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Scientific Abstracts > Regional Anesthesia

Effects of Perioperative Dronabinol Use in Total Knee Arthroplasty

Pa Thor, Matthew Perlstein, Alex Illescas, Justas Lauzadis, Joseph Oxendine, Yi Lin, Meghan Kirksey, Jacques Yadeau, Kanupriya Kumar, Lila Baaklini, Jiabin Liu, Stephanie Cheng, David Mayman, Seth Jerabek, Geoffrey Westrich, Fred Cushner, Peter Sculco, Thomas Sculco, Alejandro Gonzalez Della Valle, Alexandra Sideris, Miriam Sheetz, Maya Tailor, Angela Puglisi, Marko Popovic, Kethy Jules-Elysee
Hospital for Special Surgery

Introduction

Dronabinol is a synthetic tetrahydrocannabinol (☐9-THC) agent FDA approved for chemotherapy-induced nausea and vomiting, and as an appetite stimulant for patients suffering from HIV or AIDS. Several studies have suggested that cannabinoids may have analgesic properties, making them potential alternatives for managing chronic pain conditions, such as neuropathic pain. There is scant but controversial literature on the role of perioperative cannabinoids for pain management and opioid reduction. While post-operative pain management following total knee arthroplasty (TKA) can be effectively managed on the first day after surgery with a multimodal pain regimen including regional anesthesia techniques. It is common for patients to have a resurgence of pain the day after surgery, especially when the nerve blocks wear off and engaging in activities and ambulation.
Results of retrospective studies examining perioperative dronabinol suggested potential benefits in reducing opioid consumption in the context of shortening hospital stays for patients undergoing joint arthroplasty. In addition to its potential benefits in acute pain, ☐9-THC has been suggested to influence the apnea-hypopnea index and improve respiration. Adequately powered randomized clinical trials are required to examine the analgesic efficacy of dronabinol in different pain conditions, including acute pain. We conducted a double-blind, placebo-controlled randomized clinical trial to examine the possible opioid-sparing effect of perioperative dronabinol administration in patients undergoing TKA. The primary outcome was opioid consumption (in morphine milligram equivalents) 24-48 hours after surgery. Additional secondary outcomes included cumulative opioid requirements through postoperative day [POD] 2, pain during ambulation on POD 2, number of oxygen desaturation events, and sleep quality.

Materials and Methods

The study received approval from the Institutional Review Board (IRB) of the Hospital for Special Surgery, IRB#2019-1416 and was posted on clinicaltrials.gov prior to first study patient enrollment (NCT04734080). Eligible TKA patients were enrolled between March 8th, 2021 and October 4th, 2023 and consented on the day of surgery. A total of 114 participants were recruited and randomized to either the placebo group (sesame oil capsules), or dronabinol group. Patients in the dronabinol group received 5mg active capsules twice per day for a total of five doses, beginning in the

preoperative period and concluding on POD 2. Patients in the placebo group received same-sized and colored capsules in the same dosing regimen. Both groups received a standardized multimodal pain management regimen during admission and standard discharge opioid prescription. To measure oxygen desaturations and sleep quality, patients were connected to two wearable wrist devices in the post-anesthesia care unit (PACU), namely the Masimo pulse-oximeter adhesive sensor and the ActiLife wGT3X-BT activity respectively. Patients wore the wrist devices until POD 2 or until they were discharged from the hospital. Patients were subsequently withdrawn from the study, resulting in a final sample size of 102 (Figure 1). Categorical variables were reported as frequencies and percentages and compared using chi-square tests. Continuous variables were reported as mean and standard deviation or median and interquartile range and compared using t-test or Mann-Whitney U tests. P-values less than 0.05 were considered statistically significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results/Case Report

After exclusions, we found baseline demographics and surgical characteristics to be evenly distributed between the two groups (Table 1). From PACU to POD2, the Dronabinol group (n=51) reported lower cumulative postoperative opioid use compared to the placebo group (n=51), although not statistically significant (p=0.154) (Table 2). The dronabinol group had decreased overall pain ratings both at rest and with activity during the 7-day postoperative period, however the difference was not statistically significant compared to the placebo group. There was no statistically significant difference (p=0.582) in the incidence of desaturation events between the two groups and measurements using the ActiLife activity monitor showed that the dronabinol group did not show lower sleep quality compared to the placebo group evidenced by their sleep efficiency being higher than 85% and lower instances of wake after sleep onset (WASO). However, this difference did not reach statistical significance.

