Opioid versus Benzodiazepine-based Sedation for Mechanically Ventilated Patients in the Internal Medicine Ward

Natan Argaman MD[1,2], Avraham Meyer MD[1,2], Nisim Ifrach MD[1,2], and Sara Dichtwald MD[1,2]

[1]Department of Anesthesiology, Meir Medical Center, Kfar Saba, Israel
[2]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Opioid-base sedation is considered the first line choice in ventilated patients in intensive care units (ICU). Few studies have examined sedation in ventilated patients outside the ICU. A pilot program was initiated in an internal medicine ward at Meir Hospital in Kfar Saba, Israel. A new sedation protocol was implemented for opioid-based vs. benzodiazepine-based sedation in ventilated patients.

Objectives: To compare the rates and intensity of delirium between patients who received opioid-based sedation vs. benzodiazepine-based sedation. To compare parameters related to morbidity and mortality.

Methods: We conducted a retrospective before-after intervention study based on data collection. Patients who were admitted to an internal medicine ward from January 2020 to January 2021 and required sedation and ventilation were included. Demographic data, medical history data, admission data, Richmond Agitation and Sedation Scale scores, hemodynamic parameters, reports of falls and self-harm, and data regarding unplanned extubation were collected, as well as the need for additional sedative drugs.

Results: Chronic hypertension was more common in the opioid group. Delirium intensity tended to be higher in the benzodiazepine group. The number of ventilation days was significantly higher in the benzodiazepine group, as was the number of times adjuvant sedation was required.

Conclusions: Opioid-based sedation outside the ICU was associated with shorter ventilation days, tendency toward lower intensity of delirium, and reduction in requirement of adjuvant sedative drugs compared to benzodiazepine-based sedation. Further studies are required to confirm the findings.

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KEY WORDS: benzodiazepines, delirium, mechanical ventilation, opioids, sedation

Opioid-based sedation has been the gold standard in ventilated patients in intensive care units (ICU) around the world for several decades [1,2]. Its advantages, compared to benzodiazepine-based sedation, include better pain control, fewer ventilation days, and shorter admission times [1-3].

In most western European countries, as well as in the United States, almost all acutely ventilated patients are admitted to an ICU. In a few countries, including Japan and Israel, due to lack of ICU beds or to unfavorable prognosis, ventilated patients may also be hospitalized outside ICUs (i.e., in internal or surgical medicine wards) [1-3]. While sedation for ICU ventilated patients has been extensively studied, there are few studies of ventilated patients outside the ICU. Thus, while there is a consensus regarding the benefits of opiate-based sedation in ICUs, there is insufficient information regarding the preferred method of sedation outside the ICU [4-6].

For various reasons, in many of the internal medicine wards in Israel, the most common sedation for ventilated patients is still benzodiazepine-based. In the past year a new protocol was implemented for opioid-based sedation in ventilated patients in the internal medicine ward A at the Meir Medical Center in Kfar Saba.

The protocol is based on a continuous intravenous infusion of fentanyl as a first line of treatment for sedation in ventilated patients. If the level of sedation-agitation (as measured by the Richmond Agitation and Sedation Scale [RASS], [Appendix 1, online version only] did not correspond to the goal defined by the attending physician, the dose could be increased up to a maximum limit according to the protocol. After the defined maximum dose was achieved, a second protocol for sedation could be initiated, such as continuous intravenous infusion of midazolam (in addition to fentanyl) in hemodynamically stable patients or the addition of a continuous intravenous infusion of ketamine instead of midazolam in unstable

patients. In stable patients who did not reach the desired RASS level under continuous infusion of fentanyl and midazolam, it was possible to add ketamine in addition to the two previously administered drugs.

PATIENTS AND METHODS

The primary outcome was the comparison of the rates and maximal intensity of delirium between the two groups of patients (as reflected in the RASS score). The secondary outcomes were the comparison of parameters related to mortality within 28 days, the number of ventilation days, the hospital length of stay, the number of hypotension episodes (systolic blood pressure < 90 mmHg), the number of bradycardia episodes (heart rate < 40 beats per minute), the number of hypoxemia events (saturation < 90%), the rate of unplanned (self) extubation, the rates of falls/self-injury, and requirement of additional sedative drugs (such as ketamine).

