

Efficacy and safety of hypotonic 0.18% sodium hyaluronate solution (Vismed®) in patients with moderate dry eye - A study of the osmolarity of the tear film

A. Rapisarda¹, F. Battaglia¹, L. Bossy²,
¹ Department of Ophthalmology, "Umberto I" Hospital, Syracuse, Italy,
² TRB Chemedica International SA, Geneva, Switzerland.

Introduction

- The new definition of dry eye by the International Dry Eye WorkShop (DEWS)¹ emphasises the hyperosmolarity of tear film as a core mechanism of dry eye disease.
- The osmolarity of normal tear fluid is about 300 mOsmol/l (isotonic), but in patients with dry eye it may be as high as about 340 mOsmol/l (hypertonic). It is believed that the main cause of the clinical symptoms and signs of tear deficit is the hyperosmolarity of the tears which would increase ocular irritation^{2,3}.
- Vismed® is a unique formulation that contains sodium hyaluronate (SH) and ions namely calcium, magnesium, potassium, sodium and chloride naturally present in the tear fluid to maintain the physiology of the cornea. It has been formulated to be hypotonic (150 mOsmol/l), in order to compensate the hypertonicity of tears in patients experiencing dry eye syndrome.

Study objectives

The aim of this study was to compare the efficacy and safety of a hypotonic 0.18% sodium hyaluronate solution (Vismed®) vs. isotonic 0.3% hydroxypropylmethylcellulose (HPMC) eye drops and to evaluate their effects on tear osmolarity.

Methods

Study design

Randomised (1:1), controlled, open parallel-group, phase III trial.

Patient selection

120 patients diagnosed with moderate dry eye syndrome due to:

- Sjögren syndrome (primary or secondary), or
- Keratoconjunctivitis sicca (KCS)

Main inclusion criteria

- Male and female patients aged 18 years and over, with
- Sjögren's syndrome or KCS,
- Schirmer I test \leq 5.5 mm wetting/5 min for each eye,
- Tear film BUT \leq 7 s for each eye,
- Positive and typical corneal-conjunctival staining with rose Bengal,
- Positive and typical corneal-conjunctival staining with fluorescein

Products and treatment

- Sodium hyaluronate 0.18% (Vismed®) or HPMC 0.3% (Dacriosol®)
- 1 instillation into each eye 6 times per day for 2 months

Statistical analysis

The Student t-test was used for comparison of BUT, Schirmer I test, staining with fluorescein and rose Bengal, corrected visual acuity, and the osmolarity of the tear film. The chi-squared test was used for signs and symptoms, compliance to treatment and the global clinical judgment expressed by the investigator.

Procedures and assessments

Table 1: Efficacy parameters and schedule of assessments

	Baseline		Treatment and follow-up				
			Vismed®				
				HPMC (0.3%)			
Procedures and assessments	V1	V2	V3	V4			
	D0	D15	D30	D60			
Inclusion and exclusion criteria	X						
Signed informed consent	X						
Dispensation of allocated product	X						
Presence of signs and symptoms	X	X	X	X			
Schirmer I test	X	X	X	X			
Tear film BUT	X	X	X	X			
Staining with rose Bengal	X	X	X	X			
Staining with fluorescein	X	X	X	X			
Osmolarity of the lacrimal film	X	X	X	X			
Slit lamp examination	X	X	X	X			
BCVA	X	X	X	X			
Compliance	X	X	X	X			
Adverse event report	X	X	X	X			
Global judgment by the Investigator	X	X	X	X			

Results

Patients

Patient disposition is shown in Table 2 and demographic and baseline characteristics are summarised in Table 3.

