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Analgesic efficacy of indomethacin oral spray for oropharyngeal mucositis-induced pain: randomized, placebo-controlled, double-blind trial

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Background	<ul style="list-style-type: none">• Oropharyngeal mucositis-induced pain during anticancer therapy substantially reduces patient quality of life, sometimes necessitating dose reductions or treatment interruptions.• No high-quality studies evaluating the analgesic efficacy of indomethacin oral spray (IM-OS) for oropharyngeal mucositis-induced pain exist, although anti-inflammatory agents are recommended.
Objectives	To evaluate the analgesic efficacy and safety of IM-OS for oropharyngeal mucositis-induced pain during anticancer therapy.
Study design and participants	<ul style="list-style-type: none">• A prospective, randomized, placebo-controlled, double-blind trial in a university hospital in Japan.• Cancer patients with oropharyngeal mucositis-induced pain during chemotherapy and/or radiation therapy were enrolled.• Eligibility criteria included an age of ≥ 20 years, with pain score of ≥ 4 on the Brief Pain Inventory (BPI) item 5, and tolerated oral intake.• Assuming a few cases of withdrawal, 30 subjects are needed in each group (60 subjects in total) to detect 2 point difference of BPI score between treatment groups (SD 2.5) under a statistical power of 80% with a two-sided significance level of 5%.
Randomization and Masking	<ul style="list-style-type: none">• Patients were randomly assigned (1:1) to intervention (IM-OS) or control (placebo) groups in a web-based central randomization system using a stratified randomized model.• Randomization was stratified according to BPI item 3 (≥ 7 or not), cancer treatment (chemotherapy, radiotherapy or both), and age (≤ 65 or not).• A double-blind technique was used with a placebo identical in appearance to IM-OS container.• The IM-OS and placebo container were manufactured by an unblinded pharmacist who was not involved in providing direct care to the study.
Procedures	<ul style="list-style-type: none">• All patients received practiced oral care except for 4 hours after the initial dose of the protocol treatment.• Patients were randomly assigned to receive either IM-OS or matched placebo oral spray (4 times per dose in each group).• 0.8 mg of IM-OS or placebo was administrated 30 minutes before each meal and when patients had severe pain. (Maximum usage was up to 20ml in 24 hours)
Outcome Measures	<ul style="list-style-type: none">• The primary endpoint was the intergroup difference in the change of BPI-item 6 score at 30 minutes from baseline.• Major secondary endpoints were questionnaire on meal (4-point Likert scale) and adverse events.

Results

- From July 2015 through December 2016, 60 patients were enrolled and received IM-OS (n=33) or placebo-OS (n=27).
- The two groups had significant differences in the change of BPI-item 6 score at 30 minutes afterwards from baseline (-1.3 [95% CI: -1.94, -0.57]; p<0.001), which persist for 180 minutes.
- There were intergroup differences in scores for liquid drinkability (p=0.027) and ease of conversation (p=0.017).
- There were no acute adverse events due to IM-OS or placebo, or IM-related adverse events within 2 weeks after IM-OS administration.

Clinical Implications

- Indomethacin oral spray could be used as analgesic for oropharyngeal mucositis pain without adverse events.
- Indomethacin oral spray could be used not only as rescue, but also as prophylactic drug for meals.

Conclusion

Indomethacin oral spray reduces oropharyngeal mucositis-induced pain during anticancer therapy and could ease eating.