Discussion

In this randomized controlled trial, dronabinol did not reduce 24-48 hour opioid requirements following total knee arthroplasty compared to placebo. The number of desaturation events and sleep quality were also similar. No severe adverse effects were noted at the doses used. The prospective design and the stringent criteria employed for sample selection, standardization of protocols, and controlled conditions in our study are unique in providing data on perioperative effects of dronabinol. Of note, the study enrolled TKA patients who were opioid-naïve and cannabis-naïve preoperatively. Future studies are warranted using different doses and dosing regimens of dronabinol, and inclusion of more complex patients who have a history of cannabis use or chronic opioid use.

References

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Disclosures

No

Tables / Images

Figure 1

CONSORT flow diagram

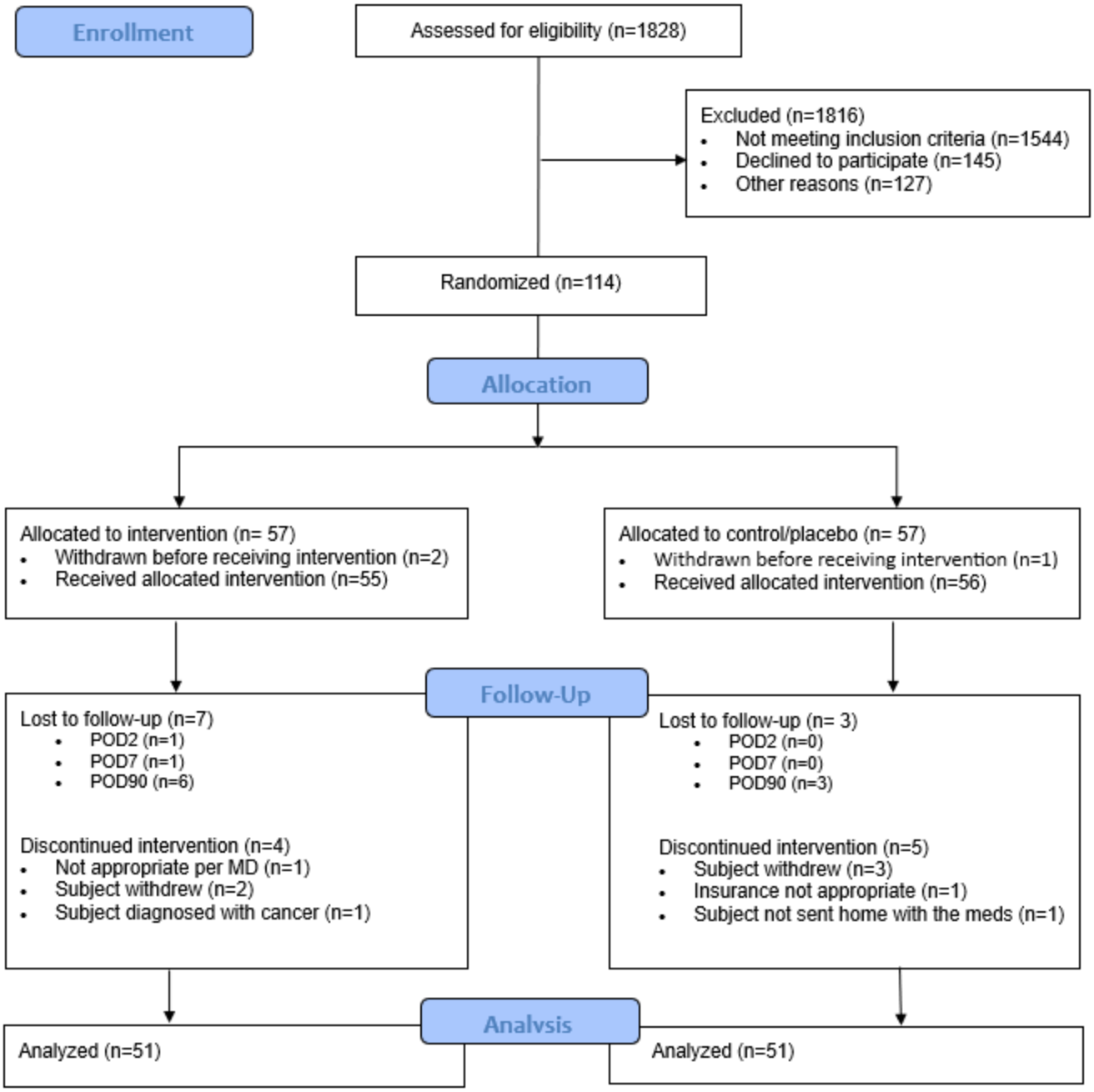

Figure 2

Oxygen desaturation events within the first 24 hours