STUDY DESIGN

The study is retrospective and evaluated before/after intervention, based on data collection. Information was collected from computer systems (Chameleon® systems, UK) regarding patients who were admitted to the internal medicine ward A at the Meir Medical Center in Kfar Saba from January 2020 to January 2021 (inclusive), and who required sedation and ventilation. Opioid-based sedation began in June 2020. The group of patients admitted from January 2020 until the end of May 2020 were included as the control group (before intervention) and the group of patients admitted from the beginning of June 2020 until the end of January 2021 were included in the treatment group (after intervention).

Inclusion criteria was patients aged 18–99 years of age admitted to Internal Medicine Ward A at Meir Medical Center in Kfar Saba from January 2020 to January 2021 (inclusive), who required sedation and ventilation.

Exclusion criteria were patients who were sedated and ventilated for palliative care with no plan to wean them off the ventilator and patients in whom there was a deviation from the treatment protocol.

Collected data included age, sex, hospital length of stay, 28-day mortality, past medical history, regular medications, etiology of hospital admission, RASS scores during hospitalization, blood pressure, heart rate, saturation, report of falls and self-harm, data regarding unplanned extubation, and requirement for additional sedative drugs.

RESULTS

The study included 46 patients. In the control group, 21 were treated with benzodiazepine-based sedation (midazolam) and in the intervention group 25 were treated with opioid-based sedation (fentanyl). Tables 1 and 2 show the demographic and clinical variables of the patients.

There were almost no statistically significant differences between the patient groups with regard to demographic data (age, sex), past medical history, chronic medications, admission etiology, and length of hospital stay. Only the rate of chronic hypertension was statistically significant in the opioid group (83.3%) compared to the benzodiazepine group (52.4%).

Regarding the primary outcome, to compare the incidence of delirium and its intensity (according to the number of RASS episodes above zero and the maximum RASS score) between the groups, two regression models were performed. The independent variable was group affiliation. The first model was performed to predict the number of delirium events. A regression was performed with the group affiliation. Group affiliation did not significantly predict the number of delirium events (RASS above zero). The second model was performed to predict the maximum intensity of delirium (maximal RASS score). A regression was performed with the group affiliation. Group affiliation showed marginal significance (with a *P*-value close to significance) according to which in the benzodiazepine group the intensity of delirium was higher than in the opioid group ($P = 0.06$) [Table 2]. Regarding the secondary outcomes, to examine the effect of group affiliation on morbidity and mortality parameters, chi-square and Mann-Whitney tests were performed [Table 1].

Table 3 shows that no differences were found between the groups in in-hospital variables to indicate the severity of the acute disease (requirement of tracheostomy, dialysis, and pressors) and parameters indicating an inadequate level of sedation (such as the requirement of antipsychotics, physical restraint, and self-extubation rates). There were no accidental falls in either group.

Table 4 shows that there were no differences between the groups in the sedation complication rates as reflected in the number of hypoxemia episodes, hemodynamic instability, and number of bradycardia events. However, a statistically significant difference was found in the number of ventilation days. In the benzodiazepine group it was significantly higher compared to the opioid group (7 ± 9 vs. 4.12 ± 4.78, *P*-value = 0.048). The benzodiazepine group required additional adjuvant sedative drugs compared to the opioid group (1.19 ± 1.71 vs. 0.82 ± 0.56, *P*-value < 0.001).