Table 2: Disposition of patients

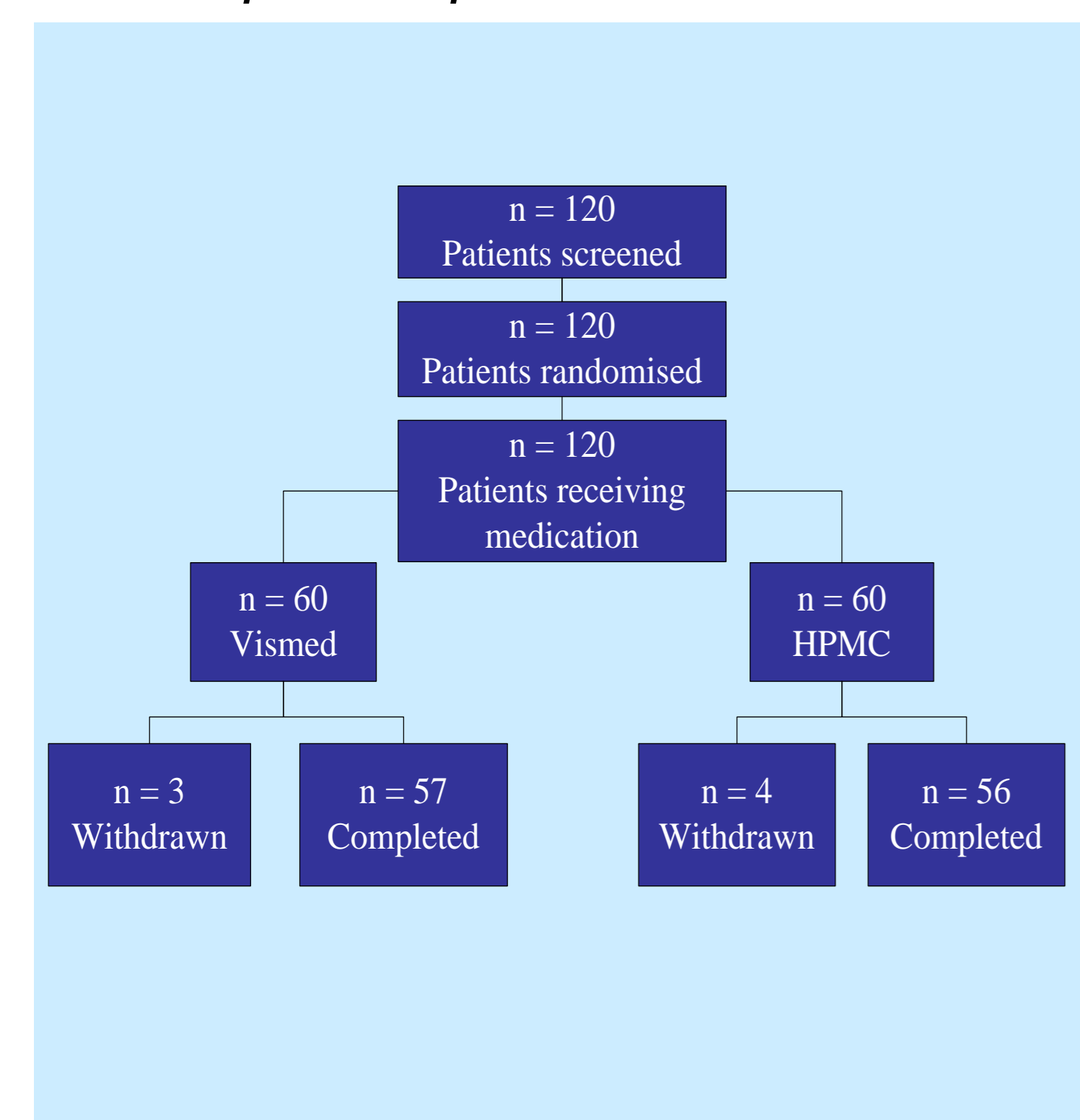


Table 3: Demographic and baseline characteristics, PP population

Characteristics	Vismed® n=57	HPMC n=56	p-value
Gender (n) (Female/Male)	52 / 5	50 / 6	p>0.05
Age (years), mean (± std)	57.07 (11.11)	53.98 (9.57)	p>0.05
Osmolarity mean (±std)	353.3 (22.5)	349.8 (21.9)	p=0.2360
Burning sensation (% of patients)	96	98	p=0.1840
Foreign body sensation (% of patients)	95	89	p=0.4350
Ocular pain (% of patients)	55	49	p=0.4820
Schirmer I test (mm wetting/5min) mean (±std)	2.68 (1.64)	2.73 (1.68)	p=0.7976
Tear film BUT (seconds) mean (±std)	1.63 (1.35)	2.14 (1.73)	p=0.0141
Rose Bengal staining (score) mean (±std)	5.58 (1.33)	5.71 (1.01)	p=0.4244
Fluorescein staining (score) mean (±std)	5.69 (1.27)	5.75 (1.35)	p=0.7448

Efficacy

Osmolarity of the tear film

Vismed® caused a significant decrease in tear film osmolarity values, compared with HPMC. At each study visit, there was a statistically significant difference (p=0.0001) between the 2 treatments in favour of Vismed®, both at 30 min (figure 1A) and 90 min (figure 1B) following the instillation of the eye drops.