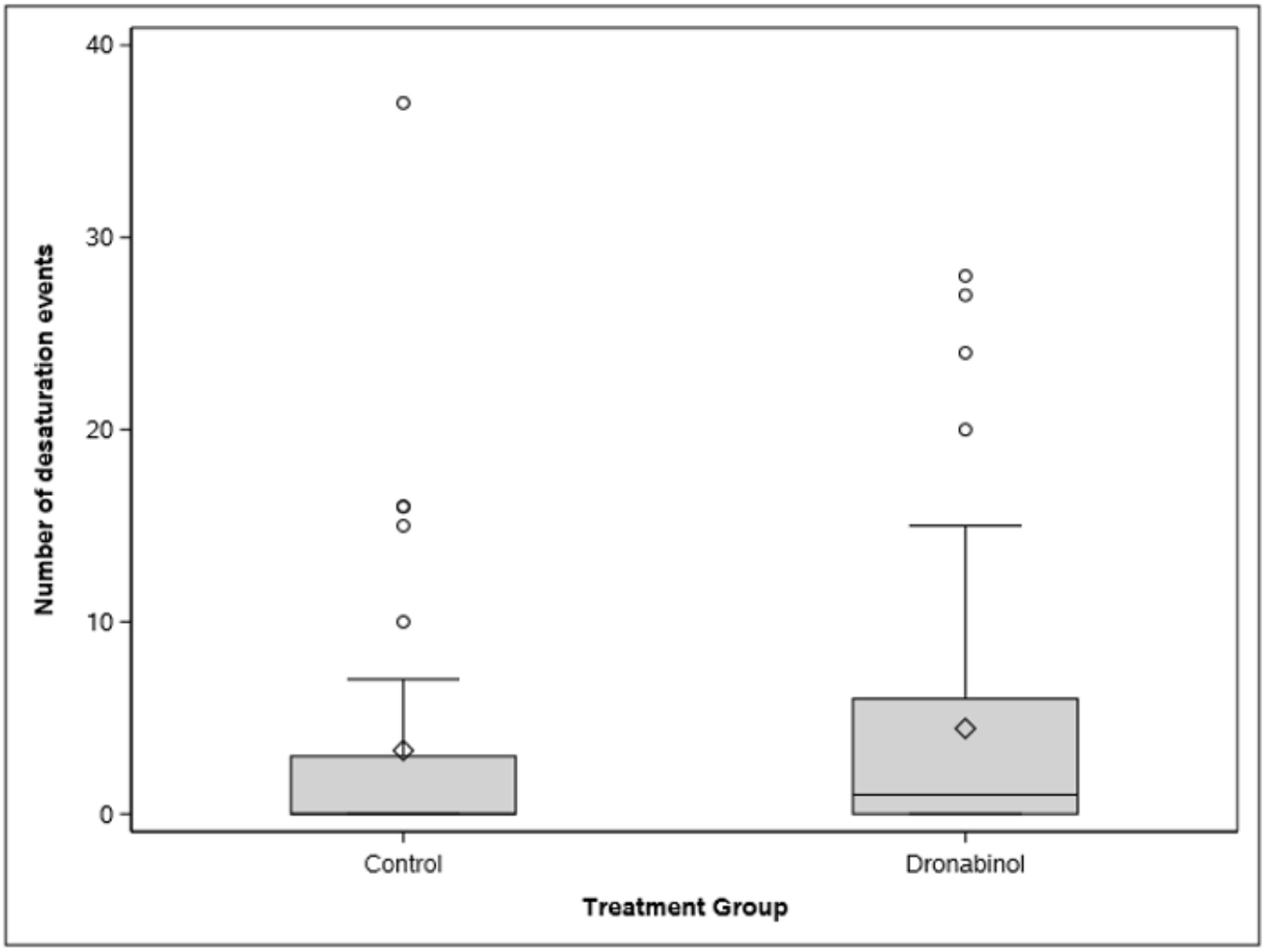

Table 1

Patient and Surgical Characteristics

	Dronabinol (n=51)		Placebo (n=51)		P-Value
	N	%	N	%	
Age, median [IQR]	62 [58-66]		63 [57-66]		0.599
BMI, median [IQR]	31.0 [28.2-34.3]		29.8 [27.9-34.1]		0.433
Gender					0.196
Male	20	39.2	27	52.9	
Female	31	60.8	24	47.1	
Comorbidities					0.458
Pulmonary Hypertension	4	8.0	0	0.0	
Hyperlipidemia	6	12.0	6	11.8	
Hypothyroidism	3	6.0	5	9.8	
Asthma	4	8.0	3	5.9	
Anemia	1	2.0	1	2.0	
None	31	62.0	33	64.7	
Other/Decline to Answer	1	2.0	3	5.9	
Total time in operating room (minutes), median [IQR]	139.0 [128.0-157.0]		144.5 [126.0-158.0]		0.852
Length of stay (hours), median [IQR]	24.3 [22.3-28.6]		23.4 [21.6-27.5]		0.665
Readiness for discharge (hours), median [IQR]	18.9 [17.5-23.1]		20.6 [17.5-23.8]		0.360

Table 2

Cumulative opioid intake, NRS Pain

		Dronabinol (n=51)	Placebo (n=51)	P-value
Opioid consumption	**POD 1 (0-24 hrs), median [IQR]**	15 [7.5-30]	23.3 [7.5-33.8]	0.320
	POD 2 (24-48 hrs), median [IQR]	15 [7.5-30]	15 [7.5-30]	0.136