Table 1. Differences between the groups in categorical research variables, demographics, and medical background

Variable	Benzodiazepines (N=21)	Fentanyl (N=25)	Chi-square	Whitney (z value)	*P*-value
Sex (male), n (%)	10 (47.6)	17 (68.0)	1.95	–	0.16
Age in years, m ± SD	73.71 ± 12.50	77.56 ± 13.56	–	0.33	0.33
Body mass index, kg/m^2, m ± SD	26.75 ± 5.81	26.71 ± 6.04	–	0.97	0.97
Hypertension, n (%)	**11 (52.4)**	**20 (83.3)**	**5.00**	–	**0.02**
Diabetes mellitus, n (%)	11 (52.4)	11 (45.8)	0.19	–	0.66
Chronic obstructive pulmonary disease, n (%)	6 (28.6)	5 (20.8)	0.36	–	0.55
Ischemic heart disease, n (%)	13 (61.9)	8 (33.3)	3.11	–	0.07
Congestive heart failure, n (%)	9 (38.1)	9 (33.3)	0.11	–	0.74
Chronic renal failure, n (%)	6 (28.6)	7 (29.2)	0.01	–	0.96
Cirrhosis, n (%)	0 (0.0)	1 (4.2)	0.89	–	0.34
Peripheral vascular disease, n (%)	1 (4.8)	0.0	1.17	–	0.28
Cerebrovascular accident, n (%)	4 (19.0)	5 (20.8)	0.02	–	0.88
Dementia, n (%)	5 (23.8)	8 (33.3)	0.49	–	0.48
Drug abuse, n (%)	2 (9.5)	0.0	2.39	–	0.12
Ethanol abuse, n (%)	2 (9.5)	2 (8.3)	0.02	–	0.89
Beta blockers, n (%)	13 (61.9)	11 (45.8)	1.16	–	0.28
Calcium channel blockers, n (%)	6 (28.6)	6 (25.0)	0.07	–	0.78
Angiotensin converting enzyme inhibitors, n (%)	4 (19.0)	6 (25.0)	0.23	–	0.63
Angiotensin receptor inhibitors, n (%)	1 (4.8)	2 (8.3)	0.23	–	0.63
Antiplatelet drugs, n (%)	9 (42.9)	8 (33.3)	0.43	–	0.51
Anticoagulation drugs, n (%)	7 (33.3)	7 (29.2)	0.09	–	0.76
Diuretics, n (%)	5 (23.8)	9 (37.5)	0.97	–	0.33
Insulin, n (%)	3 (14.3)	1 (4.2)	1.41	–	0.23
Oral hypoglycemic, n (%)	4 (19.0)	3 (12.5)	0.36	–	0.54
Steroids, n (%)	1 (4.8)	1 (4.2)	0.01	–	0.92
Anticholinergic drugs, n (%)	1 (4.8)	1 (4.2)	0.01	–	0.92
Antidepressants, n (%)	7 (33.3)	5 (20.8)	0.89	–	0.34
Antipsychotics, n (%)	4 (19.0)	3 (12.5)	0.36	–	0.54
Opioids, n (%)	0 (0.0)	0 (0.0)	–	–	–
Benzodiazepines, n (%)	9 (42.9)	11 (45.8)	0.04	–	0.84
Infectious, n (%)	8 (38.1)	10 (40.0)	0.02	–	0.89
Intoxication, n (%)	0 (0.0)	0 (0.0)	–	–	–
Congestive heart failure, n (%)	1 (4.8)	0 (0.0)	1.27	–	0.27
Acute respiratory failure, n (%)	9 (42.9)	10 (40.0)	0.04	–	0.84
Neurological, n (%)	1 (4.8)	3 (12.0)	0.75	–	0.38
Other, n (%)	3 (14.3	4 (16.0)	0.03	–	0.87

Bold indicates statistical significance

DISCUSSION

In 2018, the Society of Critical Care Medicine published guidelines for providing sedation in the ICU. Two important principles were mentioned: the principle of analgesia first and reduction of the level of sedation [7,8].

The principle of analgesia first led to the use of opioid-based sedation as the first line of treatment. Morphine was more widely used in the past. Fentanyl and remifentanil are more commonly used now [9]. However, benzodiazepines are still used for sedation in ICU patients, although their unpredictable accumulation in body tissues may result in unexpected and prolonged sedation [10]. The administration of a continuous infusion of propofol has largely replaced the benzodiazepines, which are mainly used as sedation drugs as second-line treatment in addition to opioids [10].