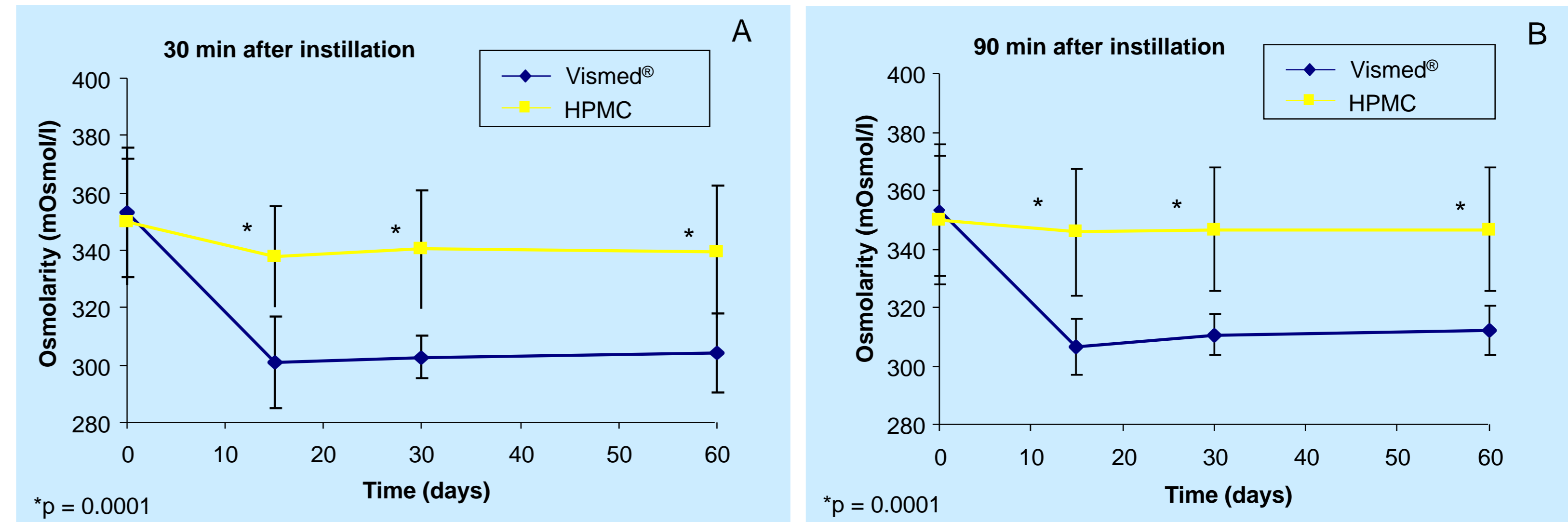


Figure 1: Mean (± SD) values for the osmolarity of the tear film (mOsmol/l) at baseline and after 15, 30 and 60 days of treatment with Vismed® or HPMC; 30 min (A) or 90 min (B) after instillation of the eye drops

Burning sensation

Vismed® caused a significantly (p=0.0001) greater decrease of burning sensation compared to HPMC (figure 2A). After 2 months of treatment, this symptom was present in 30% of the patients treated with Vismed® and in 54% patients treated with HPMC.

Foreign body sensation

At the Day 60 visit, 21% of the patients in the Vismed® group reported foreign body sensation in the eye, whereas 46% of patients in the HPMC group reported this symptom. There was a statistically significant difference between the 2 groups in favour of Vismed® (figure 2B).