	Cumulative (PACU-POD 2), median [IQR]	60.0 [37.5-82.5]	75.0 [45.0-120.0]	0.154
NRS Pain (PACU)	**at rest, median [IQR]**	0 [0-5]	0 [0-4]	0.547
NRS Pain (POD 1)	**at rest, median [IQR]**	0 [0-2]	0 [0-4]	0.795
	with movement, median [IQR]	3 [2-5]	4 [2-6]	0.588
NRS Pain (POD2)	**at rest, median [IQR]**	2 [0-3]	2 [0-3]	0.834
	with movement, median [IQR]	6 [4-8]	7 [4-9]	0.177
NRS Pain (POD7)	**at rest, median [IQR]**	0 [0-3]	1 [0-2]	0.889
	with movement, median [IQR]	4 [2-7]	5 [3-7]	0.481

Table 3

Masimo & Actigraphy

Masimo Pulse Oximetry	**Dronabinol (n=49)**	**Placebo (n=45)**	**P-value**
Desaturation events, mean (SD)	4.4 (7.3)	3.3 (6.6)	0.433
Actigraphy*	**Dronabinol (n=48)**	**Placebo (n=48)**	
Total sleep time (TST), mean (SD)	562.0 (215.4)	519.6 (211.2)	0.333
Sleep Efficiency, mean (SD)**	88.4 (5.5)	87.1 (6.5)	0.283
Wake after sleep onset (WASO), mean (SD)	69.0 (31.4)	72.2 (42.3)	0.672

*Data average across patients' hospital stay

**>85% signifies having a normal sleep period