However, in view of the hemodynamic profile of propofol, which may cause a significant decrease in blood pressure, especially among ventilated patients

who are not hemodynamically stable (trauma, sepsis, heart failure), its continuous administration outside of a well-monitored ICU setting is not considered safe.

There is a lack of information regarding sedation in patients who are ventilated outside ICUs (such as in internal medicine wards), possibly because in many parts of the world acutely ventilated patients are hospitalized in ICUs only. Since the ability to monitor patients outside the ICU is inferior, the sedative drugs chosen for these patients should not require intensive monitoring. Propofol and dexmedetomidine may cause a significant decrease in blood pressure, secondary to a decrease in peripheral resistance, cardiac output, or heart rate. Thus, neither propofol nor dexmedetomidine are suitable. Benzodiazepines, due to their preferred hemodynamic profile, are often used as the drug of choice for sedation in ventilated patients outside the ICU (mainly continuous infusion of midazolam). In dying patients or in those who require only palliative care without a plan for future weaning from mechanical ventilation, the physician may add a continuous infusion of morphine.

However, compared to opioid-based sedation, benzodiazepine-based sedation has many disadvantages, including an increase in the incidence of delirium, lack of analgesic effect, unexpected accumulation in body tissues, and unpredictable elimination time, especially in patients with renal failure. In addition, compared to opioids, the hemodynamic profile of benzodiazepines is inferior [11,12].

Therefore, opioids may be a good and safe option for sedation in patients outside the ICU, due to their safe hemodynamic profile. In patients expected to be weaned from ventilation, opioids with a shorter half-life may be preferred. Since remifentanil has an ultra-short half-life, and its administration requires careful and close monitoring, its administration outside the ICU setting may be problematic. Morphine has a long half-life and tends to accumulate, especially in patients with renal failure. In contrast, fentanyl has a short-medium half-life, has no active metabolites (contrary to morphine), and its elimination half-life does not depend on the patient's renal function [9], which may make it a safe drug for patients in internal medicine wards. It has a safe hemodynamic profile, although the tendency of patients to develop bradycardia (like with most opioids) should be considered. Other well-known side effects of opioids, such as nausea, vomiting, respiratory depression, and urinary retention, are usually not a problem in sedated and ventilated patients who require a urinary catheter regardless. Constipation is a common side effect, which requires attention

Table 2. Multiple regression model for predicting the number of delirium events and delirium intensity

Predictors	b	SE	β	*P*-value
Model 1: Number of delirium events				
(Intercept)	1.68	0.610	–	0.0090
Group	-1.14	0.710	-0.26	0.110
Model 2: Delirium intensity				
(Intercept)	-0.26	0.7	–	0.71
Group	-1.57	0.81	-0.31	0.06

Table 3. Differences between the groups in categorical research variables: in-hospital data

Group	Benzodiazepines (N=21), n (%)	Fentanyl (N=25), n (%)	Chi-square	*P*-value
Tracheostomy	4 (19%)	3 (12.5)	0.36	0.54
Dialysis	2 (9.5%)	0 (0.0)	2.49	0.11
Vasopressors	7 (33.3)	6 (24.0)	0.49	0.48
Need for antipsychotics	1 (4.8%)	4 (16.0)	1.48	0.22
Restraints	1 (4.8)	1 (4.0)	0.02	0.90
Falls and trauma	0 (0.0%)	0 (0.0%)	–	–
Unplanned extubating	2 (9.5%)	0 (0.0%)	2.49	0.11
28-day mortality	17 (81.0)	19 (76.0)	0.16	0.68

Table 4. Differences between the groups in continuous research variables: in-hospital data

Group	Benzodiazepines (N=21), mean ± SD	Fentanyl (N=25), mean ± SD	Mann-Whitney (*z* value)	*P*-value
Ventilation days	9.05 ± 7.00	4.78 ± 4.12	1.97	0.048
Saturation < 90 (episodes)	4.90 ± 7.09	2.91 ± 3.88	1.17	0.12
Blood pressure < 90 (episodes)	7.24 ± 8.45	5.88 ± 6.53	0.61	0.27
Heart rate < 50 (episodes)	1.00 ± 3.05	0.32 ± 1.07	1.04	0.15
Sedation Adjuvants (episodes)	1.71 ± 1.19	0.56 ± 0.82	3.44	< 0.001
Hospital length of stay (days)	8.20 ± 6.44	10.52 ± 7.02	1.17	0.25

and treatment [13]. In addition, as with the administration of other opioids, a rapid administration of a large bolus may cause transient chest wall rigidity, a phenomenon that must be considered and avoided [13].