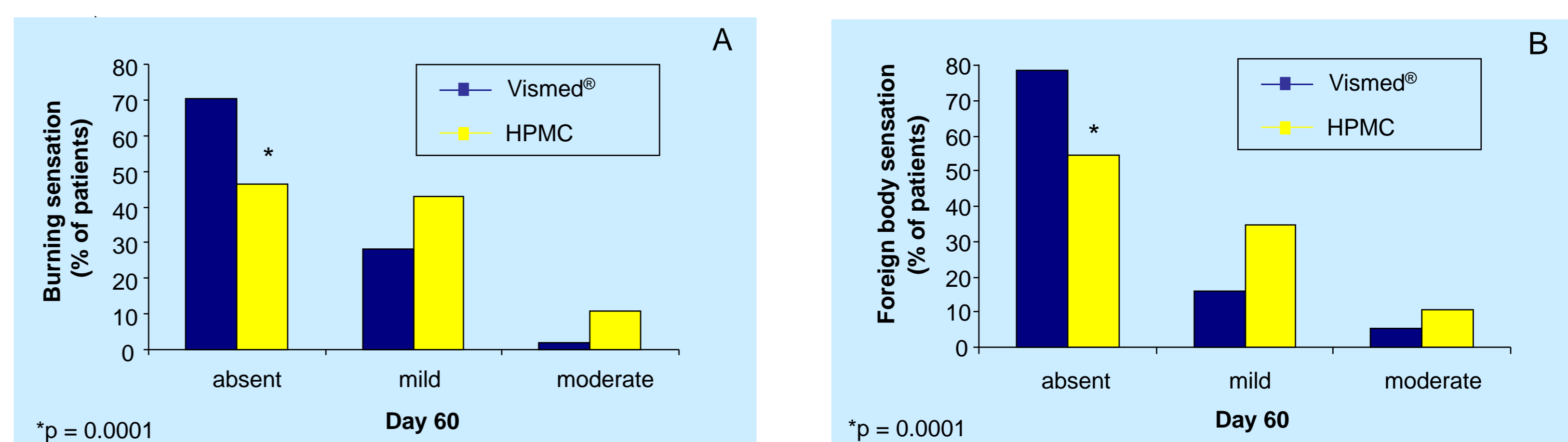


Figure 2: Percent distribution of (A) burning sensation and (B) foreign body sensation in Vismed® and HPMC groups at Day 60

Ocular pain

After 60 days of treatment, ocular pain was present in 4% of patients in the Vismed® group and in 22% of the patients in the HPMC group. There was a statistically significant difference between the 2 groups (p=0.0001) in favour of Vismed® (figure 3).

