are refractory to[3] or are recurrent[4] after hedgehog pathway inhibitors, and therefore PD-L1 inhibitors could be a useful therapeutic option. We present a proof-of-principle, nonrandomized, open-label study of pembrolizumab (200 mg intravenously every 3 weeks), with or without vismodegib (150 mg orally daily), for eligible subjects with advanced BCCs. The primary outcome was the overall response rate (ORR) for all evaluable subjects at 18 weeks.

Sixteen participants, 9 receiving pembrolizumab monotherapy and 7 receiving pembrolizumab plus vismodegib, were evaluable by the revised Response Evaluation Criteria In Solid Tumors[5] (version 1.1) at data cutoff. The ORR for all evaluable subjects was 38% (6/16 patients; 95% confidence interval 15-65%; $P = .003$) at 18 weeks (Table I, Fig 1). The ORR at 18 weeks for pembrolizumab monotherapy group was 44% (4/9 patients; 95% confidence interval 14-79%; $P = .008$), and for the dual therapy group was 29% (2/7 patients; 95% confidence interval 4-71%; $P = .15$).

The median time to response for all responders ($n = 6$) was 10.4 weeks (range 8.4-17.4 weeks). The median duration of response for all responders ($n = 6$) was 67.3 weeks (range 28.0-82.0 weeks; Table I).

One-year progression-free survival probability was 70%, and the 1-year overall survival probability was 94% for all evaluable subjects ($n = 16$; Table I).

Before pembrolizumab, 29% (2/7 patients) expressed PD-L1 at ≥1% of tumor cells. There was no significant correlation between prepembrolizumab PD-L1 expression and best percentage change in BCC diameter.

There were no life-threatening adverse events (AEs) or deaths during the study. Three severe (grade 3) AEs occurred out of 98 AEs from 16 participants. Only 1 of the severe AEs, hyponatremia, was attributed to pembrolizumab. There were 23 immune-related AEs, with dermatitis and fatigue as the most common (all grade 1 or 2), and only 1 severe immune-related AE (the aforementioned hyponatremia).

As a proof-of-principle study, we conclude that pembrolizumab is active against BCCs. Although the 2 groups were not directly compared, the response rate of the pembrolizumab plus vismodegib group was not superior to the monotherapy group. The lack of life-threatening AEs or death suggests that pembrolizumab has a reasonable safety profile in patients with BCC.

This study is limited by its sample size, because advanced BCCs are an uncommon disease. Nevertheless, the efficacy and safety data presented here could be used in future meta-analyses and compared with forthcoming multi-institutional studies on PD-L1 inhibitors against advanced BCCs.

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This study is subject to Stanford Human Subjects Approval Protocol 34925 and is listed at clinicaltrials.gov (NCT02690948).

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