In this study, we compared a group of ventilated patients in the internal medicine ward who were sedated with fentanyl-based sedation to a group of patients who were sedated with midazolam. There is a lack of information regarding the administration of opioid-based sedation in ventilated patients outside the ICU (and regarding sedation in these patients in general).

Regarding the primary outcome, we did not find a significant difference in the delirium rate between the groups, although there was a tendency in favor of the fentanyl group in the delirium intensity. Comparing these findings to studies regarding ICU patients, the results are unequivocal. Many studies included comparisons of multi-drug combinations, not just two different drug classes. In general, despite many studies, no single sedation drug has been shown to be superior to another [14], and many wards choose their sedative drugs based on drug familiarity and departmental tradition rather than scientific evidence [14]. In terms of delirium, there is a recommendation for the use of sedative drugs from non-benzodiazepine groups, but there is no unequivocal proof that opioid-based sedation is associated with a lower incidence of delirium compared to sedation based on benzodiazepines [14].

Regarding the secondary outcomes, the number of ventilation days was significantly lower in the fentanyl group. Those findings are consistent with studies in ICU patients. Although there is no proven advantage for opioid-based sedation compared to benzodiazepines-based sedation in terms of ventilation days, there is an advantage for non-benzodiazepines compared to benzodiazepines [15]. In the study by Breen and colleagues [16], the duration of ventilation days was lower in the opioid-based sedation group compared to benzodiazepines, but this study compared remifentanil to midazolam. It is possible that the advantage in shorter ventilation days was due to the ultra-short half-life of remifentanil rather than in its opioid properties.

The group treated with fentanyl required significantly less adjuvant sedative drug treatment, which may indicate a more adequate level of sedation. We did not find studies that examined this variable in opioid-based sedation compared to benzodiazepine-based sedation. We did not find a significant difference in the hospital length of stay. In contrast, in other studies, the length of stay in the ICU was shorter in the non-benzodiazepine group [15]. Similar to other studies, we found no differences in 28-day mortality between the groups [15]. The overall mortality of these patients (76–81% within 28 days) was like that reported in other studies [17].

As for the safety profile of opioid-based sedation outside ICU, we did not find a higher rate of sedation complications among patients who received opioid-based sedation compared to those who received benzodiazepines. There were no more events of hypoxemia, hypotension, or bradycardia and no unplanned extubations. The requirement of antipsychotics as an acute treatment for delirium was similar. We did not find studies that examined the safety of opioid-based sedation outside the ICU compared to the administration of benzodiazepines. According to the data from our study, it seems that the safety of opioid-based sedation is non-inferior to that of benzodiazepines.

Our study has several limitations. It is a retrospective study of before and after intervention, with all the possible biases in this type of study. Only a small number of patients were included. Since there is little information regarding sedation in ventilated patients outside the ICU, there is a need for more high-quality studies with more patients to confirm the findings in this study.

CONCLUSIONS

We found no significant difference in delirium rates between ventilated patients who received opioid-based sedation vs. benzodiazepine-based sedation in the internal medicine ward, although there was a tendency toward a lower intensity of delirium in the opioid group. The number of ventilation days and the requirement of adjuvant sedative drugs were significantly lower in the opioid group. There was no difference in the sedation complication rate between the groups. Further studies are needed to confirm these findings.

Correspondence

Dr. S. Dichtwald
Dept. of Anesthesiology, Meir Medical Center, Kfar Saba 4428164, Israel
Phone: (972-9) 747-2133
Fax: (972-9) 747-2973
Email: saradicht@gmail.com

References

1. Iwashita Y, Yamashita K, Ikai H, Sanui M, Imai H, Imanaka Y. Epidemiology of mechanically ventilated patients treated in ICU and non-ICU settings in Japan: a retrospective database study. *Crit Care* 2018; 22 (1): 329.