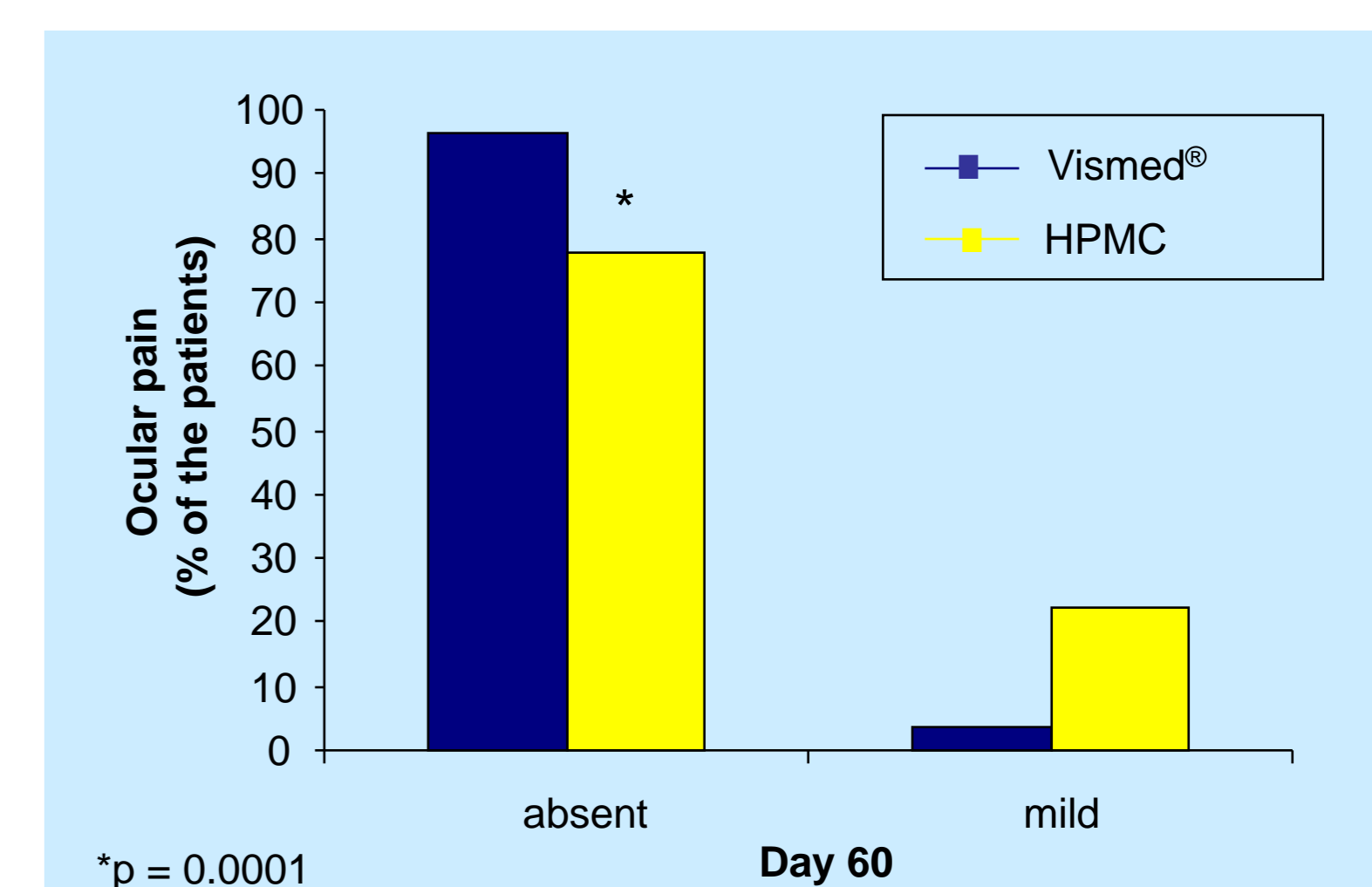


Figure 3: Percent distribution of ocular pain in Vismed® and HPMC groups at Day 60

Schirmer I test, tear film BUT, rose Bengal staining, fluorescein staining

Table 4: Results of the Schirmer I test, tear film BUT, rose Bengal staining and fluorescein staining at Day 60

Characteristics	Vismed® n=57	HPMC n=56	p-value
Schirmer I test (mm wetting/5min) mean (±std)	10.04 (2.64)	6.25 (1.85)	p=0.0001
Tear film BUT (seconds) mean (±std)	6.96 (1.62)	4.81 (1.62)	p=0.0001
Rose Bengal staining (score) mean (±std)	0.34 (0.54)	1.61 (0.97)	p=0.0001
Fluorescein staining (score) mean (±std)	0.38 (0.58)	1.36 (0.58)	p=0.0001

At Day 60, there was a significantly (p=0.0001) greater improvement of Schirmer I test, tear film BUT, rose Bengal staining and fluorescein staining in the Vismed® group compared to the HPMC group (table 4).

Safety

Both treatments were well tolerated. The instillation of 1 drop of Vismed® or HPMC (0.3%) 6 times per day for 60 days did not induce blurred vision or adverse reactions.

Conclusions

In contrast with HPMC (0.3%), Vismed® significantly decreased values of tear osmolarity. This would explain the significant reduction of ocular symptoms and signs and the significant improvement of tear film BUT and tear volume (Schirmer test I) compared to HPMC.

Both products were well tolerated and no adverse reaction was reported in any group.

References

- Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; 5(2):108-52.
- Rolando M, Baldi F, Zingirian M. The effect of hyperosmolarity on tear mucus ferning. *Fortschr. Ophthalmol.* 1986; 83:644-6.
- Gilbard JP, Carter JB, Sang DN, Refojo MF, Hanninen LA, Kenyon KR. Morphologic effect of hyperosmolarity on rabbit corneal epithelium. *Ophthalmology* 1984; 91(10):1205-12.