Table 1. Patient characteristics

Characteristics	Indomethacin spray group (n=33)	Placebo group (n=27)
Age (years), Mean (SD)	61.5 (15.6)	59.7 (15.6)
Sex		
Male	18 (54.5)	18 (66.7)
BPI-item3 category		
≤ 6	5 (15.2)	3 (11.1)
≥ 7	28 (84.8)	24 (88.9)
Therapy		
Radiation therapy	14 (42.4)	12 (44.4)
Chemotherapy	6 (18.2)	5 (18.5)
Both therapy	13 (39.4)	10 (37.0)
Primary Cancer		
Head and neck	19 (57.6)	13 (48.1)
Blood	12 (36.4)	12 (44.4)
Other	2 (6.1)	2 (7.4)
Regular analgesic		
Non-use	5 (15.2)	4 (14.8)
Acetaminophen	12 (36.4)	5 (18.5)
With opioid	9 (27.3)	2 (7.4)
Without opioid	3 (9.1)	3 (11.1)
NSAIDs	3 (9.1)	3 (11.1)
With opioid	3 (9.1)	1 (3.7)
Without opioid	0 (0.0)	2 (7.4)
Weak opioid	6 (18.2)	5 (18.5)
Dose, Mean (SD)	31.7 (16.0)	32.0 (17.9)
Strong opioid	12 (36.4)	15 (55.6)
Dose, Mean (SD)	64.2 (62.7)	46.3 (33.0)
Rescue analgesic		
Acetaminophen	4 (12.1)	0 (0.0)
NSAIDs	0 (0.0)	0 (0.0)
Weak opioid	1 (3.0)	0 (0.0)
Strong opioid	10 (30.3)	12 (44.4)
ECOG PS		
0	1 (3.0)	0 (0.0)
1	11 (33.3)	9 (33.3)
2	15 (45.5)	10 (37.0)
3	6 (18.2)	8 (29.6)
4	0 (0.0)	0 (0.0)
Grade of oral mucositis CTCAE v4.0		
Grade 1	0 (0.0)	0 (0.0)
Grade 2	22 (66.7)	21 (77.8)
Grade 3	11 (33.3)	6 (22.2)

Table 2. Difference between BPI item-6 in each group before drug administration and 30 minutes after

	IM-OS group (n=33)	Placebo group (n=27)	Difference	P value
Change from baseline, Mean (95%CI)	-1.85 (-2.37 , -1.32)	-0.59 (-1.02 , -0.16)	-1.26 (-1.94 , -0.57)	0.0005
25% reduction, n (%)	22 (66.7)	6 (22.2)	44.44 (21.98 , 66.91)	0.0006
33% reduction, n (%)	16 (48.5)	5 (18.5)	29.97 (7.48 , 52.45)	0.0155
50% reduction, n (%)	8 (24.2)	2 (7.4)	16.84 (-0.81 , 34.48)	0.0817

Table 3 .Difference in 4-point Likert scale of the question related meals before and 24 hour after drug administration.

Mean (SD) scale	IM-OS group (n=33)			Placebo group (n=27)			P value
	Baseline	24 hours	CFB	Baseline	24 hours	CFB	
<u>liquid drinkability</u>	3.1 (0.7)	2.8 (0.8)	-0.2 (0.4)	2.7 (0.9)	2.6 (0.9)	0.0 (0.2)	0.0267
pureed food swallowing	3.2 (0.8)	3.1 (0.9)	-0.2 (0.4)	3.0 (1.0)	3.0 (1.0)	0.0 (0.3)	0.0804
solid food swallowing	3.9 (0.3)	3.8 (0.5)	-0.1 (0.3)	3.6 (0.8)	3.5 (0.8)	0.0 (0.2)	0.4139
enjoys meals	1.0 (0.0)	1.0 (0.0)	0.0 (0.0)	1.1 (0.3)	1.1 (0.4)	0.0 (0.2)	0.2726
<u>ease of conversation</u>	3.1 (0.9)	2.6 (0.9)	-0.5 (0.8)	2.4 (0.8)	2.3 (0.9)	-0.1 (0.4)	0.0171

Figure 1. Changes of overall clinical impression in each group before and after drug administration

Reference

- Bowen JM, et al. Methodology for the MASCC/ISOO Mucositis Clinical Practice Guidelines Update. Support Care Cancer. 2013;21(1):303.
- Lalla R V, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120(10):1453.
- Momo K, et al. Assessment of indomethacin oral spray for the treatment of oropharyngeal mucositis-induced pain during anticancer therapy. Support Care Cancer. 2017;25(10):2997.

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Declaration of Conflicting Interests

The authors have declared no potential conflicts of interest with respect to the research, authorship, and/or presentation of this study.