2. Agarwal, S, Ray A, Anand A, et al. A study of clinical outcomes and prognostic factors associated with invasive mechanical ventilation of patients in non-ICU settings: a systematic review and meta-analysis. *medRxiv* 2021: 2021-04.
3. Chun H, Ming-Chih L, Tu-Chen L, Ren-Guang W. Mortality and readmission among ventilator-dependent patients after successful weaned discharge from a respiratory care ward. *J Formos Med Assoc* 2010; 109 (6): 446-55.
4. Latriano B, McCauley P, Astiz ME, Greenbaum D, Rackow EC. Non-ICU care of hemodynamically stable mechanically ventilated patients. *Chest* 1996; 109 (6): 1591-6.
5. Hersch M, Sonnenblick M, Karlic A, Einav S, Sprung CL, Izbicki G. Mechanical ventilation of patients hospitalized in medical wards vs the intensive care unit--an observational, comparative study. *J Crit Care* 2007; 22 (1): 13-7.
6. Basoulis D, Liatis S, Skouloudi M, Makrilakis K, Daikos GL, Sfikakis PP. Survival predictors after intubation in medical wards: a prospective study in 151 patients. *PLoS One* 2020; 15 (6): e0234181.
7. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263-306.
8. Riker RR, Fraser GL. Altering intensive care sedation paradigms to improve patient outcomes. *Crit Care Clin* 2009; 25 (3): 527-38, viii-ix.
9. Shehabi Y, Bellomo R, Mehta S, Riker R, Takala J. Intensive care sedation: the past, present and the future. *Critical Care* 2013; 17 (3): 322.
10. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; 114: 541-548.
11. Soliman HM, Melot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. *Br J Anaesth* 2001; 87: 186-92.
12. Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. *Critical Care* 2008; 12 (suppl 3): S4.
13. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008; 11: S105-S120.
14. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014; 370 (5): 444-54.
15. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Critical Care Medicine* 2013; 41: S30-S38.
16. Breen D, Karabinis A, Malbrain M, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. *Crit Care* 2005; 9 (3): R200-10.
17. Wong WT, Lee A, Gomersall CD, et al. Survival of mechanically ventilated ward patients and association with organizational factors: a multicenter prospective study. *BMJ Open* 2021; 11: e052462.

Capsule

Gene therapy knock it out and in

Gene therapy is a promising treatment for patients with mutations in recombination activating gene 1 (*RAG1*), a cause of severe combined immunodeficiency, but there are safety concerns due to the resultant constitutive *RAG1* expression. **Castiello** and colleagues used homology-directed repair (HDR)-mediated gene editing to correct *RAG1* while preserving its physiological regulation. A combined knock-out and knock-in gene-editing strategy corrected *RAG1* in patient hematopoietic stem and progenitor cells (HSPCs), leading to rescue of protein expression. When transplanted into humanized mice, these edited HSPCs led to improved B cell production. The approach also overcame the T cell differentiation block seen with *RAG1* mutations in artificial thymic organoids. These findings support further study of HDR-mediated gene editing for the correction of *RAG1* mutations.

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Eitan Israeli

Capsule

Fibroblasts help in erection

The corpora cavernosa are masses of vascular tissue that can fill with blood and thereby enlarge upon stimulation, creating the structure needed for penile erection. By studying the underlying mechanism for this process in mice, **Guimaraes** and co-authors determined that perivascular fibroblasts in the corpora cavernosa play a key role in erection physiology. Norepinephrine is a vasoconstrictor that restricts penile blood flow at baseline, whereas vasodilators released by sexual arousal counteract its effects, allowing an erection to take place. Recurrent erectile activity down-regulates Notch signaling, thereby increasing the numbers of perivascular fibroblasts, and these fibroblasts then suppress vasoconstrictive norepinephrine signaling. Conversely, aging is associated with a decrease in these fibroblasts, contributing to the risk of erectile dysfunction.

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Eitan Israeli